Part One

A pretty-good reference for the primary exam

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Part One

Part One is a reference for trainees preparing for the CICM and ANZCA Primary Exams.

- Part One **is**:
  - Designed to cover the ***assessed*** sections of the CICM and ANZCA curricula **in enough detail to pass**
  - A rough guide for the expected depth of knowledge required on a topic
  - A tool to correct your written answers
  - A source of information you might find difficult to find elsewhere
- Part One **is not**:
  - A textbook
  - The definitive guide to the primary exam
  - A complete reference
    There will be both omissions and errors. If you find any, please let me know.

Layout

The book is divided into three sections:

- **Curriculum**
  Covers statistics, physiology, equipment and measurement, and anatomy.
  - Pages are laid out using the section title, topic titles, and order from the CICM curriculum
    > A grey block indicates a topic is from the CICM curriculum OR both curricula
  - When a topic is only examinable in the ANZCA curriculum, it has been slotted in somewhere sensible
    > A purple block indicates a topic is ONLY from the ANZCA curriculum
  - Topics covered by the page are listed at the beginning of each page
- **Pharmacopoeia**
  Covers drugs.
  - For the sake of consistency, the *general principles* of pharmacology are covered in the curriculum, whilst the specifics of different agents will be found in the pharmacopoeia. If lost, use the search box.
- **Appendices**
  Includes the key definitions, graphs, and equations you should know, as well as sample structures for SAQs.

Acknowledgements + Technical Stuff

Part One is built with a number of open-source tools:

- Written in John Gruber's elegant Markdown
- Built and made pretty by the GitBook toolchain
  With plugins from:
  - Ben Lau for automatic timestamps
  - Michael Jerger for collapsible chapters
  - Rishabh Garg for top navigation
- Equations written in $\LaTeX$
- Graphs have been:
  - Written in PGF/Tikz using texworks

    - Converted to vector graphics with dvisvgm
    - Refined with svgo
    - (Some graphs have been taken from open-source sites such as Wikimedia Commons. These have been credited where used.)
- Additionally, chemical structures have been built in MarvinSketch

About the Author

Jake Barlow is an Anaesthetic and Intensive Care Registrar from Melbourne, Australia. Interested in all things critical care (with a particular fascination for physiology), as well as biotech, physical computing, teaching, analytics, and outcome prediction in intensive care. Send all comments, criticism, and complaints about Part One to him here.

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Last updated 2019-11-09

Download Part One

Part One is also provided with:

- A PDF version for offline use
  Note that:
  - The image quality of graphs is reduced in the PDF version
  - The PDF version is automatically built whenever the site is updated
    Therefore:
    - The download link will always link to the most recent version
    - This page will appear in the PDF version
- A companion set of flashcards, made in Anki

Last updated 2018-07-16

How to Pass

The first part exam is:

- Painful
  The knowledge demanded is huge, and cannot be avoided.
- **Eminently achievable**
  Remember, it is not impossible - **everybody before you has completed it**.

Plan for Success

This is not an exam you want to have to sit more than once - try to give yourself the best chance of success the first time round:

- Commit yourself early
  Decide when you are going to sit:
  - Pick a date ~9 months in advance
    - 6 months is probably pushing it
    - 9 months is achievable
    - 12 months is almost too long - you will lose motivation and knowledge will fade.
  - Accept that the time between now and the exam is not going to be the best time of your life
  - Consider paying the money as soon as possible - lock yourself in
  - Your family and friends will forgive you, eventually
- Don't lose faith
  - There will be times that you question why you have to learn this
  - Those are very legitimate feelings
  - Accept that part of **this exam is an academic hazing you must pass** through on your path to fellowship

Be Strategic

The curriculum provided is overwhelming, and probably not achievable for most of us. Have a plan about how you will approach it:

- Have a timetable
  - Content to cover each week
    - I found setting a weekly goal would allow me to plan around day-to-day variations (finishing late, good days, bad days, etc)
    - A daily timetable was often mangled by life, creating unnecessary stress
  - Time to start viva practice
    Aim to start before the written.
    - Topics that you can't explain, you probably don't understand fully
      This may not be apparent until you try and explain it.

- Know the enemy
  - Syllabus
    Read through it so you appreciate the breadth of knowledge required.
  - Know the style
    This allows you to give answers **efficiently** - the key metric for both the vivas and the SAQs is **marks per unit time**.
    - Style of exam questions
      Including the style of answers - see the SAQ.

        - Style of vivas
            - Do practice vivas
                - Record yourself, so you know your tics
                - Do a dress rehearsal
                  Make sure your suit still fits before the day.
        - Graphs
          Be able to draw them while talking about them.

- **Do past questions**
  I cannot stress this enough. This is **the** key to preparing for this exam.
    - Past questions:
        - Teach you appropriate structure
        - Teach you to write to time
        - Ensure you learn the content in the way it will be recalled
        - Ensure you don't waste time learning things that are unlikely to be examined
          When I sat the CICM exam, I had done almost all the past questions, which covered ~60% of the curriculum. There was 1 (out of 24) of the SAQs on a topic I had not answered an SAQ on before.
    - Do questions to time
      Keeping to time is **vital**.
        - It is almost impossible to write a perfect answer in 10 minutes
        - In many cases you will need to move on to the next question despite still having things to say
        - Remember that the marking follows a sigmoid distribution
            - The first 30% of marks for a question are easy to get
            - The last 30% of marks are very difficult to get
            - Therefore, the most efficient use of your time is to aim to get ~60-70% of marks for each question.

- **Remember the pass mark is 50%**
    - You are not expected to know everything
    - Breadth tends to be rewarded over depth
    - It is normal to sit the exam and have a question you have not thought about before

Suggested Approach

There are many equally valid ways to approach these exams. This is how I would do it, if I had to do it again:

1. **Read a general physiology and pharmacology textbook**
   This will help you understand the scope of the undertaking. I would recommend spending 2-3 weeks reading:
    - Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
      In my opinion, this is **the** general physiology text. I believe that if you knew everything in this book, you would pass the physiology component of both exams.
    - Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
      The first few chapters are a good introduction to pharmaceutics and pharmacokinetics, which will help you put later information from more complete texts into context.

2. **Start doing practice questions**:
   This is the key to the exam. I suggest:
    - Start doing one question at a time
      In the beginning, you will not know enough to write for 10 minutes.
        - After doing the question, check your answer against available past answers
          This forces active learning, and is far more efficient than reading. Look at:
            - Structure
              How did you structure your answer? What was the example structure?

- Content
  What did you miss? Are the numbers/graphs you used correct?
- Then study the curriculum areas that question covered, and make notes
  This would take me ~1-2 hours for a new curriculum area.
- Once you start doing questions which you know something about (having answered one similar previously), move up to three questions in 24 minutes.
  This teaches you to keep time, which is vital for success in the SAQ.
  - Still check each answer afterwards, look over that area of the curriculum, and revise and refine your notes
- When you find yourself running out of time before you run out of things to write, give yourself 9 minutes per question
  I would suggest not going beyond this - you need to allocate your time strategically on the day, and writing to time is critical.
- As this gets easier, start doing 6 or more questions at a time to train your writing hand
- Do one or two full exams to time before game day

3. **Do a *lot* of flashcards**
   Flashcards are less demanding than doing questions, and a simple form of revision.
   - They are the absolute best way of rote learning facts (in my opinion)
   - I used anki, but use whatever works for you
   - My anki deck is available here

4. **Do practice vivas**
   Start before the written. There is a lot of crossover of skills between the viva and the written. Both require a structured approach, and good content knowledge.
   - Remember to take a break after the written exams, it is exhausting

The Bottom Line

- Pick a date, and commit to it
- Work out which times work best for you with respect to study
  Different times will be better for different things. I found:
  - Days off (including weekends) were best for learning new content
  - Work days were for revising
  - Post night shift was a write-off
- Maintain a positive attitude
  Study groups are good for this - share the suffering!
- Split large topics into manageable chunks
- Don't lose your head
  Set aside time for relaxation, and don't feel guilty about it.
- You don't have to know everything
  The pass mark is 50%

References

- This is based on a talk I gave at the 2016 VPECC Course, still raw from the CICM primary

Last updated 2019-08-01

The SAQ

A good response to a short-answer question is constructed from two things:

- **Structure**
  Developing a structured approach to answering SAQs is essential to succeeding in this section of the exam. A structured approach:
    - Is easily digested by the examiner
    - Reduces the amount of filler you need to write, meaning you can write more facts
    - Typically lends itself to bullet points rather than paragraphs
    - Allows you to recall more information than you would otherwise
      Especially if you learnt it **in the same format**. This is particularly important for pharmacology.
- **Knowledge**
  Obviously.

Additionally, a good response will:

- **Answer the question**
  This is stated *repeatedly* in examiner reports. If the question asks for a discussion of the respiratory changes of pregnancy, no marks will be awarded for cardiovascular changes.
- **Be legible**
- **Not be perfect**
  This is often-overlooked.
    - Examiner reports (and some model answers), assume a perfect response
    - This not feasible given the time allowed
    - It is also not actually expected - remember that **the pass mark is 50%**

The bottom line:

- A good response will cover the major points in reasonable detail
- Will generally focus on principles rather than specifics
  Marks become progressively harder to acquire:
    - The first one or two marks on a question should be easy
    - Going from an 8/10 to a 10/10 will require time which you likely cannot spare

Answering the Question

- You have exactly **10 minutes** per SAQ
- You should practice to **8-9 minutes** per SAQ
  In many cases, the last question (or questions) goes unanswered. This demonstrates poor time management, as easy marks were thrown away by candidates reaching for harder marks on earlier questions.

- During reading time, you should evaluate each question to:

    - Decide what part of the curriculum it is assessing
    - Work out the context, if any
    - Decide what structure would be most appropriate

Last updated 2017-08-14

The Viva

The viva is the part of the exam most candidates seem most stressed about. However:

- If you make it through the written, you will most likely pass
  Very few people succeed in the written exams to fail at the viva.
    - The knowledge is there
    - Examiners want you to pass
      They will redirect you if you're off track.
        - This makes it easier to make up marks than on the written, where you can easily go off down the rabbit hole, haemorrhaging time and marks

Understanding the Viva

To do well at the viva:

- Understand **the viva is a performance piece**
  The viva is a ritualised conversation. Success requires you to know and understand the language and structure used, just like the SAQ.
- **Structure your answer**
  As with the SAQ, categorise your answer.
    - Have a good opening statement
      Don't answer more than is asked.
    - Start broad
      Often the viva will go into depth on only one or two areas of a topic. If you start going into detail on only parts of a topic, it makes it hard for the examiner to redirect you and scores you no marks.
- Be confident
  Enjoy it if you can.
- Learn to think on your feet
  The viva assesses knowledge in a different way to the SAQs.
    - The knowledge will be there, but it may require a different approach to access it
      This requires **practice**.
    - This is also important for delivering a sound answer based on incomplete knowledge
- It's okay to say "I don't know"
  But probably not on the first question.
    - If you don't know immediately, can you work it out from first principles?
- Don't get angry
    - With yourself
    - With the examiner
      Don't argue.
- Don't apologise
  Apologies:
    - Make you lose confidence
    - Don't get you marks
      Remember, marks per unit-time.
- Don't talk over the examiner
  They are interrupting you because what you are saying is gaining no marks. If you keep talking, you will:
    - Not be getting marks
    - Irritate them

Potentially losing future marks.

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Evidence-Based Medicine

> Describe the features of evidence-based medicine, including levels of evidence (e.g. NHMRC)~~, meta-analysis, and systematic review~~

What is Evidence-Based Medicine?

- Evidence-based medicine (EBM) is **"the conscientious, explicit, and judicious use and appraisal of current best evidence in making decisions about the care of individual patients."**
- The purpose of EBM is to provide a framework for acquiring knowledge and making optimal decisions around medical care. It means integrating **individual clinical expertise with the best available external clinical evidence** from systematic research."

There are five stages of EBM:

1. Ask an answerable question
2. Search
3. Critically appraise the evidence
4. **Integrate the evidence with the patients unique circumstances** and values
5. Evaluate the result

Levels of Evidence

Levels of evidence grade studies on likelihood of bias and internal validity. The NHMRC defines 6 levels of evidence, graded from I-IV (with three level III subtypes).

In general:

- Level I is evidence from a **systematic review** of RCTs
- Level II is evidence from **at least one good RCT**
- Level III-1 is evidence from a **pseudo-RCT**
- Level III-2 is evidence from a **comparative study *with* concurrent controls**, such as a cohort or case-control study
- Level III-3 is evidence from a **comparative study *without* concurrent controls**, such as a cohort study with historical controls
- Level IV is evidence from a case-series

Note that expert opinion is **not** part of NHMRC levels of evidence, though it is included on the Oxford Centre for Evidence Based Medicine system, used by the NHS.

Level	Intervention	Diagnostic Accuracy	Prognostic	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among **consecutive persons** with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
		A study of test accuracy			

III-1	A pseudorandomised controlled trial	with: an independent, blinded comparison with a valid reference standard, among **non-consecutive** persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial
III-2	A comparative study with concurrent controls	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls
III-3	A comparative study without concurrent controls	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Grades of evidence

Evidence is graded to "indicate the strength of the body of evidence underpinning a recommendation" (e.g. in a clinical guideline).The NHMRC grades recommendations from A to D as follows:

- **A**: Body of evidence can be trusted to guide practice
- **B**: Body of evidence can be trusted to guide practice, in most situations
- **C**: Body of evidence provides some support, but care should be taken in its application
- **D**: Body of evidence is weak and recommendation must be applied with caution

Study types: Systematic Reviews and Meta-analyses

Systematic Review

Process of evaluating all of the (quality) literature to answer a specific clinical question. Does not necessarily involve statistical analysis. If it involves quantitative analysis of multiple trials, it is known as a **meta-analysis**.

Meta-analysis

Mathematical technique of combining the results of different trials to derive a **single pooled estimate of effect**. Can be done by:

- Pooling the results of each trial
- Pooling all of the raw data and conducting a reanalysis

- Meta-analyses usually use **random-effects models**, which assumes there will be a variety of similar treatment effects
- Individual trials are **summarised with an odds ratio**, and **weighted**, usually by sample size

Stages of a [meta-analysis] and systematic review:

1. Inclusion and exclusion criteria are predefined
2. Search: including online databases, reference lists, citations, and experts
3. Validation of potentially eligible trials (critique of interval validity, i.e. trial quality)

4. [Heterogeneity Analysis]
5. [Meta-analysis]
6. Reliability of result determined
   i.e. Consistency across studies, statistical significance, large effect size, biological plausibility.
7. Sensitivity analysis
   Repeating the analysis with an alternative model, excluding borderline trials or outliers. If the result is unchanged, then the findings are **robust**.

Heterogeneity

For the pooling of results to be valid, the trials need to be similar. Differences between trials is called **heterogeneity**, and is important because:

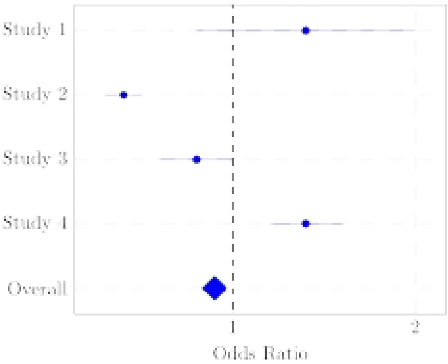
- Heterogeneity analysis affects the type of model that can be used (**fixed** or **mixed effects**)
- Highly heterogenous data is not appropriate for meta-analysis.

Heterogeneity is divided into:

- **Statistical Heterogeneity**
  The effects of the intervention are more different than would be expected to occur through chance alone.
- **Clinical Heterogeneity**
  Due to trial design it would be inappropriate to pool the results.
    - E.g., conducting a meta-analysis on the effects of the same drug in a paediatric and adult population may be inappropriate, as these two trials had different inclusion criteria.
- **Methodological Hetreogeneity**
  Where the methods used in different trials are too different to allow pooling of the data.

Forest Plots

Results of meta-analyses are presented in a blobbogram, or more boringly, a **Forest Plot**.



Where:

- The **x-axis** plots the odds ratio, remembering that an OR of 1 indicates no difference
- The **y-axis** lists the studies included, and the overall summary statistic
- The **dot** (or square) indicates the **point estimate** (from its x-location) and the **weight** given to the study (by its size)
- The **horizontal line** indicates the upper and lower bounds of the **confidence interval**
- The **diamond** indicates the **overall point estimate** and (by its width) the **confidence interval** for the point estimate
- The result of the heterogeneity test should also be displayed
  $P < 0.1$ indicates significant heterogeneity.

Funnel Plots

Funnel plots are a **graphical tool to detect publication bias**.

- Due to statistical power, larger studies should be a closer representation of the true effect
- Therefore, when evaluating an number of studies, one would expect that large studies cluster around the 'true effect', and smaller studies to scatter further
- A graph is then plotted of OR on the x-axis, and standard error on the y-axis
  - Publication bias is suggested when results cluster on one side of the funnel plot
  - No evidence of publication bias would have studies clustered around the true effect

Strengths and weaknesses of meta-analyses

Strengths	Weaknesses
Enhanced precision of estimates of effect	Publication bias
Useful when large trials have not been done or are not feasible	Duplicate publication
Generate clinically relevant measures (NNT, NNH)	Heterogeneity
	Inclusion of outdated studies

Because of these weaknesses:

- Positive meta-analyses should be considered largely hypothesis-generating, and should be confirmed by (a large) RCT
- Negative meta-analyses can probably be accepted

References

1. Sacket DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based Medicine: How to practice and teach EBM. Churchill Livingstone, London 1997.
2. Sackett David L, Rosenberg William M C, Gray J A Muir, Haynes R Brian, Richardson W Scott. Evidence based medicine: what it is and what it isn't BMJ 1996; 312:71.
3. NHMRC. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. National Health & Medical Research Council. 2009.
4. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.
5. Lalkhen AG, McCluskey A. Statistics V: Introduction to clinical trials and systematic reviews. CEACP 2008.

Last updated 2019-07-18

Study Types

> Describe the features of evidence-based medicine, including ~~levels of evidence (e.g. NHMRC),~~ meta-analysis, and systematic review

Randomised Control Trial

A prospective randomised controlled trial is the **gold standard** of experimental research.

It involves allocating patients randomly to either an intervention or a reference (control) group, and measuring the outcome of interest. Allocation can be performed in three ways:

- Simple
  Individuals allocated randomly. This may lead to uneven group sizes.
- Block
  Allocation is performed within blocks such that group sizes will remain close in size
- Stratified
  Groups are randomised within a category (i.e. men and women are randomised separately).

Strengths

- Only study design which can establish causation
- Eliminates confounding
  Randomisation controls for both known and *unknown* confounding factors, as these should be randomly allocated between groups.
- Blinding can be performed in a standardised fashion
- Decreases selection bias

Weaknesses

- Costly
- Time-consuming
- Not appropriate for all study designs
  - Ethical concerns
    e.g. Adrenaline in ALS
  - Practical concerns
    Small patient population or uncommon disease may cause recruitment difficulties

Systematic Review

The process of evaluating all of the (quality) literature to answer a specific clinical question. This:

- Does not necessarily involve statistical analysis
  If it involves statistical analysis of multiple trials to generate a combined estimate of effect, it is known as a **meta-analysis**.

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Mathematical technique of combining the results of different trials to derive a single pooled estimate of effect. Can be performed by:

- Pooling the results of each trial
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- **Statistical**; where the effects of the intervention are more different than would be expected to occur through chance alone. Heterogeneity analysis affects the type of model that can be used (**fixed** or **mixed effects**) and highly heterogenous data is not appropriate for meta-analysis.
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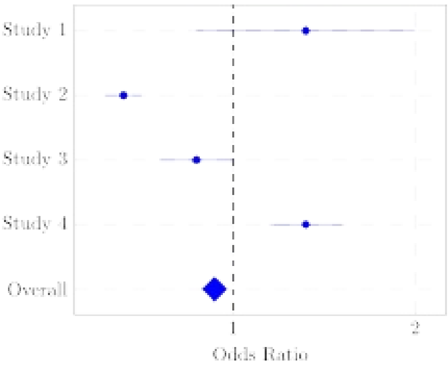

Where:

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	Inclusion of outdated studies

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References

1. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.

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Clinical Trial Design

> Describe the stages in design of a clinical trial

1. Determine research question
2. Determine target population
3. Specify outcomes
4. Determine requirement for control group
5. Sample size estimation
6. Control for confounding
7. Control for bias
8. Data handling
9. Statistical analysis plan (pre-specified)

References

1. PS Myles, T Gin. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.

Last updated 2017-09-12

Data Types

> Describe the different types of data

Data are a series of observations or measurements. Can be either **qualitative** or **quantitative**.

Qualitative Data

Using words as data rather than numbers, evaluating meaning and process. Common in the social sciences.

Quantitative Data

Uses numbers, or can be coded numerically. Divided into multiple types, each with multiple subtypes.

- **Categorical**
  Data exist in **discrete categories without intrinsic order**.
  - e.g. Medical specialty (intensive care, emergency medicine, orthopaedics, cardiology)
  - Descriptive statistics for categorical data can be reported using the absolute number for each category, percentages, or proportions
- **Ordinal**
  Data exists in **discrete categories with an intrinsic order**, e.g. age groups (0-5, 6-10, 11-15...)
  - Descriptive statistics for ordinal data are the same for categorical data, but they can also be summarised by the median and the range (e.g. median age group, age group range).
- **Numerical**
  Data is an actual number. Can be subdivided into discrete or continuous:
  - **Discrete**
    Can only be recorded as an integer (whole number), e.g. number of hospital admissions.
    - **Dichotomous** or **binary** data, which occurs when there are only two categories
  - **Continuous**
    Where data can assume any value (including fractions), e.g. white cell count.
    - Continuous data can be further subdivided into **interval** or **ratio** data:
      - **Ratio data**
        Are expressed with reference to a **rational zero**, which is where zero means **no measurement**.
        - e.g. Temperature in °K is a ratio variable, whilst temperature in °C is not
          This is because 0°K means no temperature, whilst 0°C does not; e.g. 50°K is half the temperature of 100°K, but 50°C is not half the temperature of 100°C.
        - Ratio variables can (unsurprisingly) be expressed as ratios, whilst interval variables can not
      - **Interval data**
        Do not have a rational 0 - this is just another point on the line (e.g. temperature in °C).

References

1. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.

Last updated 2019-07-18

Bias and Confounding

> Describe bias, ~~types of error,~~ confounding factors and sample size calculations, and the factors that influence them

Bias

Bias is a **systematic deviation from truth**, and causes a study to lack **internal validity**.

In a research study, an observed difference between groups may be due to:

- A true difference between groups
- An error
  Error can be due to:
  - Normal random variation, i.e. chance
  - A systematic difference, i.e. bias
    Unlike error due to chance, the effect of bias cannot be reduced by increasing the sample size.

Types of Bias

Type of bias	Description	Prevention
Selection	Where subject allocation results in treatment groups that are systematically different, apart from in the intervention being studied	Randomisation
Detection	Where measurements are taken differently between treatment groups	Blinding
Observer	Where the data collector is able to be subjective about the outcome	Blinding, Hard outcomes
Publication	When negative studies are less likely to be submitted or published than positive ones	Clinical trial registries
Recall	Altered reporting of symptoms by patients depending on which group they have been allocated to	Blinding
Response	When patients who enroll for a trial differ from the population, limiting generalisability	Random sampling
Hawthorne effect	When the process of actually doing the study improves the outcome	Control group, masking study intent from patients and observers

Confounder

A confounder is **"a variable that, if removed, results in a change in the outcome variable by a clinically significant amount."** It is a type of bias which will result in a distortion of the measured effect.

A confounding factor must be:

- **Associated with the exposure** but **not a consequence of it**
  - A confounding factor cannot be on the causal pathway between exposure and disease
  - It must be present unevenly between groups to cause distortion of the measured effect
- **An independent predictor of outcome**
  The confounding factor must also be a risk factor for the disease, but independently from exposure.

Controlling for confounding

By Design

- **Randomisation**
  All confounders (known and unknown) are distributed evenly between groups.
- **Restriction**
  Restricts participants to remove confounders.
    - Results in reduced generalisability and does not control all factors
- **Matching**
  Pairing of similar subjects between groups.
    - May introduce additional confounding, and matching by multiple characteristics is difficult

By Analysis

- **Standardisation**
  Adjust for differences by transforming data.
- **Stratification**
  Analyse the data in subgroups for each potential confounding factor.

References

1. Sackett, D. L. (1979). Bias in analytic research. Journal of Chronic Diseases 32 (1–2): 51–63.
2. PS Myles, T Gin. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.
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Last updated 2019-07-18

Frequency Distributions and Measures of Central Tendency

> Describe frequency distributions and measures of central tendency and dispersion

Frequency Distributions

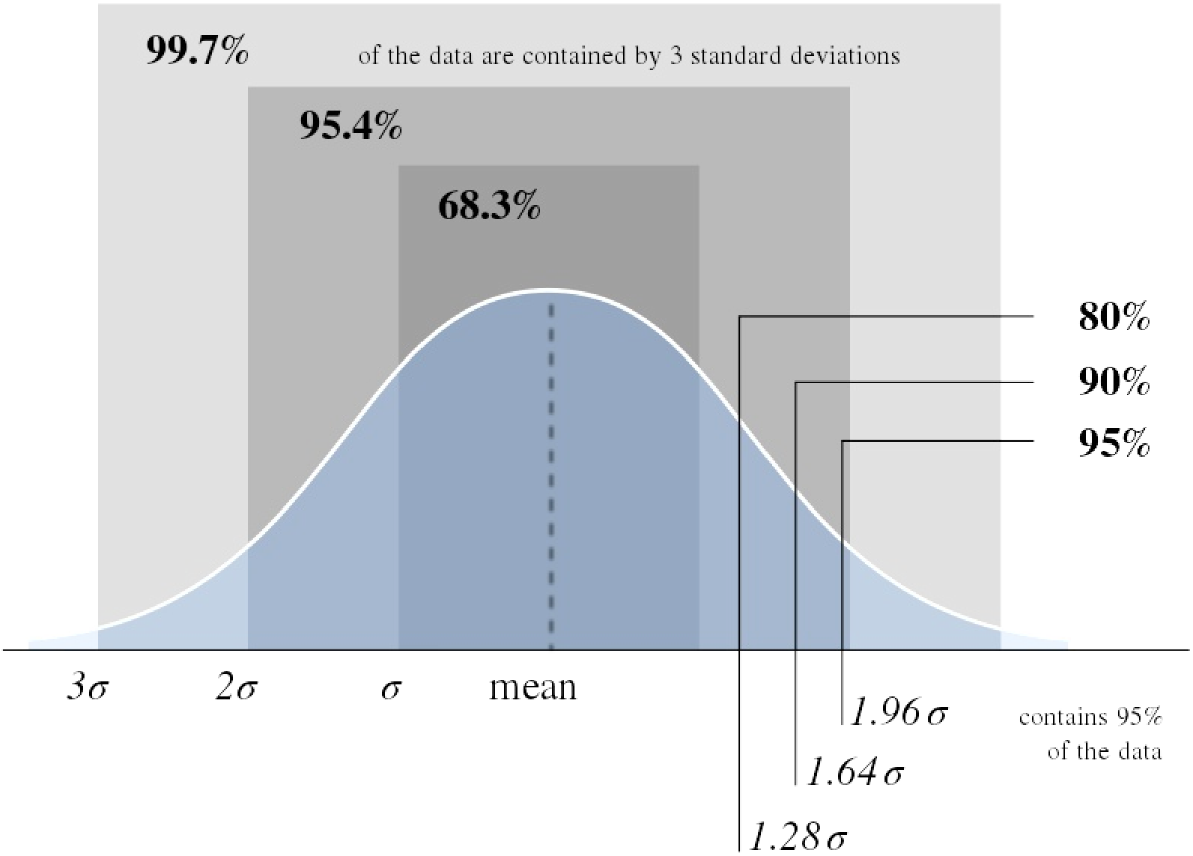
Frequency distributions are a method of tabulating or graphically displaying a number of observations.

The Normal Distribution

The normal distribution is a **gaussian distribution**, where the majority of values cluster around the mean, and whilst more extreme values become progressively less frequent.

The normal distribution is common in medicine for two reasons.

- Much of the variation in biology follows a normal distribution
- When multiple random samples are taken from a population, the **mean of these samples follows a normal distribution, even if the characteristic being measured is not normally distributed**
  This is known as the **central limit theorem**.
  - It is useful because many statistical tests are only valid when the data follow a normal distribution



The formula for the normal distribution is given by:

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{-(x-\mu)^2}{2\sigma^2}}$$

From this, it can bet seen the two variables which will determine the shape of the normal distribution are:

- μ (mu): The mean
- σ (sigma): The standard deviation

The Standard Normal Distribution

The **standard normal distribution** is a normal distribution with a mean of 0 and a standard deviation of 1. The equation for the standard normal distribution is much simpler, which is why it is used.

$$f(x) = \frac{1}{\sqrt{2\pi}} e^{\frac{-x^2}{2}}$$

Any normal distribution can be transformed to fit a standard normal distribution using a **z transformation**:

$$z = \frac{x-\mu}{SD}$$

The value of z then gives a **standardised score**, i.e. the number of standard deviations form the mean in a standardised curve. This can then be used to determine probability.

Binomial distribution

Where observations belong to one of two mutually exclusive categories, i.e.:
If $P(A) = x$ then $P(B) = 1 - x$

If the number of observations is very large and the probability of an event is small, a **Poisson distribution** can be used to approximate a binomial distribution.

Measures of Central Tendency

As noted above in the **normal distribution**, results tend to cluster around a central value. Quantification of the degree of clustering can be done using **measures of central tendency**, of which there are three:

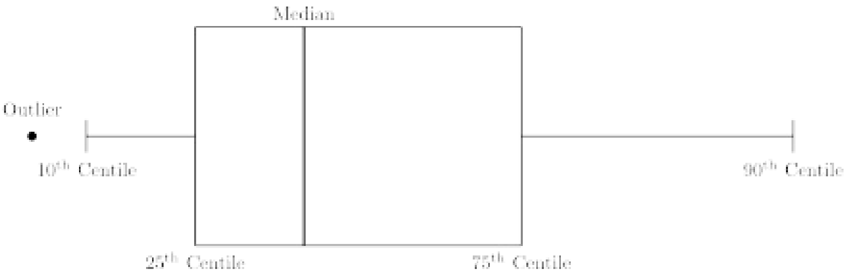
- **Mode**
  The most common value in the sample.
- **Median**
  The middle value when the sample is ranked from lowest to highest.
  - The median is the best measure of central tendency when the data is **skewed**
- **Arithmetic mean**
  The average, i.e: $\bar{x} = \frac{\sum x}{n}$
  The mean is common and reliable, though inaccurate if the distribution is **skewed**.

Measures of Dispersion

Measures of variability describe the degree of dispersion around the central value.

Basic Measures of Deviation

- **Range**: The lowest and highest values in the sample
  Highly influenced by outliers
- **Percentiles**: Rank observations into 100 equal parts, so that the median becomes the 50% percentile.
  Better measure of spread than range.
- **Interquartile range**: The 25th to 75th centile
  A **box-and-whisker plot** graphically demonstrates the mean, 25th centile, 75th centile, and (usually), the 10th and 90th centiles.
  - Outliers are represented by dots
  - Occasionally the range is plotted by the whiskers, and there are no outliers plotted



Variance and Standard Deviation

Variance is a better measure of variability than the above methods. Variance:

- Evaluates how far each observation is from the mean, and penalises observations more the further they lie from the mean
- **Sums the squares** of each difference and divides by the number of observations i.e:
  $$s^2 = \frac{\sum(x-\bar{x})^2}{n-1}$$
  - is used (instead of n) because the mean of the sample is known and therefore the last observation calculated must taken on a known quantity
    - This is known as a **degrees of freedom**, which is a mathematical restriction used when using one statistical test in order to estimate another
    - It is a confusing topic best illustrated with an example:
      - You have been given a sample of two observations (say, ages of two individuals), and you know nothing about them
      - The degrees of freedom is **two**, since those observations can take on any value.
      - Alternatively, imagine you have been given the same sample, but this time I tell you that the mean age of the sample is 20
      - The degrees of freedom is **one**, since if I tell you the value of one of the observations is 30, you know that the other must be 10
        Therefore, only one of the observations is free to vary - as soon as its value is known then the value of the other observation is known as well.
    - Different statistical tests may result in additional losses in degrees of freedom.

Standard Deviation

The standard deviation is the **positive square root of the variance**.

In a sample of normal distribution:

- 1 SD either side of the mean should include ~68% of results
- 2 SD either side of the mean should include ~95% of results
- 3 SD either side of the mean should include ~99.7% of results

Standard error and Confidence Intervals

Standard error of the mean is:

- A measure of the precision of the estimate of the mean
- Calculated from the standard deviation and the sample size
  As the sample size grows, the SEM decreases (as the estimate becomes more precise).
- Given by the formula:
  $$SE = \frac{SD}{\sqrt{n}}$$
- Used to calculate the **confidence interval**

Confidence Interval

The **confidence interval**:

- Gives a range **in which the true population parameter is likely to lie**
  The width of the interval is related to the **standard error**, and the degree of confidence (typically 95%):
    -
    -
- Is a function of the sample statistic (in this case the mean), rather than the actual observations
- Has several benefits over the *p*-value:
    - Indicates magnitude of the difference in a meaningful way
    - Indicates the precision of the estimate
      The smaller the confidence interval, the more precise the estimate.
    - Allows statistical significance to be calculated
      If the confidence interval crosses 1, then the result is insignificant.

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1. "Normal distribution". Licensed under Attribution 3.0 Unported (CC BY 3.0) via SubSurfWiki.
2. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001
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Last updated 2019-07-18

Sample Size Calculation

> Describe bias, types of error, confounding factors and **sample size calculations, and the factors that influence them**

Samples

A sample is a subset of a population that we wish to investigate. We take measurements on our sample with the aim to make inferences on the general population. An optimal sample (in quantitative research) will be **representative**, that is, it has the same characteristics of the population it is drawn from.

Sampling Error

Due to chance, the sample mean will not equal the population mean. This is called **sampling error**, and is a form of random error. A larger sample will more closely approximate the population mean, reducing random error leading to more accurate point estimates and narrower confidence intervals.

This is why large sample sizes are desirable in research. However, larger studies are also more costly and time consuming to run. Sample-size calculations are performed to find a happy medium.

Sample Size Calculation

All sample size calculations depend on:

- Acceptable **risk of Type I error (α)**, typically set at 0.05
  A **smaller α** (lower false positive risk) requires a larger sample size.
- Acceptable **risk of Type II error (β)**, typically set at 0.20
  A **smaller β** (lower false negative risk) requires a larger sample size.
- Expected **effect size**
  A **smaller effect size** requires a larger sample size, as the difference between groups will be smaller and harder to detect.
- Population **variance**
  A **larger population variance** requires a larger sample size, as there is more 'noise' in the sample.
- **Study design**
  Certain trial designs (e.g. multiple arms) require a larger sample size for a given effect size and power.
- Practical considerations
  - **Cost**
    Increasing sample size increases the cost of a study.
  - **Participant availability**
    Sample size is limited when the number of eligible participants for a study is small (e.g. rare diseases)

Different formulas for sample size calculations exist for different studies, and can be adjusted for particular study designs, such as multiple or unequal groups.

References

1. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.
2. Course notes from "Introduction to Biostats", University of Sydney, School of Public Health, circa 2013.

Last updated 2017-09-22

Statistical Tests

> Describe the appropriate selection of non-parametric and parametric tests and tests that examine relationships (e.g. correlation, regression)

Parametric Tests

Parametric tests are used when data is:

- Continuous and numerical
- Normally distributed
    - Remember that due to the central limit theorem - large data sets ($n > 100$) are typically amenable to parametric analysis, as sample means will follow a normal distribution
    - Non-normal data can be transformed so that they follow a normal distribution
- Samples are taken randomly
- Samples have the same variance
- Observations within the group are independent
  Independent results are those when one value is not expected to influence another value.
    - A common example is repeated measures: when serial measures are taken from a patient or a hospital, the results cannot be treated as independent
    - **Paired tests** are used when two dependent samples are compared
    - **Unpaired test** are used when two independent samples are compared

Tests may be one-tailed or two-tailed:

- A **two-tailed test** evaluates whether the sample mean is significantly greater or less than the population mean
- A **one-tailed test** only evaluates the relationship in one direction
  This doubles the power of the test to detect a difference, but should only be performed if there is a very good reason that the effect could only occur in one direction.

Common parametric tests include:

Z test

Used to test whether the mean of a particular sample ($\bar{x}$) differs from the population mean (μ) by random variation.

Assumptions:

- Large sample
  $n > 100$.
- Data is normally distributed
- Population standard deviation is known

Student's T Test

This is a variant of the Z test, used when the population standard deviation is not known.

- The results from T test approximate the results of the Z test when $n > 100$

F Test

Compares the ratio of variances ($\frac{Var_1}{Var_2}$) for two samples. If F deviates significantly from 1, then there is a significant difference in group variances.

Analysis of Variance (ANOVA)

ANOVA tests for significant differences between means of multiple groups, in a more efficient manner than multiple comparisons (doing lots of T tests).

There are several types of ANOVA tests used in different situations.

Non-Parametric Tests

Non-parametric tests are used when the assumptions for parametric tests are not met. Non-parametric tests:

- Do not assume the data follows any particular distribution
  This is required when:
  - Non-normality is obvious
    e.g. Multiple observations of 0
  - Possible non-normality
    Typically small sample sizes.
  - Data is ordinal
- Are not as powerful as parametric tests (a larger sample size is required to achieve the same error rate)
- Are more broadly applicable than parametric tests as they do not require the same assumptions

Non-parametric tests still require that data:

- Is continuous or ordinal
- Within-group observations are independent
- Samples are taken randomly

In general, non-parametric tests;

- Take each result and rank them
- Calculations are then performed on each rank to find the test statistic

Common non-parametric tests include:

Mann-Whitney U Test/Wilcoxon Rank Sum Test

Alternative to the unpaired T-test for non-parametric data.

Process:

- Data from both groups are combined, ordered, and given ranks
  - Tied data are given identical ranks, where that rank is equal to the average rank of the tied observations
- The data are then separated into their original group
- Ranks in each group are added to give a test statistic for each group
- A statistical test is performed to see if the sum of ranks in one group is different to another

Wilcoxon Signed Ranks Test

Alternative to the paired T-test for non-parametric data.

Process:

- As above (for the Wilcoxon Rank Sum Test), except absolute difference between paired observations are ranked
  The sign (i.e. positive or negative) is preserved.
- The sum of positive ranks is then compared with the sum of negative ranks
- If there is no difference between groups, we would expect the net value to be 0

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1. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.

Last updated 2017-09-22

Statistical terms

> Understand the terms sensitivity, specificity, positive and negative predictive value and how these are affected by the prevalence of the disease in question

> Describe bias, types of error, ~~confounding factors and sample size calculations~~, and the factors that influence them

All these terms refer to characteristics of **diagnostic tests**. The easiest way to approach this is via a 2x2 table, and has been recommended in previous exams as an approach to questions on this topic.

Types of Error

Draw a 2x2 table of disease state versus test outcome:

	Disease Positive	Disease Negative	Total
Test Positive	True Positives	False Positives	All Test Positives
Test Negative	False Negatives	True Negatives	All Test Negatives
Total	All Disease Positives	All Disease Negatives	

- **True** or **false** refers to whether the test was **correct**
- **Positive** or **negative** refers to the **test result**

- A **Type I error** is a **false positive**, when we incorrectly reject the null hypothesis
  - The type I error rate can be decreased by decreasing α
- A **Type II error** is a **false negative**, when we incorrectly accept the null hypothesis
  - The type II error rate can be decreased by decreasing β, usually expressed as increasing **power**
    Power is the chance of detecting a difference if it exists. Power is equal to 1-β.

Sensitivity and Specificity

Sensitivity

- **Sensitivity** is the probability those with the disease test positive, i.e. the **true positive rate**, and expressed mathematically as:
  $$Sensitivity = \frac{True\ Positives}{All\ Disease\ Positives} = \frac{True\ Positives}{True\ Positives + False\ Negatives}$$
- It refers to the ability of a test to **detect the condition**
- A highly sensitive test will likely be positive if the condition is present
- Therefore, a **negative** result on a **sensitive test** gives a **high likelihood the disease is not present**
  - The mnemonic for this is **SNOUT** - Sensitive, Negative, rule OUT

Specificity

- **Specificity** is the probability those without the disease test negative, i.e. the **true negative rate** ,and expressed mathematically as:
  $$Specificity = \frac{True\ Negatives}{All\ Disease\ Negatives} = \frac{True\ Negatives}{True\ Negatives + False\ Positives}$$
- It refers to the ability of a test to **detect *absence* of the condition**
- A highly specific test will likely be negative if the condition is not present

- Therefore a **positive** result on a **specific test** gives a **high likelihood the disease is present**
  - The mnemonic for this is **SPIN** - Sensitive, Positive, rule IN

Positive and Negative Predictive Values

- Positive and negative predictive values describe **the proportion of test results which are true**
- A high value indicates accuracy of the test
- Because of how they are derived, **they are dependent on population prevalence of the disease**

- **Positive Predictive Value** (PPV) is the probability that the **disease is present** when the **test is positive**:

$$Positive\ Predictive\ Value = \frac{Disease\ Positives}{All\ Test\ Positives} = \frac{Disease\ Positives}{Disease\ Positives + False\ Positives}$$

- **Negative Predictive Value** (NPV) is the probability that the **disease is absent** when the **test is negative**:

$$Negative\ Predictive\ Value = \frac{Disease\ Negatives}{All\ Test\ Negatives} = \frac{Disease\ Negatives}{Disease\ Negatives + False\ Negatives}$$

Remembering the Difference

- Rote learning these formulas is hard
- Remember that:
  - Sensitivity and specificity are **the same** for any given prevalence of disease
    Therefore they look at columns (disease positive or disease negative).
  - PPV and NPV are not
    Therefore they look at rows (test positive or test negative).

Likelihood Ratios

The weakness of PPV and NPV as tools of evaluating the utility of a test in clinical practice is that they do not take into account the population prevalence, i.e. the *prior probability*, of a condition.

A classic example is the urine bHCG, which has a high positive predictive value for pregnancy. Tested on an exclusively male group however, the true positive rate will be 0 (since there are no pregnancies), and so all test positives will be false positives.

Therefore:

- The actual utility of a test in decision making is dependent upon the **prior probability** of the disease being present
- Likelihood Ratios relate the **pre-test odds** to the **post-test odds**
  They are useful because (unlike the above values) they do not assume that the patient you are applying them to is identical to the sample from which the statistic was derived.
- The likelihood ratio multiplied by the pre-test odds gives the post-test odds of the disease being present
  - A **positive likelihood ratio** is used when the test is positive:

$$LR(+) = \frac{sensitivity}{1 - specificity}$$

  - A **negative likelihood ratio** is used when the test is negative:

$$LR(-) = \frac{1 - sensitivity}{specificity}$$

References

1. Myles PS, Gin T. Statistical methods for anaesthesia and intensive care. 1st ed. Oxford: Butterworth-Heinemann, 2001.
2. Course notes from "Introduction to Biostats", University of Sydney, School of Public Health, circa 2013.

Last updated 2019-11-02

Risk and Odds

> Understand the concepts of risk and Odds Ratio

Risk

- **Absolute Risk** is the risk of an event occurring in the exposed group
- **Relative Risk** (or risk ratio) is the risk of an event occurring in the exposed group relative to the unexposed group.

$$Relative\ Risk = \frac{Risk\ in\ Exposed}{Risk\ in\ Unexposed} = \frac{\frac{Exposed\ individuals\ with\ outcome}{Number\ of\ exposed}}{\frac{Unexposed\ individuals\ with\ outcome}{Number\ of\ unexposed}}$$

- **Absolute Risk Reduction** is the decrease in risk provided by an exposure:
  $ARR = Risk\ in\ Exposed\ -\ Risk\ in\ Unexposed$
  Is a clinical useful measure of the value of an intervention, however is better expressed as:
  - **Number Needed to Treat (NNT)** is the number of individuals who must receive a treatment to prevent one event:
    $NNT = \frac{1}{ARR}$
- **Relative Risk Reduction** is the decrease in incidence provided by treatment. It is not as useful a measure of the value of an intervention, but drug companies like it because the numbers are bigger than absolute risk reduction.

Odds

- **Odds** are the probability of an event happening compared to the probability of it not happening, usually expressed as a fraction
- The **Odds Ratio** is the ratio of the odds of the outcome occurring in the exposed compared to the odds of it occurring in the unexposed
  $OR = \frac{Odds\ of\ the\ outcome\ in\ the\ exposed}{Odds\ of\ the\ outcome\ in\ the\ unexposed}$
  - An OR < 1 suggests the risk is lower in the exposed group
  - An OR > 1 suggests the risk is higher in the exposed group
  - An OR = 1 suggests that the groups are equivalent
- In general, the OR overstates risk compared to the RR.
- It is approximately equal to the RR when the outcome is rare (< 10%)
- It is used when:
  - The denominator is uncertain, i.e.:
    - In retrospective designs, such as case-control studies when patients with the disease were identified, and then exposures ascertained
  - When it statistically appropriate (ORs are much easier to use in statistical tests), i.e.:
    - Multivariate regression
    - Systematic Reviews

Risk versus Odds

Relative Risk and **Odds Ratios** are both methods of comparing the likelihood of an outcome occurring between two groups. The difference, and particularly the concept of odds ratios, are **commonly confused**. Relative risk tends be much more intuitive than odds ratios. Imagine a trial has been performed, where group A was exposed group:

- In group A, the mortality was 50%
- In group B, the mortality was 25%

The **relative risk** is intuitive: $RR = \frac{Risk\ of\ death\ in\ exposed}{Risk\ of\ death\ in\ unexposed} = \frac{0.5}{0.25} = 2$

The **odds ratio** is not: $OR = \frac{Odds\ of\ death\ in\ exposed}{Odds\ of\ death\ in\ unexposed} = \frac{1/1}{1/3} = 3$

A RR of 2 is intuitive, but the OR of 3 is not. Now, imagine another trial where:

- In group A, the mortality was 90%
- In group B, the mortality was 10%

$$RR = \frac{Risk\ of\ death\ in\ exposed}{Risk\ of\ death\ in\ unexposed} = \frac{0.9}{0.1} = 9$$

$$OR = \frac{Odds\ of\ death\ in\ exposed}{Odds\ of\ death\ in\ unexposed} = \frac{9/1}{1/9} = 81$$

The relative risk is 9, but the OR is 81!

So why use odds ratios at all? Odds ratios are:

- Required when research subjects are selected on the basis of outcome rather than the basis of exposure
- Used by many statistical tests because the log odds ratio is normally distributed, which is a mathematically useful property

Relative Risk has a weakness as well - it is dependent on how the question is framed. Using the first trial above, we calculated that RR for death was 2 and the OR was 3. Rather than calculating mortality, an alternative method could be to look at survival:

- In group A, the survival was 50%
- In group B, the survival was 75%

$$RR = \frac{Risk\ of\ survival\ in\ exposed}{Risk\ of\ survival\ in\ unexposed} = \frac{0.5}{0.75} = 0.6\bar{6}$$

$$OR = \frac{Odds\ of\ survival\ in\ exposed}{Odds\ of\ death\ in\ survival} = \frac{1/1}{3/1} = 1/3$$

Note that the relative risk is not 0.5 (as you may initially assume), however the odds ratio is just the inverse of the previous value.

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Significance Testing'

> Understand concept of significance and testing of significance

Significance testing is:

- The process of determining whether a difference between groups in a study is due to a real difference, or chance alone
- Performed using p-values
- Does not imply clinical significance
  For a result to be statistically significant, there must be a 'real' difference between groups.
  - This difference does not have to be clinically meaningful
    - e.g. A drug may reliably cause a 5mmHg decrease in SBP - this is unlikely to cause a meaningful drop in cardiovascular mortality but may be statistically significant

P Values

The ***p*-value** is the **probability of obtaining a summary statistic** (e.g. a mean) **equal to or more extreme than the observed result, *provided the null hypothesis is true***.

The *p*-value is commonly (mis)used in frequentist significance testing.

- Prior to performing an experiment, a significance threshold (α) is selected
  - Traditionally 0.05 (5%) or 0.01 (1%)
    These values define the "false-positive rate".
    - When multiple tests are being performed on one set of data, the chance of a false-positive will increase
      - To reduce the chance of a false positive occurring, the significance threshold for each test can be reduced. One method of this is the Bonferroni correction, where α is divided by the number of tests being performed.
- Then the experiment is performed, and a value for *p* is calculated
  If $p < \alpha$, it suggests that the results are inconsistent with the null hypothesis (at that significance level), and it should be rejected.

Problems with *P*-values

P-values are, when employed correctly, are useful. However, they do have several weaknesses:

- Assume the null hypothesis is true
  The *p*-value assumes that there is no real difference between groups.
  - This may not be the case
  - Not all hypotheses are created equal
    There may be significant prior evidence supporting (or refuting) H_A - this will be ignored when interpreting a *p*-value.
    - Any study with significant results must therefore be interpreted in the context of:
      - Biological plausibility of those results
      - The previous evidence on the topic
  - It is a common misconception that the *p*-value estimates the chance that the result is true
    This is not the case. The p-value measures *how inconsistent the observed results are with the null hypothesis*.

- A threshold of 0.05 is not always appropriate
  The cost of being wrong must be included when interpreting a p-value. If this is a true result, what are the potential benefits? If this is a false positive, what are the potential harms?

- Vulnerable to multiple comparisons
  Conducting repeated analyses will eventually find a 'significant' result. At an α of 0.05, we would expect 1/20 analyses to be

a false positive. Conducting 20 analyses would therefore generate one false positive result.

- Does not quantify effect size
  A significant *p*-value simply suggests a difference exists, it does not measure how big this difference is.
    - A result may be statistically significant but clinically unimportant, e.g. an antihypertensive medication causing a decrease in SBP by 2mmHg may be statistically significant, but clinically unimportant.
- Related to sample size *p*-values are affected by sample size:
    - A large effect size may be hidden by an insignificant *p*-value if sample size is small
    - Similarly, a tiny effect size may be detected (i.e. a significant *p*-value) if sample size is large
- Does not account for bias
  Like other statistical test, the *p*-value cannot account for bias or confounding.

References

1. Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. The American Statistician. 2016 vol: 70 (2) pp: 129-133.

Last updated 2019-07-18

Drug Approval and Development

> Describe the processes by which new drugs are approved for research and clinical use in Australia, and to outline the phases of human drug trials (Phase I-IV)

Drug Approval

The Therapeutic Goods Administration (TGA) approves medicine for both research and clinical use in Australia.

Research

Drug trials are approved for research purposes under two schemes:

1. Clinical Trials Exemption
   Drugs must be evaluated by an expert committee to evaluate all aspects of pharmacology, toxicology, mutagenicity, teratogenicity, organ dysfunction, and other side-effects.
2. Clinical Trials Notification
   A drug which has been approved in another nation with similarly stringent requirements (New Zealand, Netherlands, UK, Sweden, US) may be used in a trial with oversight by a local ethics committee.

Clinical Use

The TGA classifies medicines into:

- **Registered Medicines**
  Assessed by the TGA for quality, safety, and efficacy.
  - All prescription (high-risk) medicines. Assessed on:
    - **Quality**
      - Composition of drug substance
      - Batch consistency
      - Stability data
      - Sterility data (if applicable)
      - Impurities
    - **Non-clinical**
      - Pharmacology data
      - Toxicology data
    - **Clinical**
      - Efficacy: results of clinical trials
  - Most OTC (low-risk) medicines
  - Some complementary medicines
- **Listed Medicines**
  Assessed by the TGA for quality, safety, but not efficacy.
  - Some OTC medicines
  - Most complementary medicines

Phases of Drug Development

- **"Phase 0"**
  - Pre-clinical R&D

  - *In vitro* and animal testing
- **Phase I**
  - First administration in humans
  - Basic pharmacokinetic and toxicology data
  - 20 - 100 human subjects
- **Phase II**
  - Administration to select patient groups
  - Aim to establish dose-response curve
  - Evidence of efficacy
- **Phase III**
  - Full-scale evaluation of benefits, potential risks and costs analysis
  - 2000-3000 patients, usually treated in groups of several hundred for relatively short durations (3-6 months), regardless of the length of time the drug will be used in practice[3]
  - May not reveal uncommon or long-term risks
- **Phase IV**
  - Post-marketing surveillance

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Additives

> Describe the mechanisms of action and potential adverse effects of buffers, anti-oxidants, anti-microbial and solubilizing agents added to drugs

Additives are components of a drug preparation which do not exert the pharmacological effect.

Additives include:

- **Preservatives**
  - Benzyl alcohol
    - Antimicrobial when > 2%
    - Can be used as a solvent when > 5%
    - Toxic
- **Antioxidants**
  - Sulfites
    - Hypersensitivity
    - Neurotoxic if given intrathecally
- **Solvents**
  - Water
    Appropriate for dissolving polar molecules.
  - Non-aqueous solvents
    Used to dissolve non-polar molecules, or to produce more stable preparations of semi-polar molecules. Examples include:
    - Propylene glycol
      - Hypotension
      - Arrhythmia
        With rapid injection.
      - Pain on injection
      - Thrombophlebitis
    - Mannitol
      - Diuresis
    - Soybean oil
      - Pain on injection
      - Allergy
- **Emulsion**
  Formed when drops of a liquid are dispersed throughout another liquid in which it is immiscible. Emulsions are:
  - Unstable
    Emulsifiers are used to enhance stability.
  - Prone to contamination
    Due to the water component.
  - Prone to rancidity
    Due to the oil component.
- **Buffers**
  Maintain pH in a particular range in order to:
  - Maximise stability
    Preserve shelf life.
  - Maintain solubility

- Maximise preservative function

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Isomerism

> Describe isomerism and provide examples

Isomerism describes groups of compounds which have the same chemical formula but different chemical structures. Isomerism is relevant because different isomers may have different enzymatic and receptor affinities, altering their pharmacokinetic and pharmacodynamic properties.

Types of Isomerism

Isomers can be divided into:

- **Structural Isomers**
  Identical chemical formula but different arrangement of atoms. Structural isomerism is subdivided into:
  - **Static**
    Further subdivided into:
    - Chain isomer
      The carbon skeleton varies, but position of functional groups is static.
    - Position isomer
      The carbon skeleton is static, but the position of functional groups varies.
      - e.g. Isoflurane vs. enflurane
  - **Dynamic** (also known as tautomer)
    The molecule exists in a different molecular structures depending on the environment.
    - e.g. Midazolam has pH dependent imidazole ring opening. When the pH is less than 4 the ring remains open, maintaining water solubility. Midazolam is supplied at pH of 3.5, and so is water soluble on injection but (due to its pKa of 6.5) becomes 89% unionised at physiological pH therefore able to cross lipid membranes.

- **Stereoisomers**
  Atoms are connected in the same order in each isomer, but different orientation of functional groups. Stereoisomers are **not super-imposable**, meaning the different isomers can't be rotated so that they look the same. Stereoisomers are divided into:
  - **Geometric Isomers**
    Have a chemical structure (e.g. a carbon-carbon double-bond) prevents free rotation of groups, so different locations of chemical groups will create an isomer. Geometric isomers are known as **cis-** or **trans-** depending on whether the subgroups are on the same or opposite sides (respectively) of the chemical structure.
    - e.g. Atracurium
  - **Optical Isomers**
    Optical isomers are **chiral**. This means they have **no plane of symmetry**. Optical isomers:
    - Were initially named based on how they rotated under polarised light:
      (Note this is *different* from D- and L- molecules, where the D-isomer refers to the molecule synthesised from (+)glyceraldehyde).
      - **Dextrorotatory**
        (d- or (+) isomers) molecules rotate **clockwise** under polarised light.
      - **Levorotatory**
        (l- or (-) isomers) molecules rotate **counter-clockwise** under polarised light.
    - Unfortunately, different molecules were found to rotate in different directions depending on the temperature. Therefore, a different classification scheme (R/S) is also used:
      - Based on chemical structure
      - "Priority" is assigned to each atom in the structure
      - Highest priority is usually those with the highest molecular weight, but other rules exist for ambiguous or very

large molecules
    - The molecule is arranged in space such that the lowest priority atom is facing "away"
    - An arrow is then drawn from the highest priority to the lower priority atoms:
        - If this arrow travels **clockwise** it is the **R (Rectus)** isomer
        - If this arrow travels **counter-clockwise** it is the **S (Sinister)** isomer
- Optical isomers are divided into:
    - **Enantiomers**
      Possess one chiral centre.
        - e.g. levobupivacaine is less cardiotoxic than racemic bupivacaine.
    - **Diastereoisomers**
      Possess multiple chiral centres, and may have multiple stereoisomers. Since not all are mirror images, these are not *enantiomers*.
        - For a molecule with n chiral centres up to n^2 isomers are possible, though some of these may be duplicates.

Preparations

Drugs can be provided as:

- **Racemic solutions**
  A **racemic** solution is one which where the different enantiomers are present in equal proportions.
- **Enantiopure preparations**
  A drug produced with a single isomer, which may be **more efficacious** or **less toxic** (and definitely more expensive) than the racemic preparation.

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Modeling

> Explain the concept of pharmacokinetic modeling of single and multiple compartment models.

Pharmacokinetics describes what the body does to a drug. Pharmacokinetic models are mathematical concepts used to predict plasma concentrations of drugs at different time points.

Basic Pharmacokinetic Terms

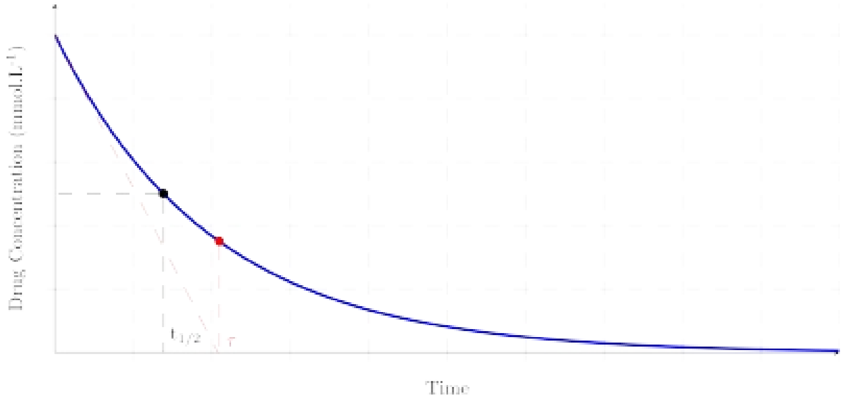
Key concepts in pharmacokinetics include:

- **Volume of distribution, V_D**
  The volume of distribution is defined as the **theoretical volume into which an amount of drug would be distribute to produce the observed plasma concentration**.
  - Units are $ml.kg^{-1}$
    - $Vd = \frac{Total\ bioavailable\ drug}{Plasma\ concentration}$
  - It is a way to describe what proportion of a drug is confined to plasma, and what proportion distributes to other tissues
  - It does not correspond to any particular volume, however a V_D of:
    - Less than $40ml.kg^{-1}$ indicates a drug is confined to plasma
    - Up to $200ml.kg^{-1}$ indicates a drug is confined to the ECF
    - Up to $600ml.kg^{-1}$ indicates a drug is dissolved into the TBW
    - Greater than $1L.kg^{-1}$ indicates a drug is highly protein bound or lipophilic
      Agents which cross the blood brain barrier typically have a V_D of $1\text{-}2L.kg^{-1}$.
  - Subtypes of the volume of distribution are used to describe drug distribution at different times or with different models
    - These include:
      - V_1
        Volume of central compartment.
      - V_Dss
        Volume of distribution at steady state.
      - V_Dpe
        Volume of distribution at peak effect.
    - Which volume to use depends on the pharmacological question
      - e.g. Intubating dose for opioid should use a volume between V_1 (very small) and V_Dss (very large) - V_Dpe is ideal as it will allow a target concentration to be selected for the time at which intubation will occur relative to drug administration

- **Half-life** ($t_{1/2}$)
  The time it takes for a process to be 50% complete. With respect to drug clearance, it is the time it takes for concentration (typically in plasma) to fall by 50%.
  - A process is considered to be complete after 4-5 half-lives
    Concentration will decrease by 50% after each half-life, so after 5 half-lives concentration will be 3.125% of its starting value.
    - This also applies to wash in - it will take ~4-5 elimination half-lives of a drug for a constant-rate infusion to reach its final concentration
  - Half-life is mathematically related to many other key pharmacokinetic terms:
    $t_{1/2} = 0.693 \times \tau = \frac{0.693}{k} = \frac{0.693 \times V_D}{Cl}$, where:
    - τ is the time constant

        - k is the rate constant for elimination
        - V_D is the volume of distribution
        - Cl is the clearance
    - Various types of half-life are described:
        - $t_{1/2}\alpha$ describes the rapidity of the distribution phase following drug administration
        - $t_{1/2}\beta$ describes the rapidity of the *elimination* phase occurring after drug distribution equilibrium
          This only evaluates clearance from plasma, and so is a composite of both excretion from the body (e.g. renal and hepatic clearance) and ongoing distribution to peripheral tissues.
            - The elimination half-life is generally not useful to predict drug offset, as this is affected by many factors
              However, it does set an **upper limit** on how long it will take plasma concentration to fall by 50%.

- **Time-constant** (τ)
  The time taken for a process to complete if it continued at its initial rate of change. Time constants are related to half-life, but are better suited when modeling change in exponential processes.
    - Time constants are discussed in more detail under respiratory time constants
    - Elimination will be virtually complete after three time constants
    - A time constant is the **inverse of the rate constant for elimination**, i.e. $\tau = \frac{1}{k}$
    - Illustration of the relationship between half-life and time constant:

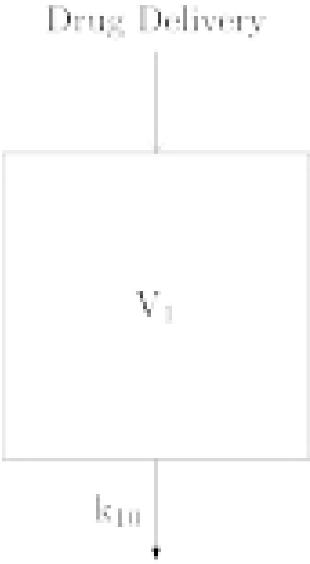


- **Clearance**
  The clearance is volume of plasma completely cleared of a drug per unit time.
    - In a one compartment model, this can be expressed as: $Cl = k.V_D$ in ml.min^{-1}.
        - As the **time constant** is the inverse of **k**, clearance can also be expressed as: $Cl = \frac{V_D}{\tau} = \frac{0.693 \times V_D}{t_{1/2}}$
    - Since k and V_D are constants, clearance is also a constant
    - Total clearance is a sum of the clearance of each individual clearance organ

- **Rate of elimination**
  Amount of drug removed by the body per unit time.
    - Rate of elimination is the product of the clearance and the current concentration:
      $Rate\ of\ Elimination = Cl \times C$, in mg.min^{-1}
    - This is not the rate constant for elimination

Compartmental Modeling

The simplest model imagines the body a single, well-stirred compartment.



In a one compartment model, the concentration of a drug (C) at time t is given by the equation:

$$C = C_0 e^{-kt}$$

Where:

- C_0 is the concentration at time 0
  As drug can only be eliminated from the compartment, this is also the peak concentration.
- **k** is the **rate constant for elimination**
  This is the fraction of the Vd from which the drug is removed per unit time. The rate constant **determines** the **slope** of the curve.
  - A high rate constant for elimination results in a steep curve and therefore a short time constant

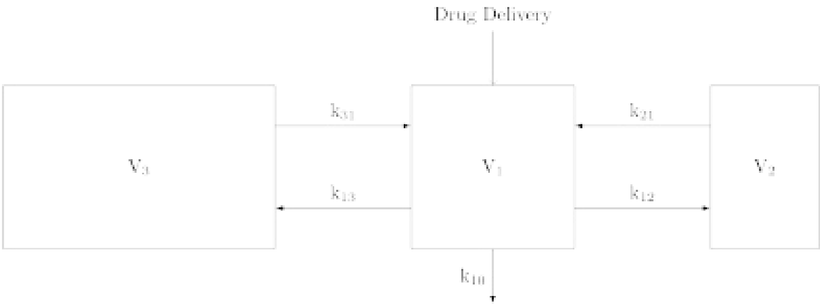
Steady state

At steady state, **input is equal to output**. Therefore concentration at steady state is:

- Proportional to the concentration of the infusion and infusion rate
- Inversely proportional to the clearance:
  $$Input = Output$$
  $$C_i . I = C_{ss} . Cl$$
  $$C_{ss} = \frac{C_i . I}{Cl}$$
  - Concentration of drug can therefore be determined by the amount infused and the clearance
- Note steady state requires peripheral compartments to be saturated, and so will only occur after an infusion of many hours

Multiple Compartment Models

- Models with multiple compartments have a better fit with experimental data than single compartment models
- Three-compartment models are typically used, as additional compartments typically offer no extra fidelity but are mathematically more complex
- A three-compartment model *can* be conceptualised as a plasma (or central) compartment, a well-perfused compartment, and a poorly-perfused compartment
  This doesn't mean that they *should* be thought of in this way - they are a mathematical technique used to calculate plasma concentration at a given time.



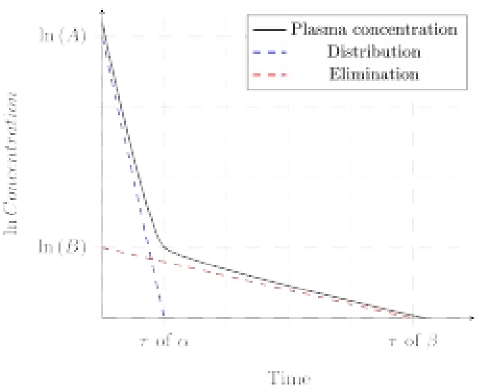
Plasma concentration in multi-compartment models is:

- Predicted through the net effect of several negative exponential equations x This is covered under two-compartment models below.
- Dependent on the effects of:
    - **Distribution**
      Distribution describes the movement of drug from the central compartment (V_1) to the peripheral compartment(s).
        - Rapid fall in plasma concentration of a drug after administration is generally due to distribution
          Distribution is an important method for drug offset in short-acting drugs.
    - **Redistribution**
      Redistribution refers to the movement of drug from the peripheral compartment(s) back into plasma.
        - Drugs which have a large V_D in a peripheral compartment tend to **distribute quickly** along this concentration gradient, and **redistribute slowly** back into plasma
        - Drugs which tend to **distribute slowly** tend to **redistribute quickly** once administration has ceased
    - **Excretion**
      Excretion is the removal of drug from the body.

Clearance in Two-Compartment Models

Removal of drug in two-compartment models is via:

- Distribution from the central to the peripheral compartment
- Elimination from the central compartment
- This produces a **bi-exponential** fall in plasma concentration
  Consists of two phases:
    - Phase α
      Distribution phase: A rapid decline in plasma concentration due to distribution to peripheral tissues.
    - Phase β
      Elimination phase: Slow decline in plasma concentration due to:
        - Elimination from the body
        - Redistribution into plasma



This curve is given by the equation $C = Ae^{-\alpha t} + Be^{-\beta t}$, where:

- C is the concentration of drug in plasma
- A is the y-intercept of the distribution exponent
  Used to calculate distribution half-life.
- B is the y-intercept of the elimination exponent
  Used to calculate elimination half-life.
- α is the rate constant for distribution

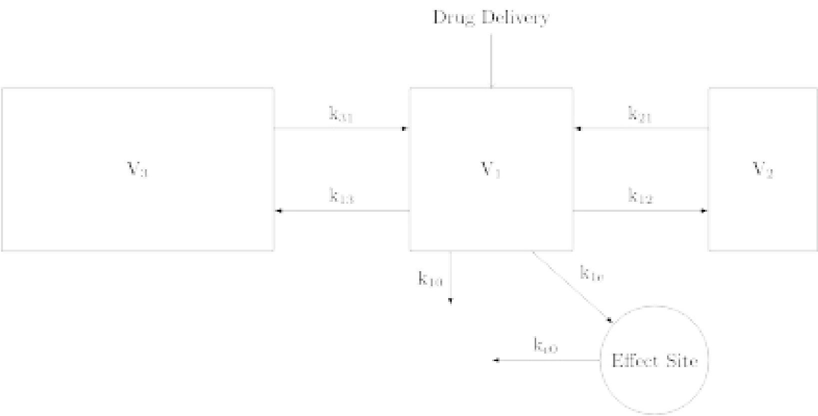
  The value of α is dependent on the ratio of rate constants for distribution and redistribution (i.e. $\frac{k_{12}}{k_{21}}$).
  - If distribution greatly exceeds redistribution, the gradient of α will be very steep and plasma concentration will fall rapidly after administration
- β is the rate constant for elimination

- Note that the distribution and elimination curves appear straight because the y-axis is log-transformed
  - If plasma concentration was plotted on the y-axis, then each of these curves would be a negative exponential (wash-out curve)

Effect Site

Pharmacokinetic models typically display the plasma concentration.

- Clinically however, we are interested in drug concentrations at the site of action (e.g. the brain)
  - Concentration at the effect site (also known as biophase) is given by **Ce**
    - This cannot be measured, and so is a calculated value
  - Effect site concentration be different from plasma concentration (**Cp**) prior to reaching steady state
    The delay between plasma and effect site concentrations is an example of hysteresis.
- The effect site can be modeled as an additional compartment in three-compartment models
  The effect site is modeled as a **compartment of negligible volume** contained **within V_1**, but does have rate constants
  - Effect site volume changes as V_1 changes
  - The k_{e1} is the rate constant for drug diffusion from plasma into the effect site
  - The $\mathbf{k_{e0}}$ is the rate constant for elimination of drug **from the effect site**
    This is a theoretical elimination pathway - drug is not usually metabolised at the effect site.
    - The $t_{1/2}$ke0 describes the effect-site equilibration time
      It describes how rapidly the effect site reaches equilibrium with plasma.
      - A large ke0 (rapid drug flow) gives a short $t_{1/2}$ke0
      - After one $t_{1/2}$ke0, 50% of the final effect site concentration will be reached provided plasma concentration remains constant
    - **A shorter $\mathbf{t_{1/2}}$ke0 indicates that that the effect site concentration will reach equilibrium with plasma more rapidly, and therefore a more rapid clinical effect following administration is seen**
    - Note that:
      - The $t_{1/2}$ke0 is not the time to peak effect
        - Neither is k_{e0}
      - For an infusion run at constant plasma concentration the peak effect will be seen at 3-5x the $t_{1/2}$ke0
      - The time to peak effect is a function of both plasma kinetics and the $t_{1/2}$ke0
        - e.g. adenosine has such a short elimination $t_{1/2}$ the effect site concentration will reach its peak rapidly regardless of the k_{e0}



Non-Compartmental Models

Compartment models are not appropriate for describing the behaviours of all drugs. Non-compartmental models are used when drug:

- Clearance is organ-independent
- Elimination does not occur solely from the central compartment

These models use **AUC**, which is calculated by measuring the plasma concentration of a drug at different time intervals, and **plotting the area under the curve (AUC)**. This can be used to:

- Determine **clearance**
  $Cl = \frac{Dose}{AUC}$
- Determine **Bioavailability**
  Difference between the AUC of the same dose of drug administered IV and via another route.

Footnotes

The formula for half-life can be derived from the equation for a wash-in exponential as follows:

- Wash in exponential is given by: $C = 1 - e^{-kt}$
- $y = 0.5$ can then be substituted and the equation solved for t as follows:

$$
\begin{aligned}
0.5 &= 1 - e^{-kt} \\
-0.5 &= e^{-kt} \\
\ln -0.5 &= -kt \\
\ln 2 &= kt \\
\frac{\ln 2}{k} &= t \\
\frac{0.693}{k} &= t
\end{aligned}
$$

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Absorption

> Describe absorption and factors that will influence it.

Absorption is dependent on the route of administration. Routes of administration are selected based on:

- Effect site of the drug
- Drug factors
    - Bioavailability
    - Available preparations
- Patient factors
    - Ability to take or absorb oral medications
    - Preference

Key Concepts

Bioavailability is the **proportion of drug given which reaches the systemic circulation unchanged**, compared to the IV form. It is affected by:

- Formulation
- Physicochemical Interactions
  Interactions with other drugs and food.
- Patient Factors
    - Malabsorption syndrome
    - Gastric stasis
- First-pass metabolism

First-pass (pre-systemic) **metabolism** is the extent to which drug concentration is reduced after its first passage through an organ, prior to reaching the systemic circulation. First pass metabolism is:

- Typically used when referring to passage of orally-administered drugs through the liver
  May also refer to metabolism by the:
    - Lungs
      First pass of intravenously injected drugs prior to entering the arterial side of the circulation, e.g. fentanyl.
    - Vascular endothelium
- Relevant in:
    - Understanding differences between PO and IV dosing
        - Alternative routes of administration for drugs with low PO bioavailability
    - Delivery of prodrugs via PO mechanisms
      Increases active drug concentration.
    - Understanding enzyme interactions
    - Understanding the effects of hepatic disease
        - Porto-systemic shunts decrease first pass metabolism
        - Altered bioavailability of drugs with high hepatic extraction ratios

Routes of administration

Intravenous

- Rapid Onset

- 100% bioavailability
  Some drugs may still undergo metabolism in the pulmonary circulation, such as fentanyl, lignocaine, propofol, and catecholamines.

Oral

- Absorption is through gut mucosa, through either:
  - Transport mechanisms
  - Unionised (lipid soluble)
    - Acidic drugs are absorbed more rapidly in the stomach
    - The small bowel absorbs both acid (despite being ionised) and alkaline drugs due to high surface area
- Lowest bioavailability of any route due to:
  - First-pass metabolism
  - Gut metabolism of drugs
  - Bacterial metabolism of drugs
- Drugs must be lipid soluble enough to cross cell-membranes and water soluble enough to cross interstitium

Factors affecting GIT Absorption

- Drug Factors
  - Molecular Weight
  - Concentration Gradient
  - Lipid Solubility
    - pH and pKa
  - Pharmaceutical Preparation
  - Physiochemical Interactions
    - Food
    - Other drugs

- Patient Factors
  - GIT blood flow
  - Surface Area
    - Small bowel has the largest surface area of any GIT organ
  - pH
  - Motility
  - Digestive Enzymes
  - GIT bacteria and subsequent metabolism
  - Disease
    - Critical Illness
    - Bowel Obstruction
    - Emesis/Diarrhoea

Epidural

- May be via bolus or infusion
- Onset determined by proportion of unionised drug available
  Lignocaine has a more rapid epidural onset than bupivacaine as it has a pKa of 7.9 (compared to 8.4) and therefore a greater unionised portion at physiologic pH.

- Additional factors include additives and intrinsic vasoactive properties of the delivered drug

Subarachnoid/Intrathecal

- Very small dosing
- Minimal systemic spread
- Extent of subarachnoid spread is dependent on volume and type of solution
- Appropriate positioning of the patient, with higher-specific gravity solutions, is required to avoid superior spread of the block
- Additional factors include additives and intrinsic vasoactive properties of the delivered drug

Inhalation

- Systemic absorption dependent on particle size
    - Large particles reach the bronchioles
    - < 1 micron diameter particles may reach the alveolus
- Rapid diffusion to circulation due to high surface area and no first-pass metabolism

Transdermal

- Systemic absorption dependent on:
    - Dose requirement
        - Large dose requirements cannot be effectively given transdermally
    - Fick Principle
        - Amount of drug given
        - Amount of drug in skin
            - Regional blood flow
                - Histamine release
        - Surface Area
        - Skin thickness
        - Lipid solubility
            - pH of skin and emulsion
            - pKa of drug
        - Molecular weight
    - Advantages
        - Convenient
        - Painless
        - No first pass metabolism
        - Steady plasma concentration once established
    - Disadvantages
        - Slow onset
        - Variable plasma concentration initially
        - Overdose and abuse potentials

Subcutaneous

- Absorption dependent on regional blood flow

Sublingual

- Rapid onset
- Bypass portal circulation (drains into SVC)

Rectal

- Variable absorption

- Distal rectal absorption bypasses portal circulation
- Proximal rectal absorption does not and may result in hepatic first pass metabolism
- Small surface area for absorption

Intramuscular

- Bioavailability close to 1
- Absorption dependent on regional blood flow
- Potential local complications:
  - Abscess
  - Haematoma

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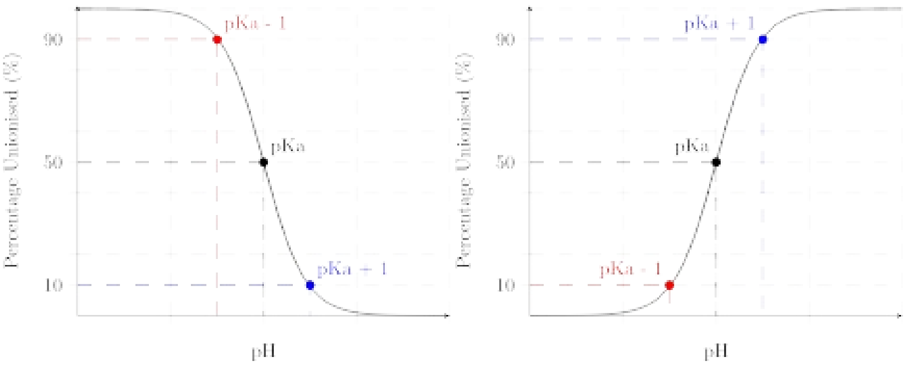
Distribution

> Describe factors influencing the distribution of drugs.

Drug distribution is dependent on many factors, all of which can be related to Fick's Law of Diffusion:

- **Concentration gradient**
- **Tissue mass**
- **Molecular Weight**
  Larger molecules are less able to cross cell membranes, and so a greater portion will remain in the compartment they are delivered to.
- **Lipid Solubility**
- **Ionisation**
  Ionised drugs are polar, and so are less lipid soluble.
  - Ionisation is a function of:
    - pKa
      The pKa is the pH at which a weak acid or weak base will be 50% ionised.
      - As solvent pH changes, the proportion of ionised vs. unionised drug will differ
      - How depends on whether the drug is an acid or base:
        - **B**ases are ionised **B**elow their pKa
        - **A**cids are ionised **A**bove their pKa
    - pH
      In combination with pKa, affects the ionised portion.
  - Unionised drugs:
    - Cross cell membranes more readily than the ionised form
    - Are typically hepatic metabolised
    - Are typically not renally eliminated
  - Ionised drugs:
    - Are typically renally excreted without undergoing metabolism
    - Are poorly lipid soluble and do not cross cell membranes readily
    - May be ion trapped
      This occurs when an unionised drug moves across a membrane and becomes ionised due to a change in pH. The now-insoluble drug is trapped in the new compartment. This is relevant in:
      - Placenta
        Foetal pH is lower than maternal pH, which can trap basic drugs (e.g. LA, opioids) in foetus.
        - This becomes more significant with a greater divergence of pH (e.g. placental insufficiency)
      - Renal elimination
        Urinary alkalinisation is used to accelerate elimination of acidic drugs, as they become ionised and trapped in urine.



- **Protein binding**
  Proteins and drugs may be bound together by weak bonds. These include ionic bonds, van der Waal's forces, and hydrogen bonds.
  - Drugs may bind to proteins in:
    - Plasma
      - **Albumin**
        Binds acid and neutral drugs.
        - High capacity
        - Two major binding sites (six total)
          - Site I (warfarin)
          - Site II (diazepam)
      - **α1-acid glycoprotein**
        Binds basic drugs.
        - Single binding site
        - Low capacity
          Typically results in lower total binding (compared to albumin) of alkaline drugs, despite its increased affinity.
      - Lipoprotein
        For lipid soluble drugs.
    - Tissue
    - Receptor
  - Protein binding is important as:
    - Only unbound drugs are able to:
      - Cross cell membranes
      - Interact with receptors
      - Undergo metabolism
        Reduced protein binding increases clearance of drugs with low **extraction ratios**.
      - Be filtered by the kidney
    - Highly tissue bound drugs:
      - Have a long duration of action
      - Have a high volume of distribution, prolonging their elimination
      - May build up in tissues, leading to adverse effects
        e.g. Corneal deposition, lung fibrosis.
  - Protein binding is affected by:
    - Affinity of drug for protein
      - Ionised drugs do not bind to protein
        pH.
      - Competition between drugs for binding sites
    - Amount of protein
      - Disease

        - Due to:
            - Hypoalbuminaemia
              Negative acute phase reactant.
            - Increased α1-acid glycoprotein
              Acute phase reactant.
        - Competition
          Source of pharmacokinetic interactions.
    - Protein binding *typically*:
        - Correlates with lipid solubility
        - Is important only when it is very high
        - Results in a decreased V_{DSS} when plasma binding is high
        - Results in an increased V_{DSS} when tissue binding is high
        - Is important in duration of action as it also relates to affinity for *tissue* proteins

- **Regional blood flow**
  Affects concentration gradients between blood and tissue, and is affected by cardiac output. Regions include:
    - Vessel Rich Group
        - Brain
        - Heart
        - Liver
        - Kidneys
    - Vessel Poor Group
        - Connective tissue
            - Bones
            - Ligament
            - Teeth
            - Hair
    - Muscle groups
    - Fat

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Last updated 2019-07-18

Metabolism

> Describe the mechanisms of drug clearance and metabolism.

Removal of drug from the body requires either:

- Metabolism of active drug to an inactive substance
  Typically by the liver, but other organs (kidney, lungs) also metabolise some substances.
- Excretion of active drug
  Often by the kidneys, but may also be in bile, or exhaled.
  - Removal of drugs from the body is achieved predominantly through renal excretion of water-soluble compounds
  - As many drugs are lipophilic, metabolism to water soluble compounds is required to clear drugs from the body

Clearance

Clearance describes the elimination of drug from the body. Clearance is:

- The **volume of plasma completely cleared of a drug per unit time**
  Measured in ml.min^{-1}.
  - Discussed further in modeling
- Does not include redistribution
- Is calculated from the area under the concentration time curve:
  $Cl = \frac{Dose}{AUC}$

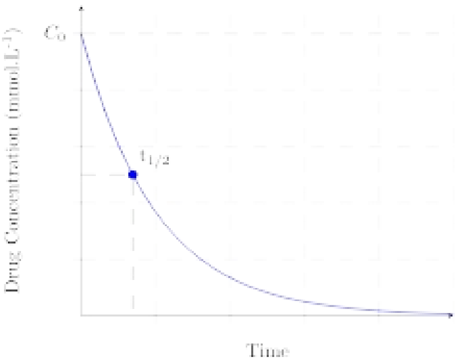
Total clearance is the sum of clearances from individual organs, e.g.:

- $Cl_{total} = Cl_{renal} + Cl_{liver} + Cl_{lung} + Cl_{organ\ independent} + Cl_{other}$, where:
  - , where:
    - $[U]$ is urine concentration in mmol.L^{-1}
      Function of glomerular filtration, reabsorption, and secretion.
    - V is the urine flow in ml.min^{-1}
    - $[P]$ is the plasma concentration in mmol.L^{-1}
  - , where:
    - HBF is the hepatic blood flow in ml.min^{-1}
    - ER is the extraction ratio

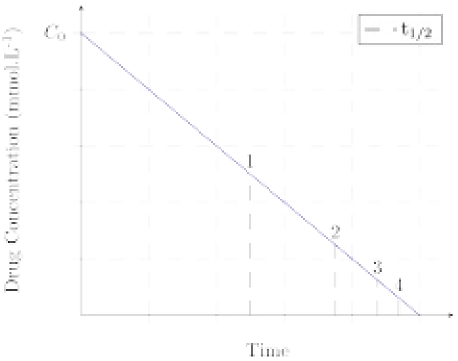
Kinetics

Drug clearance can follow either first order or zero-order kinetics:

- **First-order Kinetics**
  A constant **proportion** of the drug in the body is eliminated per unit time.
  - Most drugs are eliminated by first order kinetics, as the capacity of the elimination system exceeds the concentration of drug

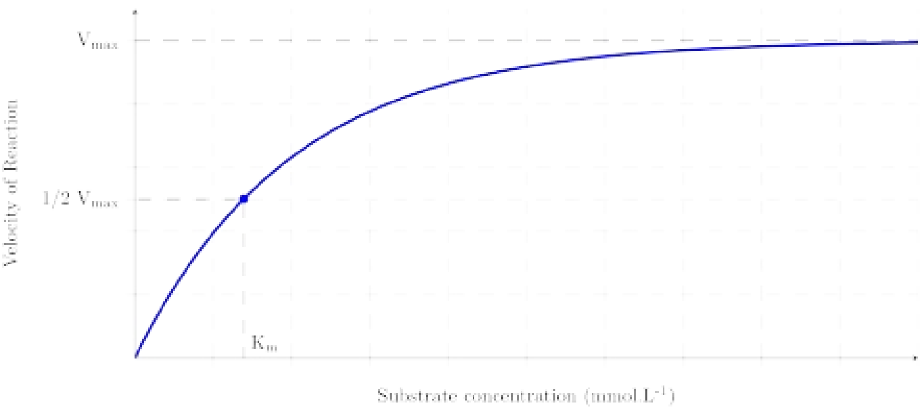


- **Zero-order kinetics**
  A **constant amount of drug** is eliminated per unit time, independent of how much drug is in the body.
  - Occurs when there is saturation of enzyme systems
    It is also known as **saturation kinetics** for this reason.
    - e.g. Phenytoin follows first order kinetics at lower doses, but zero-order kinetics at doses within the therapeutic range
      This is clinically relevant as the narrow therapeutic index means that toxic levels may occur rapidly with a small increase in dose.
    - e.g. Ethanol also follows zero-order kinetics within the "therapeutic range", as it is a very weak (doses are in grams) positive allosteric modulator of the $GABA_A$ receptor
  - Zero-order kinetics is concerning as:
    - Plasma concentrations will **rapidly increase** with only modest dose increase
    - There is essentially **no steady state**: if drug input exceeds output, plasma levels will continue to rise



Michaelis-Menten

The Michaelis-Menten equation describes the transition from first order to zero order kinetics as drug concentration increases:



- Metabolism increases proportionally with concentration as long as the concentration of drug leaving the organ of metabolism (e.g. in the hepatic vein) is less than half of the maximal concentration of drug that organ can metabolise

rd

  - This is ~1/3rd of the maximal rate of metabolism

Hepatic Metabolism

The principle organ of drug metabolism is the liver. Hepatic metabolism:

- Usually decreases the function of a drug, though:
  - **Prodrugs** have increased pharmacologically activity after liver metabolism
  - Some drugs have active or toxic metabolites
- Can be divided into **two phases**

Phase I

Phase one reactions:

- Occur in the **endoplasmic reticulum**
- Improve water solubility by exposing a functional chemical group
- Typically occur prior to phase II reactions for most drugs
- Include:
  - **Oxidation**

    Loss of electrons.
    - Main phase I reaction
    - CYP450 driven
  - **Reduction**

    Gain of electrons.
    - CYP450 driven
  - **Hydrolysis**

    Addition of a water molecule, which may result in two new compounds.
    - Esterase driven

      Therefore rapid, high capacity, organ-independent elimination.
      - Butylcholinesterase
      - Non-specific plasma cholinesterase
      - RBC esterase

CYP450 System

CYP450 enzymes are:

- A superfamily of enzymes vital in drug metabolism
- Named after the wavelength of light they absorb when:
  - Reduced
  - Combined with CO
- Located in:
  - Liver

    Endoplasmic reticulum of hepatocytes.
  - Lungs
  - Kidney
  - Gut
  - Brain
- Over 1000 enzymes, with ~50 functionally active
- Classified by the degree of shared amino-acid sequence into:
  - Families

CYP1, CYP2, CYP3...
- Subfamilies
  CYP1A, CYP1B...
- Isoforms
  CYP1A1, CYP1A2...

CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4	CYP3A5
Propofol	Propofol, Parecoxib, Warfarin	Diazepam, Omeprazole, Clopidogrel, Phenytoin	Codeine, Metoprolol, Flecainide	Volatile anaesthetic agents, paracetamol	Common benzodiazepines, Fentanyl, Alfentanil, Lignocaine, Vecuronium	Diazepam

Key CYP enzymes include:

- **CYP2E1**
  Metabolises volatiles and paracetamol.
- **CYP3A4**
  Responsible for 60% of metabolic activity.
- **CYP2D6**
  - Important because genetic polymorphism leads to significant inter-patient variability
    May result in significant over- or under-metabolism of drugs, and therefore significant inter-individual variability in response.
    - 5-10% of the population are poor metabolisers
    - 2-10% are intermediate metabolisers
    - 1-2% are ultra-rapid metabolisers
    - Bulk of the population (70-90%) are extensive metabolisers
  - Clinical effect will depend on the type of drug
    - Pro-drugs
      - Extensive/ultra-rapid metabolisers will convert more drug to the active form, and see a greater effect
        May lead to overdose.
      - Poor metabolisers will excrete more pro-drug prior to metabolism, and see a reduced clinical effect
    - Active drug
      - Extensive/ultra-rapid metabolisers will inactivate more drug, and see a reduced effect
      - Poor metabolisers will see a prolonged clinical effect
  - Clinical effect may be altered by enzyme interactions
    - e.g. Oxycodone use by an ultra-fast metaboliser, in combination with a CYP3A4 inhibitor (e.g. diltiazem) will result in a significant increase in the clinical effect of oxycodone
  - Drugs metabolised by CYP2D6 include:
    - Analgesics
      - Codeine (prodrug)
      - Oxycodone (metabolised to the significantly more potent oxymorphone)
      - Methadone
      - Tramadol (metabolised to form with greater MOP selectivity)
    - Psychiatric drugs
      - SSRIs
      - TCAs
      - Haloperidol
    - Cardiovascular drugs
      - Amiodarone
      - Flecainide
      - Mexiletine

Phase II

Phase II reactions:

- Involve conjugation with another compound, producing a highly polar metabolite
  This increases water solubility and therefore renal elimination.
- Typically occur in the hepatic endoplasmic reticulum
- Include:
  - **Glucuronidation**
    Addition of glucuronic acid.
  - **Sulfation**
    Addition of a sulfa group.
  - **Acetylation**
    Addition of an acetyl group.
    - Also occurs in the **lung** and **spleen**.
  - **Methylation**
    Addition of a methyl group.

Extraction Ratio

Extraction ratio is the proportion of a drug that is cleared from circulation during each pass through the organ, typically the liver:

$$ER = \frac{Drug\ Absorbed - Drug\ reaching\ systemic\ circulation}{Drug\ Absorbed}$$

Extraction ratio is dependent on:

- Blood flow
- Hepatocyte uptake
- Enzyme capacity
  Described by the **Michaelis Constant**: The concentration of a substrate which causes an enzyme to work at 50% of its maximum capacity.

Drugs can have either a high or low extraction ratio:

- **High extraction ratio**
  These drugs have a rapid uptake and high capacity, so elimination is **perfusion dependent**.
  - Free drug is rapidly removed from plasma, bound drug is released from plasma proteins and a concentration gradient is maintained
  - Metabolism of drugs with a high extraction ratio is:
    - **Independent of protein binding**
    - **Dependent on liver flow**
      Typically doubling liver blood flow will double hepatic clearance.
  - There is a **high variability** in plasma concentration between individuals due to the variation in liver blood flow
  - Drugs with high extraction ratios are generally independent of enzyme activity - decreasing enzyme activity from 99% to 95% has a minimal effect on hepatic clearance
    - The **key exception** is **first pass metabolism**, as the above change will result in a five-fold difference in dose reaching the systemic circulation
      Therefore drugs with a high extraction ratio have low PO bioavailability.

- **Low extraction ratio**
  Elimination is **capacity-dependent**.
  - Amount of free drug available for metabolism is greatly affected by the degree of protein binding
  - Metabolism is:
    - Largely **independent of flow**

Drugs have good PO bioavailability.
- **Dependent on hepatocyte function and protein binding**

Factors Affecting Hepatic Metabolism

Drug Factors	Patient Factors
Lipid solubility	Age
Ionisation	Obesity
Protein binding	Pregnancy
Enzyme competition	Genetics: Slow vs. fast acetylators
	Hepatic flow/Extraction Ratio
	Enzyme Inhibition/Induction
	Hepatic disease
	Smoking, ETOH

Organ Independent Metabolism

Mechanisms of organ independent metabolism include:

- **Hofmann Degradation**
  Spontaneous degradation or metabolism of substances occurring in plasma.
  - e.g. Cisatracurium undergoes Hofmann degradation
- **Plasma Esterases**
  Plasma esterases are non-microsomal enzymes which hydrolyse ester bonds. They:
  - Are typically synthesised in the liver and erythrocytes
  - Have a **high capacity**
    This, combined with the organ-independent elimination, means drugs metabolised by plasma esterases have a reliable offset.
  - e.g. Suxamethonium is hydrolysed by plasma esterases

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1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
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Elimination

> Describe the mechanisms of drug clearance and metabolism.

Drugs can be eliminated in:

- **Urine**
- **Bile**
- Sweat
- Breast milk
- Tears
- Exhaled gas

Renal Elimination

Drugs can be:

- Filtered at the glomerulus
  Filtered drugs are:
  - **Not protein bound**
    Only free drug present in filtered plasma will be excreted.
    - Concentration of filtered drug will be the same as in *unfiltered* plasma
    - **Highly protein bound** drugs are **poorly filtered**
      There is only a weak concentration gradient favouring dissociation from plasma proteins.
  - **Small**
    - Substances less than 7,000 Da are freely filtered
    - Substances greater than 70,000 Da are essentially impermeable
  - **Hydrophilic/lipophobic**
    Lipophilic drugs may be filtered at the glomerulus but will be freely reabsorbed during their passage down the tubule, such that only trivial amounts are eliminated in urine.
- Secreted in the tubules
  - **Active** process allows secretion **against concentration gradients**
  - Separate mechanisms for acidic and alkaline drugs
    - Saturatable process
      Saturation may occur of a basic transporter whilst still allowing excretion of acidic drugs, and vice versa.
- Reabsorbed in the tubules
  Passive diffusion down a concentration gradient.
  - Hydrophilic molecules can only be reabsorbed by a specialised transport mechanism
    - Acidic drugs will be become ionised in an alkaline urine (and vice versa), reducing their solubility
      This is the physiological justification for urinary alkalinisation.

Hepatic Elimination

Biliary elimination occurs for drugs unable to be filtered by the glomerulus. These are typically:

- Large
  Greater than 30,000 dalton.
- Lipid soluble

Enterohepatic recirculation

Drugs excreted in bile may:

- Be hydrolysed in the small bowel by bacteria and then reabsorbed
- Then pass through the portal circulation and get metabolised again
- This process may occur many times

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Bolus and Infusion Kinetics

> Explain the concepts of intravenous bolus and infusion kinetics. To describe the concepts of effect-site and context sensitive half time.

Continuous Infusions

Plasma concentrations of an IV infusion are influenced by:

- Distribution
- Metabolism
- Elimination

Onset of Continuous Rate Infusions

Without a loading dose, the concentration of drug infused at a constant increases in a **negative exponential fashion**:

- Plasma concentration initially rises rapidly
- **Distribution** into peripheral compartments is the **main method** for drugs to **leave plasma**
  This is because at the start of an infusion there is a large concentration gradient between plasma and peripheral compartments.
- Elimination becomes more important in prolonged infusions
  As peripheral compartments fill the concentration gradient between plasma and compartments falls, and redistribution becomes relatively less important.
- **Steady state** is achieved when **concentrations in compartments are equal**, **and input is equivalent to clearance**
  - Concentration at steady state is determined by the ratio of infusion rate to clearance: $C = \frac{Infusion\ Rate}{Clearance}$
    - Therefore, at steady state with drugs with 100% bioavailability:
      $Infusion\ Rate = C_{target} . Cl$
    - For drugs given by a route with less than 100% bioavailability:
      $Route\ Dosing\ Rate = \frac{Cld.C_{target}}{Bioavailability}$
    - If the dosing is given intermittently, then:
      $Dosing\ Rate = Dose. Dose\ Interval$
  - **Volume of distribution** at **steady state** is termed **$V_D$ss** and is the apparent volume into which a drug will disperse during a prolonged infusion, and is the sum of all compartment volumes in the model.

Continuous Rate Infusions with Bolus Dosing

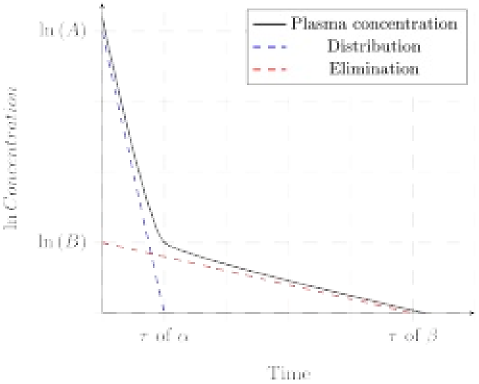
As seen, above starting an infusion at the rate required to maintain steady state is inefficient:

- For any desired plasma concentration, it will take three time constants (4-5 half-lives) for a continuous infusion to reach this concentration
  - If the half-life is long, then achieving a therapeutic level will take some time
- A bolus dose aimed to fill the V_D will allow steady-state to be reached immediately:
  $Loading\ dose = V_D . C_{target}$

Stopping an Infusion

For a bi-exponential model (i.e. only one peripheral compartment), decline in plasma concentration can be modeled by the equation $C = Ae^{-\alpha t} + Be^{-\beta t}$. In this model:

- α is the time-constant for redistribution
- β is the time-constant for **terminal elimination**
  (Provided the infusion has reached steady-state).
- Neither α or β correspond to any individual rate constant



Factors affecting rate of offset of an infusion can be classified into pharmacokinetic, pharmacodynamic, and other drug factors:

- **Pharmacokinetic factors**
  - Distribution
    - **V_D**
      High V_D will decrease clearance from central compartment. Factors affecting V_D include:
      - Ionisation
        Ion trapping can cause drug to be sequestered.
      - Protein binding
      - Lipid solubility
        Affected by body fat.
    - Speed of distribution
      - CO
        Affects organ blood flow.
    - **Redistribution**
      During an infusion, peripheral compartments become saturated with drug. When an infusion ceases, drug is redistributed central compartment.
      - This is related to **context-sensitive half time** (see below)
  - Metabolism
    - Route of clearance
      - Organ-dependent
        - Organ failures
        - Extraction ratio
        - Organ blood flow
      - Organ-independent
      - Saturatable kinetics
        Zero-order kinetics.
    - Presence of active metabolites
  - Elimination
    Route of excretion of active drug or active metabolites.

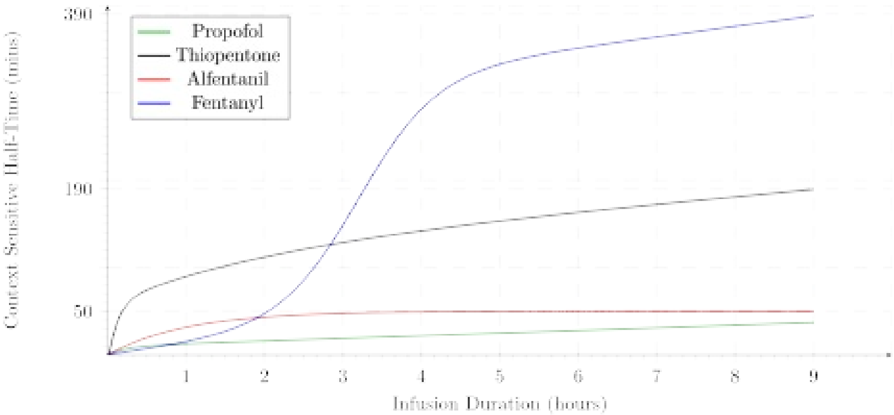
    - Organ failures
- **Pharmacodynamic Factors**
  - Age
    - Sensitivity
      Dose required for effect and dose required for recovery.
  - Organ failures
  - Pregnancy
- **Other drug factors**
  - Pharmacokinetic interactions
    - Enzyme inhibition/induction
  - Pharmacodynamic interaction
    - Drug tolerances
      - Tachyphylaxis
  - Drug action
    Drugs which alter gene or receptor expression, or bind irreversibly (e.g. clopidogrel) may show ongoing effects even after the drug has left the system.

Context-Sensitive Half-Time

Context-sensitive half time is:

- **Defined** as the time for plasma concentration to fall to half of its value at the time of stopping an infusion
- A method to describe the variability in plasma concentrations after ceasing an infusion
  The "**context**" is the **duration of infusion**.
- Used because terminal elimination half-life has little clinical utility for predicting drug offset
  Half-lives are often misleading when discussing drug infusions.
- Dependent on:
  - **Duration of infusion**
    During an infusion, drugs distribute out of plasma into tissues. When the infusion ceases, drug is cleared from plasma and tissue drug redistributes back into plasma.
    - The longer an infusion, the more drug has distributed out of tissues, and the longer the redistribution phase
    - The longest context-sensitive half time occurs when an infusion is at steady-state
  - **Redistribution**
    The maximal CSHT reached depends on the:
    - **$V_D$ss**
      Drugs with a larger $V_D$ss have a longer CSHT, as only a small proportion of the drug in the body will be in plasma and able to be cleared.
    - **Rate constant for elimination**
      Drugs with a smaller rate constant for elimination have a longer CSHT.

Drugs with longer context-sensitive half-times will wear off less predictably.



- Remifentanil has little redistribution and a small Vd, and so has a very short context-**in**sensitive half time
  It wears off reliably and quickly following cessation of infusion.

Context-Sensitive Decrement Time

- Describe the time it takes for a drug level to fall to a particular percentage of its starting value following cessation of an infusion
- They are used because the half-times do not describe **mono-exponential decay**
  i.e. The time taken for drug concentration to reach 25% of its starting value is not twice the context sensitive half-time.
- The context-sensitive half-time could also be described as the 50% context-sensitive decrement time

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References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
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Drug Monitoring

> Explain clinical drug monitoring with regard to peak and trough concentrations, minimum therapeutic concentration and toxicity

Drug monitoring:

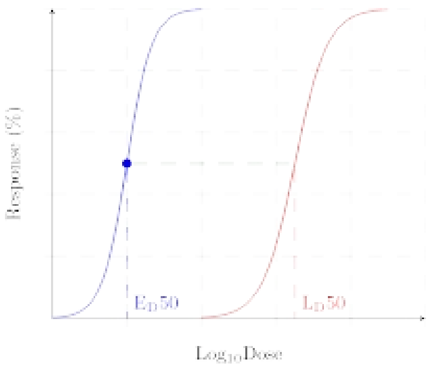
- Describes the individualisation of dosing by maintaining plasma drug levels within a target range
- Is important in adjusting dose to account for inter-patient variability in response
  Variability can be:
  - Pharmacokinetic
    Adjusting drug dose by monitoring plasma levels reduces pharmacokinetic variability.
  - Pharmacodynamic
    Drug dose is adjusted by evaluating the clinical effect.

Drug levels are measured to ensure the concentration is above the minimum therapeutic concentration but below toxic levels:

- **Minimum therapeutic concentration**
  The ED_{50}, i.e. the dose required to have an effect in 50% of the population.
  - Determines desired **trough levels**
- **Minimum toxic concentration**
  The LD_{50}, or the dose which is lethal in 50% of the population.
  - Determines the acceptable **peak levels**

From these levels two related terms are derived:

- Therapeutic range (also known as the therapeutic window)
  Difference between these levels.
- Therapeutic index
  Ratio between these levels, i.e.
  $$Therapeutic\ Index = \frac{LD_{50}}{ED_{50}}$$
  - A higher therapeutic index gives a greater margin for safety



Indications

Drugs are monitored in order to:

- Avoid **toxicity**
- Adjust dosing for **efficacy**
- **Monitor** compliance or determine failure of therapy

Drugs that typically require monitoring have a:

- Narrow target range
- Significant pharmacokinetic variability
- Relationship between the concentration in plasma and clinical effects
- Determined concentration range
- Validated monitoring assay

Drugs where the effect can be measured clinically (e.g. antihypertensives) tend to be adjusted based on observed effects. This is not possible when:

- The clinical response is the *absence* of a condition, e.g. antiepileptics
- The drug has a narrow therapeutic range

Drugs commonly monitored in the ICU setting include:

Drug	Therapeutic Range
Digoxin	0.8-2 microgram/L
Vancomycin	10-20 mg/L*
Tacrolimus	5-20 microgram/L
Serolimus	5-15 microgram/L
Phenytoin	10-20 mg/L
***Trough**	

Timing of samples

- Sampling for **toxicity** should occur at times of **peak concentration**
  - This requires accounting for absorption and distribution
    - e.g. Digoxin levels should be performed >6 hours following a dose to allow time for distribution to occur
  - If symptomatic, samples taken at this time may demonstrate toxic concentrations

- Sampling for **monitoring** should ideally occur at **steady state**
  - i.e. after 4-5 elimination half-lives
  - For drugs with very long half-lives (such as amiodarone), sampling tends to occur earlier to ensure toxic levels have not been reached, as steady state may take months to achieve

- For drugs with short half-lives, **trough levels** (i.e. pre-dose levels) should be taken
  This is the least variable point in the dosing interval.
- For drugs with long half lives, timing of sampling is less important

Interpretation

Interpretation of drug levels is dependent on:

- **Timing** of sample
- Duration of treatment at the current dose and **dosing** schedule
- Individual characteristics that may affect the **pharmacokinetics**
  - Age
  - Physiology
  - Comorbidities (hepatic, renal, cardiac)

    - Drug interactions
    - Genetics
    - Environmental
- **Protein binding**
    - Assays measure bound and unbound drug
      Only unbound drug is pharmacologically active.
    - If binding is changed by disease or displacement by other drug, the proportion of unbound drug may change and targeted levels may need to be adjusted accordingly
- **Active metabolites**
  Active metabolites are not measured but will contribute to the response.

References

1. Birkett DJ. Therapeutic drug monitoring. Aust Prescr 1997;20:9-11.
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Last updated 2018-09-21

Epidural and Intrathecal

> Describe the pharmacokinetics of drugs in the epidural and subarachnoid space

In both spaces, speed of onset is determined by **Fick's Law**.

Epidural Space

Factors important to epidural administration:

- Dose given
- Volume given
  Increased volume increases area of subarachnoid that the drug is in contact with, increasing rate of diffusion.
- Solubility
  Affected by:
  - pKa and pH
    Determines unionised portion available to cross into CSF.
  - Protein binding
    Determines free drug portion able to cross into CSF.
  - Lipid solubility
- CSF flow
  Alters concentration gradient between epidural and subarachnoid space.

Intrathecal

Factors important to intrathecal administration:

- Dose
  Much smaller doses required.
- Volume
  Affects extent of spread.
- Baricity
  Affects direction of spread:
  - Hyperbaric solutions will sink with gravity
    e.g. Heavy bupivacaine (0.5% bupivacaine with 8% dextrose)
  - Hypobaric solutions will rise against gravity

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. ANZCA February/April 2007
3. Factors influencing distribution of bupivacaine after epidural injection - Diaz Notes.

Last updated 2017-09-17

Total Intravenous Anaesthesia and Target-Controlled Infusion

> Describe the pharmacological principles of and sources of error with target controlled infusion

Total intravenous anaesthesia involves using IV agents alone to achieve hypnosis, analgesia, and muscle relaxation. TIVA:

- Advantages
  - Avoids adverse effects of anaesthetic agents
    - Nausea/vomiting
    - Pollution
    - Increased cerebral blood flow
- Disadvantages
  - Drug must be metabolised
  - Potential increased likelihood of awareness
    - Likely related to poor application of technique rather than the technique itself
      - Mostly related to disconnection of infusion without EEG monitoring
    - Variable plasma concentration

Target Controlled Infusion

TCI is the use of pharmacokinetic models (typically combined with microprocessor-controlled infusion pumps) to achieve a target concentration of drug in a particular body compartment.

TCI-systems:

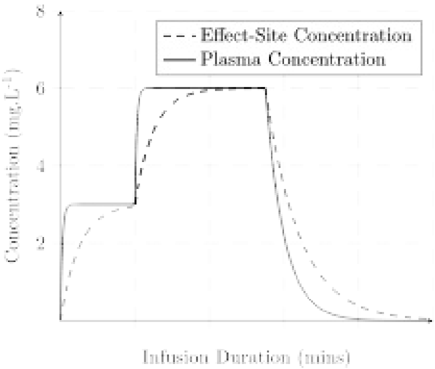
- Are **open-loop**
  Effects of drug are not measured (unlike with end-tidal gas monitoring), which introduces a vulnerability that can lead to awareness.
  - e.g. Compared to inhalational anaesthetics, where the loop is closed by using end-tidal drug monitoring
- Follows the BET (Bolus, Elimination, Transfer) principle:
  A loading dose is given to saturate the volume of distribution to achieve target concentration
  -
  - Infusion rate is then set to maintain a target plasma concentration:
    $$Maintenance\ Infusion\ Rate\ (MIR) = Cl \times C_P$$
  - Rate compensates for:
    - Drug elimination
    - Drug distribution (transfer)
  - Target C_P can be adjusted:
    - For a higher concentration:
      - A small bolus is given
      - Infusion rate is increased
    - For a lower concentration:
      - Infusion is paused until desired level is reached
      - Infusion rate restarts at a lower rate

Models can **target** either:

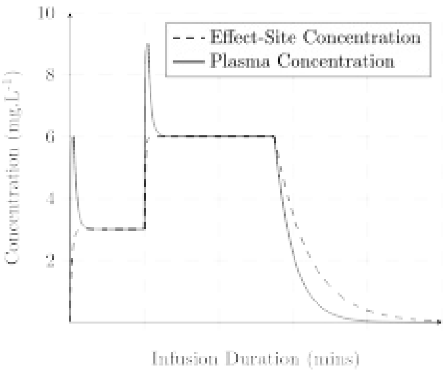
- **Plasma concentration**, C_P

Will not approximate C_E until stead state is reached. Therefore:

- Increase C_P during induction, so that C_E will rise more quickly
- should be adjusted to the level of the surgical stimulus



- **Effect-site** concentration, C_E
  Over-pressure occurs automatically, so there is no requirement to increase target during induction.



TCI Models for Propofol

The Bristol Model:

- First pharmacokinetic model
- Based on three-compartment model of health patients
- Assumes:
  - Premedication with temazepam
  - Fentanyl 3μg.kg^{-1} on induction
  - Inhaled N_2O
  - A target plasma concentration (C_P) of 3μg.ml^{-1}
- The model:
  - 1mg.kg^{-1} induction bolus
  - 10-8-6 maintenance:
    - 10mg.kg^{-1}.hr^{-1} for 10 minutes
    - 8mg.kg^{-1}.hr^{-1} for 10 minutes
    - 6mg.kg^{-1}.hr^{-1} thereafter

Marsh and Schnider Models:

- These are computer controlled models
- Both were derived on very small groups of patients (18 and 24 respectively)
- The models differ mostly in the first 10 minutes after induction, and progressively converge

The initial behaviour of the model is key in deciding which model to apply to any particular patient.

Property	Marsh	Schnider
Targets	Typically target plasma concentration, but can target effect site. Effect site targeting is usually done with the modified Marsh model, due to the large bolus dosing given by the standard Marsh model.	Typically effect site, but can target plasma concentration. Plasma targeting gives inconsistent results, as the fixed size of V_1 means any increase in desired plasma concentration results in the same size bolus being given, irrespective of patient parameters.
Required variables	TBW (overestimates induction (but not maintenance) in obese patients, consider using IBW), Age (but not used in calculation)	Age, height (to calculate lean body mass), TBW
Values	Variable compartment sizes but bigger V_1	Fixed V_1 (4.27L) and V_3, variable V_2 and K_{eo}
Other	The 'modified Marsh' model uses a k_{eo} of 1.2L.min^{-1} instead of 0.26L.min^{-1}, which decreases the C_P required to achieve the target C_e quickly. The modified Marsh is therefore preferable in patients at higher risk of overdose.	Limits BMI to < 42 for males and < 35 for females, to prevent absurd compartment sizes being calculated from the method used to calculate lean body mass
Overall	Faster induction due to larger V_1, which results in a larger loading dose	Reduced rate of adverse events. Overall less propofol used.

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Last updated 2019-07-20

Receptor theory

> To explain the concept of drug action with respect to: receptor theory

> To define and explain dose-effect relationships of drugs, including dose-response curves with reference to: therapeutic index, potency and efficacy, competitive and non-competitive antagonists, partial agonists, mixed agonist-antagonists and inverse agonists

> To explain the Law of Mass Action and describe affinity and dissociation constants

A **receptor** is a component of a cell which interacts with a drug and **initiates a sequence of events leading to an observed change in function**.

- Existence of receptors is inferred from the response of tissues to drugs, genome sequencing, and molecular biology.
- A drug binds to a receptor forming a **receptor-drug complex**, which initiates a cascade of events to exert a pharmacological effect.

Dissociation Constants

Interaction between a receptor and a drug is based upon the **law of mass action**, which states the rate of a chemical reaction is proportional to the masses of reacting substances. This can be expressed as:
$[Drug] + [Receptor] \Leftrightarrow [Drug - Receptor]$

The ratio of the **rate constant** for the forwards reaction (**$K_{association}$**) and the backwards reaction (**$K_{dissociation}$**) is the **dissociation constant**. This is the concentration of drug when 50% of receptors are occupied:

$$K_D = \frac{[D][R]}{[D-R]}$$

A **low K_D** value indicates that a lower concentration of drug is required to occupy 50% of the receptor, indicating that the drug has a **high affinity** for the receptor.

Physiological factors which affect the dissociation constant are determined by the **Arrhenius equation**:

$k = Ae^{\frac{-E_A}{RT}}$, where:

- A is a constant
- T is **temperature** in kelvin
- E_A is the activation energy required, which may be lowered by a **catalyst**
- R is the gas constant

Properties of Drugs

Key properties of drugs include:

- **Potency**
  The **amount** of drug required to have an effect.
  - Given by the (typically the E_D50)
  - This relates to **Bowman's principle**, which states that the **least potent** anaesthetic agents have the **quickest onset**
    This is because they are administered in **higher doses** (as they are less potent, more is required to get an effect), which

results in a **high concentration gradient** and a **rapid distribution** into tissues.

- **Efficacy**
  The **maximal** effect that a drug can generate.

- **Intrinsic activity**
  The size of effect a drug has when bound, which is graded from 0 to 1.
    - This is also known as **activity**

Drug-Receptor Interactions

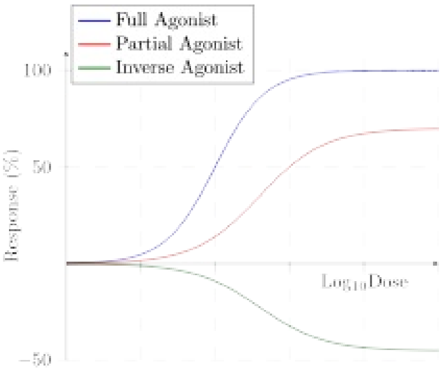
Drugs can be classified by the way they interact with receptors into:

- **Agonists**
    - Partial agonists
    - Inverse agonists
- **Antagonists**
    - Indirect antagonists
- **Allosteric Modulators**
- **Mixed Agonist-Antagonists**

Agonists

An agonist will generate a **maximal** response at the receptor site. An agonist has **high affinity** and an **activity of 1**. Agonists can be compared by:

- **Relative potency** implies that if two agonists are equally efficacious, a smaller dose of one is required to get an effect
- **Relative efficacy** implies that the maximal effect of one agonist is greater than the other



Partial agonist

A partial agonist generates a **submaximal** response at the receptor. A partial agonist has a **high affinity** and an **activity between 0 and 1**. A partial agonist can act as an effective antagonist in the presence of a full agonist, as it will prevent maximal binding at a receptor, even with a high agonist concentration.

Inverse agonist

A drug which has a **negative activity** (between 0 and -1) producing the **opposite** response (compared to the endogenous agonist) at receptor.

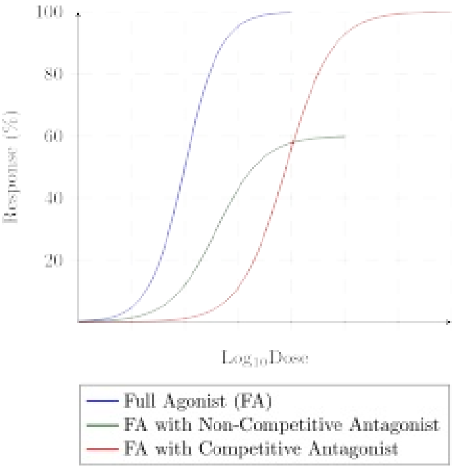
- Occurs due to loss of **constitutive activity** at that receptor

Antagonist

An antagonist produces no response at the receptor site, and prevents other ligands binding. Antagonists have **high affinity** and an **activity of 0**.

Antagonists with these properties are also known as **direct antagonists**, which can be either:

- **Competitive antagonists**
  Displace other ligands from a binding site. Competitive antagonists can be:
  - Reversible
    The effect can be overridden by increasing the dose of agonist.
  - Irreversible
    Drug cannot be overridden by increasing dose of agonist. Dose-response curve appears similar to that of the non-competitive antagonist.
- **Non-competitive antagonists**
  Create a conformational change in the receptor. They cannot be overridden by increasing the dose of agonist.



Indirect Antagonist

Indirect antagonists reduce the clinical effect of a drug, but do so via means other than receptor interaction. They include:

- **Chemical antagonists**
  Where the drug binds directly to another. Examples include protamine and heparin, and sugammadex and rocuronium.
- **Physiologic antagonists**
  A countering effect is produced by agonism of other pathways.

Allosteric Modulator

A drug which binds to an allosteric site on the receptor and produces conformational change that alters the affinity of the receptor for the endogenous agonist.

Allosteric modulators can be:

- Positive
  Increases affinity for endogenous agonist.
  - e.g. Benzodiazepines are positive allosteric modulators at the $GABA_A$ receptor
- Negative
  Decreases affinity for endogenous agonist.

Mixed Agonist-Antagonist

A drug which has different effects on different receptors.

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2. Encyclopaedia Britannica. Available at: https://www.britannica.com/science/law-of-mass-action
3. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

Last updated 2019-07-20

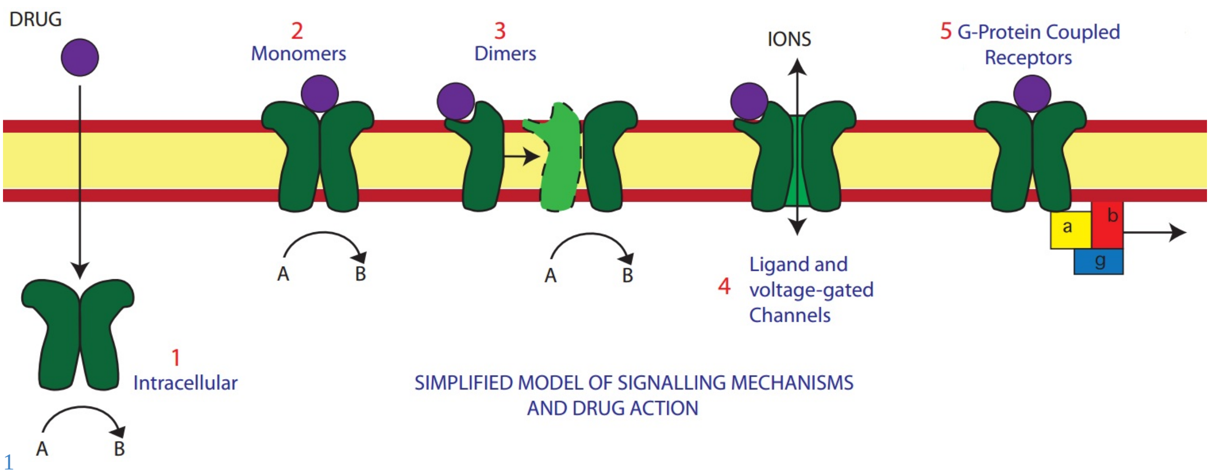
Receptor Types

> To explain the concept of drug action with respect to: receptor theory, enzyme interactions, and physicochemical interactions.

> To explain receptor activity with regard to: ionic fluxes, second messengers and G proteins, nucleic acid synthesis, evidence for the presence of receptors, regulation of receptor number and activity, structural relationships.

Receptor Types

A receptor is a protein, usually in the cellular membrane, to which a ligand may bind to generate a response.



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- **Intracellular** receptors
  May be either **cytoplasmic** or **intra-nuclear**.
  - Intranuclear receptors are activated by lipid soluble molecules (such as steroids and thyroxine) to alter DNA and RNA expression
    This results in an alteration of production of cellular proteins, so the effects tend to be slow acting.
- **Enzyme-linked** receptors
  Are activated by a ligand and cause enzymatic activity on the intracellular side. They can be either:
  - **Monomers**
  - **Dimers**
    Where two proteins join, or diamerise, on binding of a ligand.
- **Ion-channel** receptors (inotropic)
  Create a channel through the membrane that allows electrolytes to flow down their electrical and concentration gradients. They can be either:
  - **Ligand-gated** channels
    Undergo conformational change when a ligand is bound. There are three important families of ligand channels:
    - Pentameric family
      Consist of five membrane spanning subunits. Include:
      - Nicotinic ACh receptor
      - $GABA_A$ receptor
      - $5\text{-}HT_3$ receptor
    - Inotropic glutamate receptors Bind glutamate, a CNS excitatory neurotransmitter. Include:
      - NMDA receptor

      High Ca^{2+} permeability
    - Inotropic purinergic receptors
      Form cationic channels that are permeable to Ca^{2+}, Na^{+}, and K^{+}
      Activated by ATP

  - **Voltage-gated** channels
    Open when the **threshold voltage** is reached, facilitating electrical conduction in excitable tissues.
    - In their normal physiological state, voltage gated channels do not generally behave as receptors for a ligand, however some drugs (e.g. local anaesthetics) will bind to voltage gated channels to exert their effect
    - Have a common 4-subunit structure (each with 6 transmembrane segments) surrounding a central pore
      This pore is selective for the particular ion, which include:
      - Na^{+}
        - Located in myocytes and neurons
        - Important in generating and transmitting an action potential by permitting sodium influx into cells
        - Inhibited by local anaesthetics, anti-epileptics, and some anti-arrhythmics
      - Ca^{2+}
        Divided into subtypes, including:
        - L
          Muscular contraction.
        - T
          Cardiac pacemaker.
        - N/P/Q
          Neurotransmitter release.
        - K^{+}
          Located in myocytes and important in repolarisation following an action potential.
    - Undergo a conformational change when the threshold potential is reached
      This is sensed by the **S4 helix**, which acts to open and close the channel.
    - Exist in one of three functional states:
      - Resting
        Pore is closed.
      - Active
        Pore is open, and ions can pass.
      - Inactive
        Transient refractory period where the pore is open, but ions cannot pass. This creates the **absolute refractory period** of a cell.

- **G-protein** coupled (metabotropic) receptors:
  G-proteins are a group of heterotrimeric (containing three units; α, β, γ) proteins which bind GDP. When stimulated, the GDP is replaced by GTP and the α-GTP subunit dissociates to activate or inhibit an effector protein. The effect depends on the type of α-subunit:
  - G_s proteins
    Are **stimulatory**. These
    - Increase cAMP, leading to a biochemical effect
  - G_i proteins
    Are **inhibitory**. These:
    - Inhibit adenylyl cyclase, reducing cAMP
  - G_q proteins
    Have a variable effect, depending on the cell. These:
    - Activate phospholipase C
      This affects the production of:
      - Inositol triphosphate (IP_3)

2+

        Stimulates Ca^{2+} from the SR, affecting enzymatic function or causing membrane depolarisation.
    - Diacylglycerol (DAG)
      Activates protein kinase C, which has cell-specific effects.
- Activate intracellular **second messenger proteins** when stimulated
  Second messenger systems:
  - Result in both transmission and **amplification** of a stimulus, as a single activated receptor can activate multiple proteins and each activated protein may activate several other intermediate proteins
    - This is known as a G-protein **cascade**

Enzyme interaction

Drugs can interact with enzymes by **antagonism** or by being a **false substrate**.

Enzyme antagonism

Most drugs which interact with enzymes inhibit their activity. This results in:

- Increased concentration of enzymatic substrate
- Decreased concentration of the product of the reaction

Drugs can be competitive, non-competitive, or irreversible inhibitors of enzymatic activity. Examples include:

- Ramipril is a competitive inhibitor of angiotensin-converting enzyme.
- Aspirin is an irreversible inhibitor of cyclo-oxygenase.

False substrates

False substrates compete with the enzymatic binding site, and produce a product. Examples include:

- Methyldopa is a false substrate of the enzyme dopamine decarboxylase.

Physicochemical

Drugs whose mechanism of action is due to their physicochemical properties. Examples include:

- Mannitol reduces ICP because it increases tonicity of the extracellular compartment (and is unable to cross the BBB), drawing free water from the intracellular compartment as a consequence.
- Aluminium hydroxide reacts with stomach acid to form aluminium chloride and water, reducing stomach pH.

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1. Anderson, C. Pharmacodynamics 2. ICU Primary Prep.
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4. Catterall WA. Structure and Function of Voltage-Gated Ion Channels. Annu. Rev. Biochem. 1995. 64:493-531.

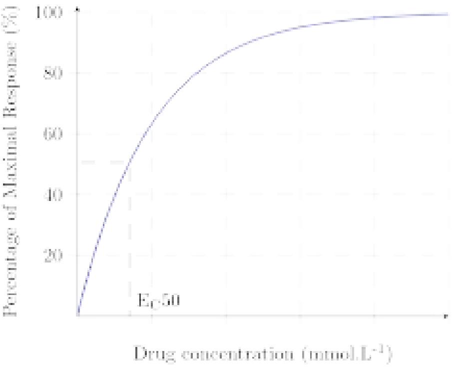
Last updated 2019-07-18

Dose-Response Curves

> To define and explain dose-effect relationships of drugs, including dose-response curves with reference to: graded and quantal response.

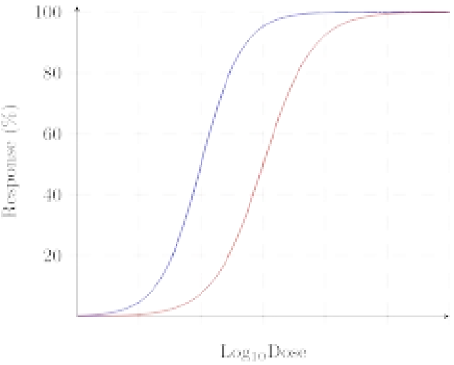
Standard Dose-Response Curves

A dose-response curve is a graph of concentration against the fraction of receptors occupied by a drug.



Log-Dose Response Curves

It is difficult to compare drugs using standard dose-response curves. Therefore, dose is commonly log-transformed to produce a log-dose response curve.



This curve:

- Compares log-dose versus clinical effect
- Demonstrates that the blue drug has greater **potency** than the red drug, though both are full agonists

Responses can be either **graded** or **quantal**:

- **Graded responses** demonstrate a **continuous increase** in effect with dose
  - E.g. Blood pressure and noradrenaline dose
- **Quantal responses** demonstrate a response once a certain proportion of receptors are occupied
  Examples include:
  - ED_{95}
    Median dose of neuromuscular blocker required to produce a 95% loss of twitch height.
  - MAC
    Mean alveolar concentration of agent required to prevent movement in response to a surgical stimulus.

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Last updated 2017-10-04

Mechanisms of Action

Drugs can act in four ways:

- **Receptors**
    - GPCR
    - Intracellular
        - Cytoplasmic
        - Intranuclear

          e.g. Steroids, which alter RNA expression.

- **Ion Channels**
    - Blockade
    - Allosteric modulation

- **Enzyme interaction**

  An enzyme is a biological catalyst, increasing the speed of reaction. Enzyme interaction can be:
    - Irreversible inhibition
        - e.g. Aspirin, which irreversibly inhibits platelet thromboxane production.
    - Reversible inhibition
    - Competitive antagonism
        - e.g. ACE-I.
    - Non-competitive antagonism

- **Physicochemical**
    - Osmotic
        - e.g. mannitol.
    - Acid-base
        - e.g. antacids.
    - Chelation
    - Redox reactions

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

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Adverse effects

> Classify and describe adverse drug effects.

An **adverse effect** is:

- A noxious or unintended effect associated with administration of a drug at the **normal dose**
  - i.e., not an overdose
  - Occur:
    - Mainly in young and middle-aged individuals
    - Twice as common in women
    - May be exacerbated by asthma and pregnancy.
- Distinct from an **adverse event**, which is an untoward occurrence during treatment that does not necessarily have a causal relationship to drug administration

Adverse effects can be classified by mechanism as follows:

Type A Adverse Reactions

These are related to the pharmacological action of the drug. They are:

- Common
- Related to dose (dose-response relationship)
- Temporally associated with drug administration
- Reproducible
- Pharmacologically predictable based on understanding of the drug in question
  - e.g hypokalaemia secondary to diuretic use

They typically result in:

- Organ-selective injury
- More pronounced with long-term use and in risk groups:
  - Extremes of age
  - Pregnancy
  - Renal failure
- High morbidity but low mortality
  Treatment is to decrease dose.

Type B Adverse Reactions

These are patient-specific or idiosyncratic reactions. They are:

- Rare
  Potentially genetic, but poorly understood.
- Independent of dose
  - Occur with low doses
  - Do not have a dose-response relationship
- Not pharmacologically predictable
  Important causes include:
  - Acetylator status
  - CYP450 variants

    - Receptor abnormalities
    - Enzyme alterations/deficiencies
        - e.g. Suxamethonium apnoea
- Not necessarily reproducible

They typically result in:

- Immuno-allergic reactions
- Pseudo-allergy
- Idiosyncratic reaction
- Low morbidity but high mortality
    - e.g. Stevens-Johnson Syndrome or anaphylaxis following penicillin administration

Treatment is to cease the medication.

Type C Adverse Reactions

These are 'statistical effects' associated with monitoring. They are:

- Typically an increased frequency of background disease that is detected due to increased screening
- Atypical for a drug reaction and not pharmacological predictable
- No identifiable temporal relationship
- Not reproducible

References

1. RHB Meyboom, M Lindquist, ACG Egberts. An ABC of Drug-Related Problems. Drug Safety 2000;22:415-23.
2. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. BMJ. 1998 Apr 25;316(7140):1295-8. Open Access Review.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients—a meta-analysis of prospective studies. JAMA 1998;279: 1200-5.

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Drug Interactions

> Classify and describe mechanisms of drug interaction.

Drug interactions occur "when the action of one drug modifies that of another".

Mechanisms of Drug Interaction

Drug interactions are best classified into **three** categories:

- **Physicochemical**
- **Pharmacokinetic**
- **Pharmacodynamic**

Physicochemical

Physicochemical interactions occur because of an incompatibility between chemical structures.

- e.g. Thiopentone and suxamethonium precipitate out of solution if prepared together or delivered together in the same line

Pharmacokinetic

Pharmacokinetic interactions can be sub-classified into those affecting absorption, distribution, metabolism, or elimination.

Absorption

For oral medications, absorption may be affected by drugs which alter:

- Gastric pH
- Gastric emptying time

> Metoclopramide resolves gastric stasis and improves absorption of orally administered drugs

Distribution

Distribution may be affected by:

- Competition for plasma protein binding
  Loss of albumin and α1-acid glycoprotein
- Medications which alter cardiac output
- Displacement from tissue binding sites This typically occurs due to alteration of metabolic capacity of one drug by the other.
- Chelation of drug from tissues
  Chelating agents bind toxic elements and prevent tissue damage

> Phenytoin is usually highly (90%) protein bound. A reduction in protein binding to 80% will double the free phenytoin level. For drugs with first-order kinetics, metabolism will increase proportionally however phenytoin rapidly saturates the enzyme system, leading to zero-order kinetics and a high plasma level.

> β-blockers reduce cardiac output and will prolong the time to fasciculation of suxamethonium.

Metabolism

Metabolism may be affected by changes to the CYP450 enzymes:

- Enzyme induction
  - Barbiturates
  - Phenytoin
  - Carbamazepine
- Enzyme inhibition
  - Amiodarone
    Amiodarone inhibits metabolism of S-warfarin by CYP2C9, enhancing it's effect.
  - Diltiazem
  - Verapamil
  - Ciprofloxacin
  - Macrolides
  - Metronidazole
  - Grapefruit juice

Elimination

Renal elimination can be affected by:

- Changes in urinary pH
- Competition for active tubular transport mechanisms

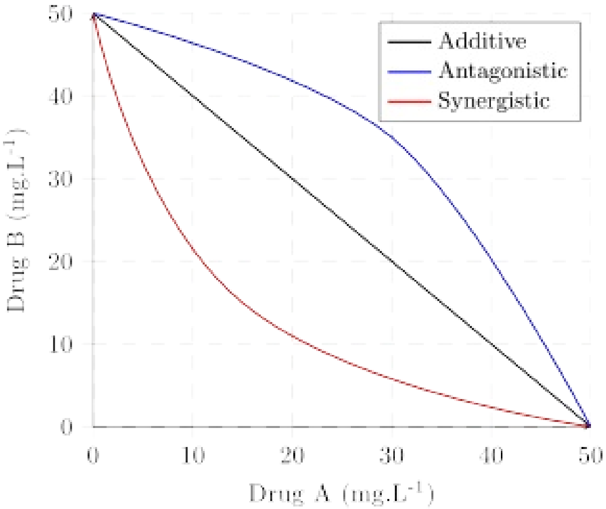
> Sodium bicarbonate increases urinary pH and enhances excretion of weak acids such as aspirin.

Pharmacodynamic

Pharmacodynamic interactions can be **direct**, due to interaction on the same receptor system; or a **indirect**, when they act on different receptor system. These interactions can be classified as either:

- **Additive**
  When the effects summate.
  - e.g. Administering midazolam with propofol reduces the amount of propofol required to generate an effect.
- **Antagonistic**
  When the effects oppose each other.
  - e.g. Neostigmine indirectly antagonises the effect of NDMRs by increasing the level of ACh at the NMJ.
- **Synergistic**
  When the combined effect is greater than would be expected from summation alone.
  - e.g. Co-administration of remifentanil and propofol has a synergistic effect in maintenance of anaesthesia.

These three interactions can be graphically demonstrated using an **isobologram**, which draws a **line of equal activity** versus **concentration** of two drugs.



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Last updated 2019-07-18

Alterations to Drug Response

> Define tachyphylaxis, tolerance, addiction, dependence and idiosyncrasy

There are four mechanisms which result in variable response to drug:

- Alteration in drug that reaches the receptor
  This is typically due to pharmacokinetic factors.
- Relative difference in presence of exogenous and endogenous ligands
  Antagonists will have a greater effect in the presence of high endogenous ligand concentration.
- Variation in receptor function and number
  Up-regulation and down-regulation of receptors may occur as a consequence of prolonged stimulus.
- Alteration in function distal to the receptor

Key Terms

- **Tachyphylaxis** is the **rapid decrease in response** to repeated dosing over a **short time period**, usually due to depletion of transmitter

- **Desensitisation** is the **loss in response** over a **long time period**, usually due to change in receptor morphology or loss in receptor numbers

- **Withdrawal** is a pathological response when a drug is ceased

  - During administration receptors may be:
    - **Up-regulated** in the continued presence of an antagonist
    - **Down-regulated** in the continued presence of an agonist
  - Loss of receptor numbers may precipitate withdrawal when the agonist or antagonist is ceased
- **Addiction** is a behavioural pattern characterised by compulsive use and fixation on acquiring and using a drug

- **Idiosyncrasy** is an individual patient response to a drug
  Typically mediated by a reactive metabolite rather than the drug itself.

Tolerance

Tolerance is the requirement for a **larger dose** to achieve the **same effect**, due to altered sensitivity of the receptors to the stimulant. Mechanisms can be classified into:

- **Pharmacokinetic**
  - **Altered drug metabolism**
    Metabolism may be **increased or decreased**:
    - Enzymatic induction and increased drug metabolism
      Increased hepatic enzyme pathway capacity increases metabolism and lowers plasma concentration.
    - Decreased metabolism
      Decreased metabolism of a prodrug can result in a reduced effect.

- **Pharmacodynamic**
  - **Change in receptor morphology**
    Can occur with ion-channel receptors and GPCRs:
    - Ion-channel receptors bind the ligand but do not open the channel
    - GPCR become 'uncoupled' - phosphorylation of the receptor makes it unable to activate second messenger cascade, though it can still bind the ligand.

    - **Receptor down-regulation**
      Prolonged exposure to agonists causes transmembrane (typically hormone) receptors to become **internalised**. This occurs more slowly than uncoupling.
    - **Receptor up-regulation**
      Prolonged exposure to antagonists causes an up-regulation of receptor.
        - Can lead to rebound effects when a drug is ceased (e.g. hypertension with cessation of clonidine)
    - **Exhaustion of mediators**
      Similar to tachyphylaxis - depletion of a mediating substance decreases the effect.
    - **Physiological adaptation**
      Actions of a drug may be countered by a compensatory homeostatic response.
    - **Active removal of the drug from the cell**

Alterations in Drug Response: Patient Factors

Pharmacokinetics and pharmacodynamics are affected in pregnancy and at extremes of age.

Pregnancy

- **Absorption**
    - Decreased gastric emptying
    - Nausea and vomiting
    - Increased cardiac output
        - Increases IM and SC absorption
    - Volatiles:
        - Increased onset due to increased MV and reduced FRC
        - Decreased onset due to increased CO

- **Distribution**
    - Increased V_D due to:
        - Increased TBW
        - Increased plasma volume
        - Increased fat mass
    - Decreased albumin and α_1-glycoprotein

- **Metabolism**
    - No change to HBF
    - Progesterone induces enzymes
    - Oestrogen competes for enzymes
    - Decreased plasma cholinesterase activity

- **Elimination**
    - Increased RBF
    - Increased GFR

- **Pharmacodynamic**
    - Decreased MAC
    - Increased LA sensitivity due to decreased α_1-glycoprotein

Foetus

Drugs that cross the placenta can be teratogenic to the foetus, besides exerting their usual pharmacological effects.

Pharmacokinetic factors predominantly **affect placental transfer**, and include:

- **Lipid solubility**
  Lipid soluble drugs diffuse more rapidly.
- **Molecular size**
  Drugs with a molecular weight >1000 dalton cross the placenta slowly.
- **Protein binding**
- **Placental transporters**
  Some medications are actively removed from foetal circulation.
- **Placental metabolism**
  The placenta can metabolise some medications, although in some cases results in toxic metabolites.

Maternal **pharmacodynamic** factors predominantly affect the uterus and breast, but **major organ systems** are **not significantly affected**.

Drugs that cross the placenta can have dramatic effects in the foetus. These include:

- **Teratogenesis**
  A drug which adversely affects foetal development causing a permanent abnormality. Multifactorial mechanisms that are not well understood.

Neonates

At < 1 year of age, pharmacokinetics are significantly altered:

- **Absorption**
  - Delayed gastric emptying, increasing absorption of drugs metabolised in the stomach
  - Decreased secretion of pancreatic enzymes and bile salts impairs absorption of lipid soluble medications
  - Smaller muscle mass and higher relative muscle blood flow increases IM onset
  - Increased V_A:FRC ratio increases onset of volatiles
- **Distribution**
  - TBW is 70-75% (compared to 50-60% for an adult), and extracellular water is 40% (compared to 20%), which typically **increases V_D**
  - Preterm infants have reduced body fat
  - Greater proportion of cardiac output goes to head, increasing onset of centrally acting (e.g. anaesthetic) drugs
  - Decreased albumin and α_1-glycoprotein
  - Immature BBB increases uptake of partially ionised drugs
- **Metabolism**
  - Enzymatic capacity of all pathways is reduced, which prolongs elimination half-lives and reduces clearance.
    - Hepatically metabolised drugs must be dose adjusted accordingly
      - The glucuronide pathway may not mature until age 4
- **Excretion**
  - **GFR is proportionally lower** and dose not reach adult equivalence until 6-12 months
    - GFR is **further reduced** in **pre-term** infants
    - GFR is increased in **1-3 year** olds
- **Pharmacodynamic**
  - Smaller ACh reserves increase sensitivity to NMBs
  - Increased MAC but more rapid onset
  - NSAIDs cause closures of ductus arteriosus

Geriatric

Though there is a linear decrease in functional capacity of major systems beginning at 45, alterations are predominantly a consequence of polypharmacy and drug interactions.

- **Absorption**
  - Laxatives and prokinetic increase gastric emptying and reduce absorption of oral agents
- **Distribution**
  - There is a proportional increase in fat
  - There is a proportional decrease in:
    - Lean body mass
    - Total body water
    - Albumin
- **Metabolism**
  - ↓ Hepatic blood flow
  - ↓ Enzymatic activity
    Phase I > Phase II.
- **Elimination**
  - Loss of nephron number with age reduces renal clearance
- **Pharmacodynamic**
  - Increased sensitivity to sedatives, opioids, and hypnotics
  - Decreased sensitivity to β-agonists and antagonists
  - Decreased MAC
  - Polypharmacy increases potential for drug interactions

Alterations in Drug Response: Disease Factors

Cardiac Disease

- Absorption
  - Decreased cardiac output decreases PO absorption due to decreased gradient
- Distribution
  - Decreased CO prolongs arm-brain circulation time
  - Increased α_1-glycoprotein increasing binding of basic drugs
  - Decreased V_D
- Metabolism
  - **Low-cardiac** output states reduce hepatic flow and will **reduce** metabolism of drugs with a **high extraction ratio**
  - **High-output** states have the opposite effect
- Elimination
  - Decreased renal blood flow

Hepatic Disease

- Absorption
  - Porto-caval shunting
    Decreased first pass metabolism.
- Distribution
  - Impaired synthetic function reduces plasma proteins and increases unbound fraction
  - Increased V_D due to fluid retention

    - Metabolic acidosis changes ionised fraction

- Metabolism
    - Impaired phase I and II reactions
    - Reduced plasma esterase levels

- Elimination
    - Reduced biliary excretion

- Pharmacodynamics
    - Hepatic encephalopathy increases sensitivity to sedatives and hypnotics

Renal Disease

- Absorption
    - Uraemia prolongs gastric emptying

- Distribution
    - Increased V_D due to fluid retention
    - Metabolic acidosis adjusts ionised fraction

- Metabolism
    - Buildup of toxic metabolites may inhibit drug transporters
    - Uraemic toxins inhibit enzymes and drug transporters

- Elimination
    - Reduced clearance of active metabolites/active drug cleared renally

Obesity

- Absorption:
    - Delayed gastric emptying
    - Decreased subcutaneous blood flow
    - Practical difficulty with IM administration

- Distribution:
    - Increased V_D of lipid soluble drugs
        - Dosing of lipid-soluble drugs by actual body weight
        - Dosing of water-soluble drugs by lean body weight
    - Increased CO
    - Increased α_1-glycoprotein
    - Increased blood volume
    - Greater lipid binding to plasma proteins, increasing free drug fractions

- Metabolism:
    - Increased plasma and tissue esterase levels
    - Normal or increased hepatic enzymes

- Elimination
    - Increased renal clearance due to increased CO

Non-Specific Alterations to Drug Response

- **Absorption**:

    - Site of administration

Drugs given centrally will act faster than those given into peripheral veins.

- Rate of administration
  Faster rate of administration will increase rate of onset.

- **Pharmacodynamic**
  - Drug tolerance Increase requirement of drug.
    - e.g. induction anaesthetic agents in patients tolerant to CNS depressants.
      - Drug interaction
        May be:
      - Synergistic
      - Additive
      - Antagonistic

References

1. Anderson C. Variability in Drug Response 1. ICU Primary Prep.
2. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. Sixth Edition. Churchill Livingstone.
3. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.
4. CICM Examiner Report: Sep/Nov 2012
5. Alfred Anaesthetic Department Primary Exam Tutorial Series

Last updated 2019-07-18

Pharmacogenetics

> Outline genetic variability.

> Explain the mechanisms and significance of pharmacogenetic disorders (eg malignant hyperpyrexia, porphyria, atypical cholinesterase and disturbance of cytochrome function).

Genetic polymorphism occurs when several functionally distinct genes exist within a population. Genetic polymorphism is:

- Common
- Important in determining an individuals susceptibility to adverse drug reactions
- A goal of **personalised medicine**
  Aims to adjust drug therapies for interpatient variability.

Pharmacogenetic disorders

Pseudocholinesterase

A condition where plasma cholinesterase is unable to breakdown suxamethonium, prolonging its duration of action. This disease:

- May be congenital or acquired
    - Congenital is autosomal recessive
      Has four alleles
        - Usual
        - Atypical (dibucaine-resistant)
        - Silent (absent)
        - Fluoride-resistance
    - Acquired is due to a loss of plasma cholinesterase
        - Pregnancy
        - Organ failure
            - Hepatic
            - Renal
            - Cardiac
        - Malnutrition
        - Hyperthyroidism
        - Burns
        - Malignancy
        - Drugs
            - OCP
            - Ketamine
            - Lignocaine and ester local anaesthetics
            - Metoclopramide
            - Lithium
- Has been traditionally measured using the **dibucaine number**
  Dibucaine is:
    - An amide local anaesthetic which **inhibits plasma cholinesterase**
      Different forms are inhibited to different extents, with greater inhibition indicating a less severe mutation.
        - Percentage inhibition correlates with different genotypes, e.g.:
            - Normal (Eu:Eu) has a dibucaine number of 80 (80% inhibited)

        - Dibucaine resistant (Ea:Ea) has a dibucaine number of 20 (20% inhibited)
    - Note that acquired disease will have a normal dibucaine number, as the enzyme itself is working correctly, however does not exist in a large enough quantity to metabolise suxamethonium rapidly

G6PD

A common x-linked recessive condition that may cause haemolysis following administration of oxidative drugs. These include:

- Aspirin
- Sulfonamides
- Some antibiotics

Malignant Hyperthermia

Autosomal dominant deficiency in the skeletal muscle ryanodine receptor gene resulting in a defect of intracellular calcium regulation. This mutation:

- Causes massive calcium release from sarcoplasmic reticulum in the presence of volatile anaesthetic agents (and potentially suxamethonium)
  Leads to:
    - Increased muscle activity
    - Rapid increase in body temperature and lactic acidosis
    - High mortality from hyperthermia, hyperkalaemia/rhabdomyolysis, leading to ventricular arrhythmia and cardiac arrest
- Mutation present in 1:5,000 - 1:50,000
- Presents with:
    - Initially:
        - Tachycardia
        - Masseter spasm
        - Hypercapnea
        - Arrhythmia
    - Intermediate:
        - Hyperthermia
        - Sweating
        - Combined metabolic and respiratory acidosis
        - Hyperkalaemia
        - Muscle rigidity
    - Late:
        - Rhabdomyolysis
            - Myoglobinuria
            - Elevated CK
        - Coagulopathy
        - Cardiac arrest
- Management consists of:
    - Cease administration of volatile
        - Start TIVA
    - Give **dantrolene**
        - 2.5mg.kg^{-1} increments up to 10mg.kg^{-1}
        - 20mg vials reconstituted with 60ml sterile water
            - 3g mannitol as additive
            - Highly alkaline

Damaging if extravasation occurs.

- Treat complications:
    - Hyperkalaemia
    - Hyperthermia
    - Acidosis
    - Arrhythmias
    - Renal failure

Porphyria

Autosomal dominant deficiency in the first step of haeme synthesis. These mutations:

- Result in a partial deficiency of enzymes
- Lead to accumulation of porphyrin precursors
- May be precipitated by many drugs:
    - Ketamine
    - Clonidine
    - Ketorolac
    - Diclofenac
    - Phenytoin
    - Erythromycin
    - Barbiturates

References

1. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. Sixth Edition. Churchill Livingstone.
2. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
3. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

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Drugs in Pregnancy

The Therapeutic Goods Administration classifies drugs for suitability in pregnancy based on the potential of a drug to cause:

- Birth defects
- Detrimental effects at birth
- Problems in later life

The classification system is:

- Valid only for the dose and route of administration listed
  - Does not apply in overdose
- Not hierarchical
  - 'B' drugs are not safer than 'C' drugs

Categories

- **Category A**
  Taken by *large number* of women without detrimental effects.

- **Category B**
  Subclassified into:
  - Category B1
    - Taken by a *limited number* of women without detrimental effect
    - Animal studies show no evidence of detrimental effect to the foetus
  - Category B2
    - Taken by a *limited number* of women without detrimental effect
    - Animal studies are inadequate or lacking, but available data shows no evidence of detrimental effect to the foetus
  - Category B3
    - Taken by a *limited number* of women without detrimental effect
    - Animal studies show evidence of foetal damage, but the significance of this in humans is unknown

- **Category C**
  - Drugs which have caused (or a suspected to cause) detrimental foetal effects, but without malformations
  - These effects may be reversible

- **Category D**

  - Drugs which have caused (or are suspected to cause) an increased incidence of foetal malformations or damage
  - May also have detrimental effects
- **Category X**

  - Drugs which have a high risk of causing permanent damage
  - Should not be used in pregnancy, or when pregnancy is possible

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References

1. Australian categorisation system for prescribing medicines in pregnancy. Therapeutic Goods Administration.

Last updated 2017-09-23

General Management of Poisoning

> Understanding of the general principles of poisoning and its management.

Principles of management of poisoning:

"Recognition-Resus-RSI-DEAD"[1]

- **Recognition**
    - Degree of emergency
    - Getting senior help
    - Application of 100% oxygen early
- **Resuscitation**
    - A: Control in any patient with significantly impaired conscious state
    - B: Oxygen if not previously applied. Mechanical ventilation if required.
    - C: Intravenous access is always required. Central venous access may be required.
    - D: Glucose level. Control seizures.
    - E: Control hypothermia
- **Risk assessment**
    - History including timing, amount, co-administered drugs, current patient status.
- **Supportive care**
- **Investigations**
    - ECG
    - Invasive monitoring may be required if haemodynamics are unstable.
    - Drug levels
- **Decontamination**
    - Activated charcoal *may* be appropriate if recent ingestion (<1 hour) and the airway is secured
- **Enhanced Elimination**
    - Used in severe poisoning when supportive care is likely to be inadequate. Includes:
        - Urinary alkalinisation
        - Filtration
- **Antidotes**
    - E.g. naloxone for opiates
- **Disposition**

Footnotes

LITFL has a fantastic section on the approach to the poisoned patient if you want more information.

References

1. Nickson, C. Approach to the Acute Poisoning. LITFL.
2. Leslie RA, Johnson EK, Goodwin APL. Dr Podcast Scripts for the Primary FRCA. Cambridge University Press. 2011.

Last updated 2019-07-18

Tricyclic Antidepressant Overdose

Tricyclic antidepressants are weak bases typically used for depression and as an adjunct for analgesia. They have a complex mechanism of action, competitively inhibiting noradrenaline and serotonin reuptake, and also blocking muscarinic receptors, histaminergic receptors, α-adrenoreceptors, GABA-a receptors, and fast sodium channels.

Toxicity

In overdose, toxicity is predominantly due to cardiac and central effects, though there are effects on most of the major organ systems.

Cardiac toxicity

Cardiac toxicity is due to antagonism of α-adrenoreceptors use-dependent blockade of fast sodium channels.

α-antagonism results in vasodilatation and subsequent **hypotension**. Hypotension may also be due to myocardial depression from sodium channel blockade.

Blockade of fast sodium channels occurs in the His-Purkinje system, as well as the atrial and ventricular myocardium. This results in **decreased myocardial impulse conduction**. They block channels in the inactivated state, resulting in a **use-dependent blockade** such that the **effect is greater at faster heart rates**. This results in an increased depolarisation and repolarisation time. ECG findings are consistent with this and are essentially pathognomonic:

- Widened QRS
- Right axis deviation of the terminal QRS
  $\geqslant$3mm terminal R wave in aVR.

Additional ECG findings include:

- Tachycardia
- Any degree of heart block
- Ventricular arrhythmias

Central toxicity

Central toxicity is predominantly due to anticholinergic effects, though antihistaminic effects contribute.

Anti-cholinergic effects tend to occur prior to cardiac effects, and include:

- Confusion
- Agitation
- Seizures
- Pupillary dilatation and blurred vision

Antihistaminic effects include obtundation.

Management

Standard management of poisoning applies. TCAs are not dialysable and as they are weak bases are not amenable to urinary alkalinisation.

Cardiac toxicity

$NaHCO_3$ and hyperventilation to a pH >7.5 is used to manage cardiac toxicity. There are a number of proposed mechanisms of action for the benefit of alkalinisation:

- Plasma **alkalosis** results in **less ionised drug** and **increases distribution** into tissues
- Plasma **alkalosis increases protein binding** of drug
- Intracellular alkalosis results in less bound intracellular drug, favouring its movement out of cells
- Extracellular alkalosis results in reduced H^+/K^+ exchange, increasing intracellular potassium and **hypopolarising the cell**.
- In addition to the alkalinising effects, sodium load from the $NaHCO_3$ improves the sodium concentration gradient into cells

α-adrenoreceptor antagonism can be countered with use of an α-agonist such as noradrenaline.

Arrhythmias should be managed with drugs that do not prolong the action potential - so amiodarone and beta-blockers are contraindicated. Initial management should be using $NaHCO_3$, though $MgSO_4$ and lignocaine can be considered in refractory cases.

Central toxicity

Seizures should be managed with benzodiazepines, phenytoin, propofol, and phenobarbital. Avoid agents which result in QRS prolongation.

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.
3. CICM July/September 2007
4. Salhanick SD, Traub SJ, Grayzel J. Tricyclic Antidepressant Poisoning. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2017.
5. Nickson, C. Toxicology Conundrum 22. LITFL.
6. Nickson, C. Tricyclic Antidepressant Toxicity. LITFL.
7. UpToDate. Tricyclic antidepressant poisoning

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Organophosphate Poisoning

Organophosphates are substances bind **irreversibly** to **acetylcholinesterase**, causing cholinergic excess. Examples include fertilisers and sarin gas.

Toxicity

Effects (as expected) are signs of muscarinic and nicotinic over-activation. This can be remembered by 'BLUDGES' for the muscarinic effects:

- **B**radycardia (and subsequent hypotension)
- **L**acrimation
- **U**rination
- **D**efecation
- **G**IT upset
- **E**mesis
- **S**weating and **S**alivation

and 'M' for the nicotinic effects:

- **M**uscular spasm

Management

Management is aimed at reducing ACh burden:

- **Atropine**
  Competitive antagonises ACh at the muscarinic receptor.
  - Atropine is preferred over glycopyrrolate as it will cross the blood brain barrier and treat central ACh toxicity
- **Pralidoxime**
  Reactivates acetylcholinesterase by luring the organophosphate away from the enzyme with a tantalising oxime group.
  - Pralidoxime must be used within the first few hours of poisoning
    After which the organophosphate-enzyme group 'ages' and is no longer susceptible.
  - Does not cross the blood-brain barrier and so cannot treat central effects

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References

1. CICM March/May 2009
2. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.

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The Cell Membrane

> Describe the cell membrane and cellular organelles and their properties.

Cell membranes are:

- Formed by a **phospholipid bilayer**
  Separates the intracellular and extracellular fluid.
- **Semi-permeable**
  Leads to different ionic concentrations (and therefore electrical charge) on either side of the membrane.
  - Alteration in charge means the membrane acts as a **capacitor**, with most cells having a **resting potential 70-80mV lower** than extracellular fluid

Ion Permeability

At rest, the cell is:

- Permeable to **potassium**
  - Potassium flows out down its concentration gradient
    This makes the resting potential becomes more negative.
    - This negative charge opposes the further movement of potassium and so an equilibrium is established between opposing electrical and chemical gradients
- Impermeable to other cations
  The membrane is not perfectly impermeable to sodium, and Na^+ will leak in down its concentration gradient.
  - The $3Na^+$-$2K^+$ ATPase pumps **three sodium ions** outside in exchange for **two potassium ions** in order to maintain these gradients
    As there is an unequal exchange of charge, this pump is **electrogenic**.

Ion	[Intracellular]	[Extracellular]
Na^+	15	140
K^+	150	4.5
Cl^-	10	100

References

1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Organelles

> Describe the cell membrane and cellular organelles and their properties

Organelles are specialised functional subunits within a cell, typically contained within their own lipid bilayer.

Key organelles include:

- Mitochondria
- Endoplasmic reticulum
- Golgi apparatus

Mitochondria

Mitochondria:

- Produce ATP via aerobic metabolism
  Only method of aerobic metabolism in the body.
  - Mitochondria exist in greater numbers in more metabolically active cells
- Consist of two membranes (outer and inner), which create three spaces,
  - Cytoplasm
    Outside the outer membrane.
  - Intermembrane space
    Between the membranes.
    - Outer membrane separates mitochondria from cytoplasm, but contains pores allowing some substances (pyruvate, amino acids, fatty acids) to pass
    - Inner membrane:
      - Isolates the electron transport chain from the intermembrane (space between inner and outer membranes) space.
      - Proteins on the inner membrane conduct the redox reactions important for ATP production
      - Electron transport chain pumps hydrogen ions into the intermembrane space
  - Inner mitochondrial matrix
    Contents important in many metabolic processes:
    - Citric acid cycle
    - Fatty acid metabolism
    - Urea cycle
    - Haeme synthesis

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Excitable Cells

> Explain the basic electro-physiology of neural tissue, including conduction of nerve impulses and synaptic function.

Membrane Potential

At rest, membranes are:

- Permeable to potassium
- Impermeable to other cations

Generation of membrane potential:

- Intracellular potassium concentration is much higher than extracellular potassium concentration
  Due to the action of the Na^+-K^+ pump.
- As the membrane is permeable to potassium, potassium will attempt to diffuse down this gradient, generating a negative intracellular charge which opposes further diffusion
- At some point, an electrochemical equilibrium is reached between:
  - The concentration gradient dragging potassium out of the cell
  - Negative electrical charge pulling it in
- This equilibrium is the **resting membrane potential**
  - RMP is determined by:
    - Permeability of the membrane to different ions
    - Relative ionic concentrations on either side of the membrane
  - Impermeable ions do not contribute to the resting membrane potential
    Altering membrane permeability causes a flow of ions and a change in voltage.

Nernst Equation

The potential difference generated by a **permeable** ion in electrochemical equilibrium when there are different concentrations on either side of the cell can be calculated via the **Nernst Equation**:

$E\ (mV) = \frac{R.T}{z.F} ln \frac{[ion]_{outside}}{[ion]_{inside}}$, where:

- E is the equilibrium potential for the ion
- R is the gas constant (8.314 $J.deg^{-1}.mol^{-1}$)
- T is the temperature in Kelvin
- F is Faraday's Constant
- z is the ionic valency (e.g. +2 for Mg^{+2}, -1 for Cl^-)

Goldman-Hodgkin-Katz Equation

The Nernst equation describes the equilibrium potential for a single ion, and assumes that the membrane is completely permeable to that ion.

However, calculation of membrane potential requires examining the effects of many different ions with different permeability. This can be performed with the **Goldman-Hodgkin-Katz equation**:

$$E\,(mV) = \frac{R.T}{F} ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$, where:

- P_x is the permeability constant for the ion, x
  If the membrane is impermeable to x, then $P_x = 0$.

Note that:

- This model does not consider valency
- The concentrations of negative ions are reversed relative to positive ions

Action Potential

Excitable cells can respond to a stimulus by a changing their membrane potential. This may be mediated:

- Chemically
  e.g. ACh receptors causing Na^+ channels to open.
- Physically
  Pressure receptors physically deforming and opening Na^+ channels.

- Stimulating an excitable cell increases Na^+ permeability
  This increases (i.e. makes less negative) membrane potential
- If several stimuli, or a large enough stimuli raises the membrane potential above the **threshold potential**, then an action potential will be generated
- This is due to **fast Na^+ channels**
  - Also known as **voltage-gated** Na^+ channels
  - Open when **membrane potential** exceeds **threshold potential**
    Threshold potential is typically -55mV.
  - Fast sodium channels generate the **all-or-nothing** response:
    - Stimuli below the threshold potential do not generate an action potential
    - Stimuli above threshold potential generate an action potential
      The size of the stimulus does not affect the magnitude of the action potential, as this is determined by the fast sodium channels.

Key Players in the Action Potential

Fast Na^+ channels are responsible for depolarisation. They exist in three states:

- Closed
  Impermeable to Na^+.
- Open
  Permeable to Na^+. Occurs when the membrane potential reaches threshold potential.
  - Different voltage-gated channels may have slightly different opening (threshold) potentials
- Inactivated
  Impermeable to Na^+. Occurs shortly after the open state, and lasts until the membrane potential falls below -50mV.

Voltage-gated K^+ channels:

- Are vital for repolarisation
- **Open slowly** with depolarisation
  This increases potassium permeability and reduces membrane potential.

Phases of the Action Potential

This describes the peripheral nerve action potential. The heart is covered under the cardiac action potential.

1. **Rising Phase**
   A stimulus which rises above the threshold potential opens fast Na^+ channels, increasing Na^+ influx.
   - Additional Na^+ has a positive feedback effect, causing additional Na^+ channels to open and further depolarisation
   - This drives the membrane potential towards the Nernst equilibrium for Na^+
2. **Peak Phase**
   Inactivation of fast-channels and delayed activation of K^+ channels slows depolarisation.
   - Membrane potential **peaks** at **30mV**
3. **Falling Phase**
   As potassium exits the cell, membrane potential continues to fall.
   - Voltage-gated K^+ channels start to close at **-50mV**
   - Inactivation of fast sodium channels defines the **absolute refractory period**
     No Na^+ can be conducted, regardless of the intensity of the stimulus, and so an action potential cannot be generated
     - The absolute refractory period lasts **~1ms**
4. **Hyperpolarisation**
   As potassium channels close slowly, the membrane potential slightly undershoots resting potential, causing slight hyperpolarisation of the cell.
   - This is the **relative refractory period**
     A large enough stimulus may overcome the additional hyperpolarisation and generate a second action potential.
     - The relative refractory period lasts **10-15ms**
5. **Resting**
   Cell is stable at resting membrane potential.

Propagation of the Action Potential

- An increase in Na^+ in one region will diffuse down the cell, raising the membrane potential above the resting potential in the adjacent membrane
- This causes local fast Na^+ channels to open, and the cell depolarises
- This results in a propagating wave of depolarisation and repolarisation

- Regions of a nerve cell covered by a myelin sheath do not have ion channels
- In these cells, propagation is **saltatory**
  This describes the "jumping" of the action potential between gaps in the myelin sheath.
  - These gaps are known as **nodes of Ranvier**
    Ion channels generate an action potential at the nodes in the usual manner.
  - Between nodes, conduction is via local electrical currents
- Myelination:
  - **Increases conducting velocity**
  - **Reduces energy expenditure**
    Via reduction in total ion flux.

Classification of Nerve Fibres

Classified on their diameter and conduction velocity:

- Type A
  Myelinated, 12-20μm in diameter, conduct at 70-120$m.s^{-1}$. Subdivided into:
  - Aα
    Motor fibres.
  - Aβ
    Touch fibres.

    - Aγ
      Intrafusal (proprioceptive) muscle fibre.
    - Aδ
      Pain fibres.
- Type B
  Myelinated, < 3μm, conduct at 4-30m.s^{-1}. Innervate pre-ganglionic neurons.
- Type C
  Unmyelinated, 1μm, conduct at 0.5-2m.s^{-1}. Pain fibres.

References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Transport Across Cell Membranes

> Explain mechanisms of transport of substances across cell membranes, including an understanding of the Gibbs-Donnan effect.

Substances can cross cell membranes by **diffusion**, **active transport**, and **exo-** or **endocytosis**.

Diffusion

There are several types of diffusion:

- **Simple diffusion**
  Molecules pass through the cell membrane or via a channel. This process is **passive**, and occurs down a concentration gradient.
  - Only lipid soluble molecules (gases, steroids) can pass directly through the lipid bilayer without a specialised channel
  - Voltage-gated and ligand-gated channels facilitate simple diffusion
- **Facilitated diffusion** (uniporters)
  Molecules bind to a carrier protein, and move together through the lipid bilayer, before separating on the other side.
  Facilitated diffusion is **concentration gradient-dependent**, and **limited by** the amount of **carrier protein** available..

The rate and extent of diffusion is affected by:

- Hydrostatic pressure gradients
- Concentration gradients
- Electrical gradients

Active Transport

Substances that are moved against a concentration gradient require active transport, and requires energy in the form of ATP. Active transport mechanisms may be:

- **Primary** active transport
  The substance itself is moved.
- **Secondary** active transport
  The substance moves against a concentration gradient with another molecule that had a gradient established by active transport.
  - This molecule is typically sodium
- **Co-transporters** (symporters)
  Uses carrier proteins and moves two substances (e.g. sodium and an amino acid) across a membrane.
  - This process will be passive if the energy gained moving one substance down its concentration gradient is greater than the energy required to move the other substance up its concentration gradient
- **Counter-transporters** (antiporters)
  Use carrier proteins and moves two substances in opposite directions across the membrane.
  - May be active or passive

Key transporters include:

- The **Na^+-K^+ ATP-ase** pump
  This moves three sodium ions out of a cell and two potassium ions in, cleaving one ATP in the process. This pump has many functions:

- Maintenance of cellular volume (which would otherwise burst from the influx of water with changing ECF tonicities) by net loss of osmoles
- Maintenance of the potential difference across the membrane
- Establishment of chemical gradients to be used in secondary active transport mechanism
  - e.g. Reabsorption of glucose in the kidney via the S-GLUT transporter

Exo- and Endocytosis

These processes describe the formation of a vesicle (typically from membrane phospholipid) to transport substances:

- **Exocytosis**
  Vesicle containing a substance to be secreted fuses with the cell membrane when activated by calcium, depositing the substance outside the cell.

- **Endocytosis**
  The cell membrane invaginates around the substance, absorbing the substance into the cell. A vesicle (or vacuole) may or may not be created. Endocytosis may be subdivided into:
  - Phagocytosis, where leukocytes engulf bacteria into a vacuole
  - Pinocytosis, where substances are endocytosed but not into a vacuole

Gibbs-Donnan Effect

Describes the tendency of diffusable ions to distribute themselves such that the ratios of the concentrations are equal when they are in the presence of non-diffusable ions.

The Gibbs-Donnan Effect:

- Occurs when:
  - A semi-permeable membrane separates two solutions
  - At least one of those solutions contains a non-diffusable ion
- The distribution of permeable charged ions will be influenced by both their valence and the distribution of non-diffusable ions, such that at equilibrium **the products of the concentrations of paired ions on each side of the membrane will be equal**:
  $$[Na^+]_A \times [Cl^-]_A = [Na^+]_B \times [Cl^-]_B$$
- Alters tonicity on either side of the cell membrane, causing movement of water which then upsets the Gibbs-Donnan effect
  This results in no 'steady' stable state.

The two main contributors to the Gibbs-Donnan effect in the body are sodium and protein. This occurs because cell membranes:

- Are impermeable to protein
  Intracellular protein concentration is high.
- Effectively impermeable to sodium
  Due to the Na^+-K^+ ATP-ase pump.

Changing Gibbs-Donnan equilibriums also change the tonicity on each side of the cell membrane, causing movement of water which then upsets the Gibbs-Donnan effect - therefore there is no stable state.

The Gibbs-Donnan Effect is important for:

- Maintenance of cell volume
  Na^+ acts as an effective osmole, reducing cellular swelling.
- Plasma oncotic pressure
  Increased plasma ion concentration increases oncotic pressure.

- Resting Membrane Potential

References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
2. Eaton DC, Pooler JP. Vander's Renal Physiology. 6th Ed (Revised). McGraw-Hill Education - Europe. 2004.

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Fluid Compartments

> To describe the composition and control of intracellular fluid ~and the mechanisms by which cells maintain their homeostasis and integrity~

On average, the human body is **~60% water**. Distribution of water content can be divided conceptually into:

- Intracellular fluid
  Composes 2/3^{rds} of total body water. ICF is:
    - Not a contiguous fluid space
    - Useful as the composition of cellular contents is relatively uniform:
        - Potassium is the dominant intracellular cation
          Sodium concentrations are low.
        - The dominant anion is protein
          Chloride concentration is relatively low.
        - Low in magnesium
- Extracellular fluid
  Composes the remaining 1/3rd of total body water, and is further divided into:
    - Intravascular fluid
      Composes ~20% of ECF. This refers solely to plasma volume (as the volume of blood from cellular components is ICF). The ICF is:
        - Vital for transporting nutrients, waste, and chemical messengers between the plasma and cells
    - Transcellular fluid
      Composes ~7% of ECF, and describes the volume of CSF, urine, synovial fluid, gastric secretions, and aqueous humor.
    - Interstitial fluid
      Composes the bulk of ECF volume, and describes the fluid that occupies the volume between cells.

Variations

Actual total body water content varies predominantly with **fat content**. This leads to differences concentrations in:

- Neonates
  ~75-80%.
- Elderly
  ~50% by the age of 60, due to increased adiposity.
- Women
  Typically ~55%.

Measuring Volumes of Fluid Compartments

All methods rely on the indicator-dilution method:

- A known amount (i.e. known volume of a known concentration) of indicator with affinity to a particular compartment is given and allowed to equilibrate
- The concentration of the indicator is then measured
- The difference between the measured concentration and the initial concentration is proportional to the volume of the compartment

Indicators used for calculation of:

- Plasma volume
  A colloid that will be retained in the vascular compartment; e.g. radio-labeled albumin.
- ECF volume
  A substance which can enter the interstitium but not cells; e.g. thiosulfate.
- Total body water
  A substance which can enter all compartments freely; e.g. heavy water (^2H_2O).
- ICF volume
  Can be measured by the difference between calculated ECF volume and TVW.

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Last updated 2019-07-18

Cell Homeostasis

> To describe the ~composition and control of intracellular fluid and the~ mechanisms by which cells maintain their homeostasis and integrity

Cellular respiration describes the production of ATP through a series of redox reactions. Oxygen is used as the oxidising agent, whilst the catabolic fuel may be glucose, fat, or protein.

Cellular respiration can be broken down into:

- Glycolysis/Lipolysis/Proteolysis
- Citric Acid Cycle
- Electron Transport Chain

Glycolysis

Glycolysis, or the **Embden-Meyerhof pathway**, describes the production of pyruvate from glucose. Glycolysis:

- Occurs in the cytoplasm
- Begins with the **phosphorylation of glucose** to glucose-6-phosphate
- Produces:
    - 2 ATP
    - 2 Pyruvate
    - 2 NADH

- Note that **oxygen is not consumed and carbon dioxide is not produced**
- In aerobic conditions:
  NADH exchanges electrons across the mitochondrial wall, regenerating NAD^+ and allowing glycolysis to continue
- In anaerobic conditions:
  NAD^+ is regenerated through the production of lactate
    - When aerobic conditions are restored, lactate can be oxidised back to pyruvate and enter the CAC
    - Transported to the liver and converted back to pyruvate (and enter the CAC), or produce glucose (**Cori cycle**)

Citric Acid Cycle/Kreb's Cycle

- Takes place in the mitochondria
- Complicated
- Can take many various substrates:
    - Acetyl CoA
      Produced by β-oxidation of fatty acids and pyruvate.
    - Pyruvate
    - Ketoacids
- Does **not consume oxygen** but also **doesn't function under anaerobic conditions**, due to its requirement on fresh NAD^+ from the ETC
- Produces:
    - NADH
    - $FADH_2$
    - CO_2

Electron Transport Chain

- Final stage of carbohydrate, fat, and protein catabolism
- ETC consists of five protein complexes
- Electrons are passed along the chain and combine with oxygen, releasing energy which stimulates the movement of hydrogen ions
- Each time a hydrogen ion crosses the mitochondrial matrix, an ATP is produced
  - This is called **coupled phosphorylation**
  - Uncoupled phosphorylation allows hydrogen ions to travel down their gradient without generating ATP, which produces excess heat instead
- 36-38 ATP are produced by aerobic glycolysis
  Sources disagree on exactly how much ATP is produced.
  - 2 from the Embden-Meyerhof pathway
  - 34-36 from the CAC and ETC

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

Last updated 2019-07-18

Airway and Alveolar Anatomy

> Describe the function and structure of the upper, lower airway and alveolus.

Upper Airway

The upper airway consists of the:

- **Mouth**
- **Nasal cavity**
  - Hairs filter large particles
  - Olfactory receptors detect harmful gases prior to inhalation
- **Pharynx**
- **Larynx**

Breathing can be oral or nasal. Nasal breathing offers:

- Good **humidification** and **filtration** of inhaled particles because the septum and turbinates have:
  - High mucosal surface area
  - High mucosal blood flow
  - Generate turbulent flow
- High resistance to flow
  At a **high minute ventilation**, oral breathing is favoured.

Structures

- **Pharyngeal dilator muscles**
  Including genioglossus and levator palati. Prevent pharyngeal collapse during negative-pressure ventilation and during sleep.

- **Larynx**
  Important for **airway protection**, **speech**, and **effort closure**.
  - Prevents aspiration during swallowing by elevating the epiglottis and occluding of the aryepiglottic folds
  - **Phonation** is achieved by adjusting tension (and therefore resonance) of the vocal cords by action of the cricothyroid
  - During **inspiration**, **cricoarytenoid** muscles rotate the arytenoid cartilage and abduct the vocal cords to reduce resistance to airflow
  - During **expiration**, the **thyroarytenoid** muscles adduct the cords and increase resistance, providing **intrinsic PEEP**
    - 3-4 cmH_2O of PEEP is generated
    - Maintains patency of small airways
      Prevents alveolar collapse and therefore maintains FRC.
  - **Effort closure** is tighter occlusion of the laryngeal inlet, in which the aryepiglottic muscles contract strongly to act as a sphincter, allowing the airway to withstand up to 120cmH_2O of pressure.

Lower Airway

The lower airway consists of the **tracheobronchial tree**:

- From trachea to alveolus, the airways of the lungs **divide 23 times**
  The tracheobronchial tree is divided into two zones, based on whether they contain alveoli and therefore are able to participate in gas exchange:
  - The **conducting zone** is the first **16 divisions**

- The **respiratory zone** is the last 7 divisions

Conducting Zone

The **first 16 divisions** constitute the **conducting zone**:

- Anatomically, the conducting zone consists of:
    - **Trachea**
        - Mean diameter of 1.8 cm and a length of 11cm
        - D-shaped cross section
          Curved cartilages anteriorly and longitudinal muscle (trachealis) posteriorly. External pressure of 40cmH_2O is sufficient to occlude the extrathoracic trachea.
        - Flow is typically turbulent in the trachea and large airways
    - **Bronchi**
        - Comprise the first four divisions of the trachea
        - Right main bronchus is wider and deviates less from the axis of the trachea (the left main bronchus has a tighter turn over the heart), which is why foreign bodies will tend to the right side
        - The two main bronchi divide into a total of 5 lobar bronchi, which in turn divide into a total of 18 segmental bronchi
            - Cross-sectional area of the respiratory tract is lowest at the third division
            - These bronchi will collapse when intrathoracic pressure exceeds intraluminal pressure by ~5cmH_2O.
            - Segmental bronchi travel with branches of the pulmonary artery and lymphatics
              These are the bronchi that demonstrate peribronchial cuffing and perihilar haze in early pulmonary oedema.
            - Flow is typically transitional in the smaller bronchi and bronchioles
    - **Bronchioles**
        - Embedded in the lung parenchyma
        - Do not have cartilage in their walls to maintain patency - are held open by lung volume
        - Resistance to flow tends to be negligible due to large cross sectional area, unless there is spasm of helical muscle bands in bronchial wall
    - **Terminal bronchioles**
        - Flow may become laminar in the smallest bronchioles as flow decreases
- Flow in the conducting zone during inspiration is fast and turbulent
- No gas exchange occurs in the conducting zone
  The volume of the conducting zone therefore contributes to **anatomic dead space**.
- Blood supply to the conducting zone is via the **bronchial circulation**

- **Mucous** is secreted by **goblet cells** in the bronchial walls to trap inhaled particles
- **Cilia** in the bronchial walls move rhythmically to drive the mucociliary elevator, driving mucous up to the epiglottis, where it is then swallowed or expectorated

Respiratory Zone

The **remaining 7 divisions** make up the **respiratory zone**. This region:

- Makes up the majority of lung volume
  All non-anatomical dead space volume is in the respiratory zone, and is **~30ml.kg^{-1}** (FRC) at rest
- Blood supply is via the pulmonary circulation

- Gas flow in the terminal respiratory zone is slow due to the exponential increase in cross-sectional area with each airway division
    - Diffusion is the predominant mechanism of gas movement

Alveolus

The alveolus is optimised for gas exchange:

- Spherical shape maximises surface area to volume ratio
- Total surface area of lung alveoli is 50-100m^2
- Alveolar walls are extremely thin (0.2-0.3μm)
  Consequently, they are fragile and can be damaged by increases in capillary pressure
- Alveolar walls contain a dense mesh of capillaries **7 to 10μm** thick, which is just large enough for an erythrocyte to pass through
  The alveolar-capillary barrier consists of three layers:
    - Type I pneumocytes
    - Extracellular matrix
    - Pulmonary capillary endothelium

Alveoli are composed of three types of cells:

- **Type I pneumocytes**
  Thin-walled epithelial cells optimised for gas exchange.
    - Form ~90% of the alveolar surface area
- **Type II pneumocytes**
  Specialised secretory cells.
    - Secrete surfactant
      Alveoli are inherently unstable, and surface tension of alveolar fluid favours collapse of the alveoli. **Surfactant** reduces surface tension, allowing the alveoli to expand.
    - Form ~10% of alveolar surface area
- **Alveolar macrophages**
  Alveoli have no cilia - inhaled particles are phagocytosed by alveolar macrophages in alveolar septa and lung interstitium.

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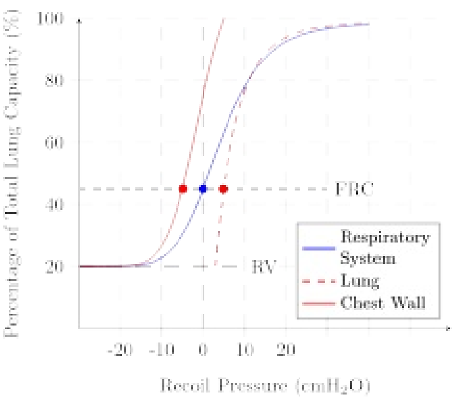
Chest Wall and Diaphragm

> Describe the structure of the chest wall and diaphragm and to relate these to respiratory mechanics.

The chest wall is formed by the ribs and intercostal muscles:

- **Ribs**
  Slope antero-inferiorly, and are connected by the external, internal, and innermost intercostal muscles.
- **Intercostal muscles**
  - External intercostals slope antero-inferiorly
  - Internal and innermost intercostals slope infero-posteriorly
- **Diaphragm**
  Complex dome-shaped membranous structure, consisting of a central tendon and peripheral muscles
  - Performs the majority of inspiratory work of breathing
  - Able to dramatically increase intraabdominal pressure, so is essential in:
    - Coughing
    - Vomiting
    - Sneezing
  - Role in maintaining lower oesophageal sphincter tone
  - It has three perforations:
    - **T8** for the **vena cava** (eight letters)
    - **T10** for the **oesophagus** (ten letters)
    - **T12** for the **aorta**, thoracic duct, and azygos vein



Inspiration

- During **inspiration**, the **diaphragm** and **external intercostal** muscles **contract**
  - Diaphragm pushes the intraabdominal contents down, increasing thoracic volume and generating a negative intrathoracic pressure
    - Diaphragm is supplied by the phrenic nerves from C3/4/5.
  - External intercostals pull the ribs antero-superiorly, which increases the cross-sectional area of the chest, further increasing thoracic volume (and negative pressure)
    - Intercostal muscles are supplied by intercostal nerves from the same spinal level
    - Paralysis of the external intercostals does not have a dramatic effect on inspiratory function provided the diaphragm is intact

- **Accessory muscles** include **sternocleidomastoid** and the **scalene**, which elevate the sternum and first two ribs respectively. They are active in hyperventilation.

Expiration

- Expiration is passive during quiet breathing as elastic recoil of the lung will return them to FRC
- When minute ventilation is high, expiration becomes an an active process:
  - **Abdominal wall** muscles (rectus abdominis, internal oblique, external oblique, transversus abdominis) contract, raising intraabdominal pressure and forcing the diaphragm up
  - **Internal** and **innermost** intercostals contract, pulling the ribs **downwards** and **inwards**, further decreasing thoracic volume

Respiratory Mechanics in Spinal Injury

- Paralysis of the abdominal wall muscles (e.g. spinal injury) has significant affect on respiratory mechanics:
  - In the initial phases of injury, spinal shock results in a flaccid paralysis of the abdominal wall
    - Intraabdominal pressure is low, and so the diaphragm moves inferiorly
      This results in a higher FRC but limits tidal volumes, as contraction of the diaphragm only increase thoracic volume by a small fraction.
    - Nursing in a supine position causes the abdominal contents to push the diaphragm superiorly, causing:
      - Lower FRC
      - Greater proportional expansion with respiration, improving tidal volumes
  - Once spastic paralysis ensues, the abdominal wall is rigid and the patient can be sat up

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1. West J. Respiratory Physiology: The Essentials. 9th Edition. Lippincott Williams and Wilkins. 2011.

Last updated 2019-07-18

Variations in Upper Airway Anatomy

> Understand the differences encountered in the upper airway for neonates, children and adults.

Neonates and Children

Changes are most obvious below 1 year of age. They typically resolve by ~8 years of age.

- Head and neck changes
  - Obligate nose breathers
    Nasal obstruction may significantly impair respiration.
  - Proportionally **enlarged head** and occiput
    Optimal intubating position is neutral rather than ramped.
  - Proportionally **short neck**
    Favours airway obstruction when flexed.
- Laryngeal changes
  - Disproportionately **large tongue** that complicates laryngoscopy
  - **Epiglottis** is **u-shaped**, **longer**, and **stiffer**
  - **Larynx lies at C4** (rather than C6 in adults)
  - Narrowest part of the upper airway is **the transverse diameter of the vocal cords**
    Not at the cricoid.
- Intrathoracic changes
  - Intrathoracic trachea is also shorter
    May be only 4cm long, so there is little margin for error in tube placement.
  - Left and right bronchi arise at similar angles, so endobronchial intubation may occur on either side
  - Airways themselves are narrower, and have a higher resistance to flow.

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2. Anderson, C. Anatomy of the Respiratory system.. ICU Primary Prep.
3. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
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Control of Breathing

> Describe the control of breathing

Ventilation is controlled by a feedback loop involving:

- Inputs
- Integration and control centres
- Effectors

Inputs

Inputs to the respiratory centre comes from a number of sensors:

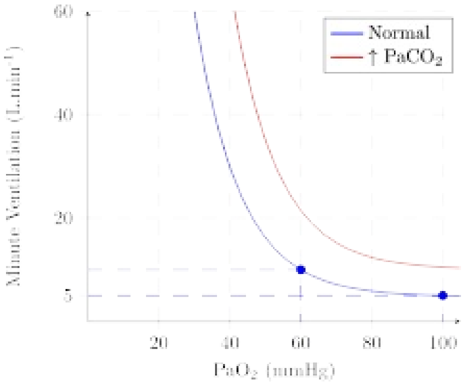
- Chemoreceptors
  Chemoreceptors act synergistically. Chemoreceptors are divided into:
  - Peripheral
  - Central
- Mechanoreceptors
- Other effects

Peripheral Chemoreceptors

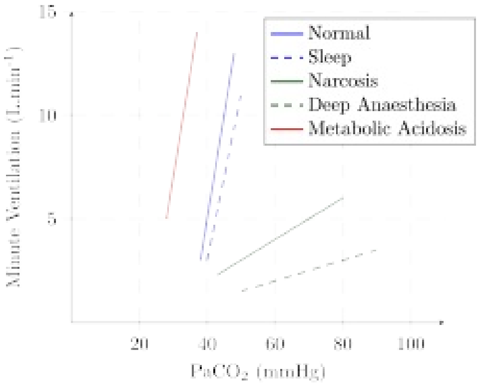
Peripheral chemoreceptors are divided into:

- The **carotid body**
  Located at the bifurcation of the common carotid artery, and are innervated by the glossopharyngeal nerve (CN IX).
- The **aortic body**
  Located in the aortic arch, and innervated by the vagus (CN X).

Peripheral chemoreceptors are stimulated by:

- **Low PaO_2**
  Peripheral chemoreceptors are stimulated by **low O_2 tension**
  

- **High $PaCO_2$**
  Peripheral receptors have a **rapid** (~1-3s) but **weaker** (~20% of response) to changes in CO_2, compared to central chemoreceptors



- **Acidaemia**
  (Carotid bodies only)
- **Hypotension**

Central Chemoreceptors

- Central chemoreceptors are located on the **ventral medulla**, and are **stimulated** by a **fall** in **CSF pH**
  - H^+ and HCO_3^- are ionised, and cannot cross the BBB by diffusion
  - Because of this, central chemoreceptors **respond indirectly** to **changes in arterial $PaCO_2$**
    - Carbon dioxide is lipid soluble and freely diffuses into CSF
    - In CSF, carbon dioxide combines with water (catalysed by carbonic anhydrase) to form H^+ and HCO_3^-
- This gives the central chemoreceptors a number of special properties:
  - **Increased sensitivity**
    Increased relative to plasma due to minimal buffering (as there is less protein in CSF)
  - **Respond to respiratory acidosis**
    Fixed acid does not cross the blood brain barrier and so have a minimal response on CSF pH. **Cerebral hypoxia** increases **CSF lactate**, which will stimulate respiration.

Mechanism of CO_2 Retention

- Prolonged respiratory acidosis (i.e. prolonged CSF acidosis) stimulates active secretion of bicarbonate into the CSF
- When pH normalises, the stimulation of central chemoreceptors ceases
- Similarly, renal absorption of bicarbonate increases, which normalises arterial pH and reduces peripheral chemoreceptor stimulation

Mechanoreceptors

Stretch receptors in bronchial muscle are stimulated by overinflation, and stimulate the **apneustic centre** to reduce inspiratory volumes. This is the **Hering-Breuer reflex**.

Other Stimulants

Other inputs which stimulate respiration include:

- Juxtacapillary receptors (J-receptors)
  Receptors in alveolar walls, potentially stimulated by oedema and emboli.
- Irritant receptors
  Inhalation of noxious gases stimulates respiration.
- Pain receptors
- Thalamus

Increased core temperature stimulates respiration.
- Limbic system
  Emotional responses.
- Cerebral cortex
  Conscious control of breathing.
- Muscle spindles
  Ventilatory response to exercise.

Integration and Control

The respiratory centre is located in the **medulla** and the **pons**. It consists of four groups:

- **Dorsal Respiratory Group (DRG)**
  Controls the diaphragm, and is so only involved with inspiration.
- **Ventral Respiratory Group (VRG)**
  Controls the intercostal muscles, and so is involved in inspiration and expiration.
- **Apneustic Centre**
  Modulates DRG function to prevent over-expansion. Loss of this area causes **apneusis** - long, deep breaths.
- **Pneumotaxic Centre**
  Also modulates the DRG, increasing RR and decreasing V_T to maintain MV.

References

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4. Brandis K. The Physiology Viva: Questions & Answers. 2003.

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Respiration

> Describe the inspiratory and expiratory process involving the chest wall, diaphragm, pleura and lung parenchyma

> Explain the significance of the vertical gradient of pleural pressure and the effect of positioning

Change in lung volume occurs due to change in intrapleural pressures. Therefore, respiration relies on the thoracic cavity being **airtight**, with the trachea being the only method gas can enter or exit the chest.

Intrapleural pressure (P_{pl})

Intrapleural pressure is the pressure in the space between the visceral and parietal pleura, or (physiologically) between the lungs and the chest wall.

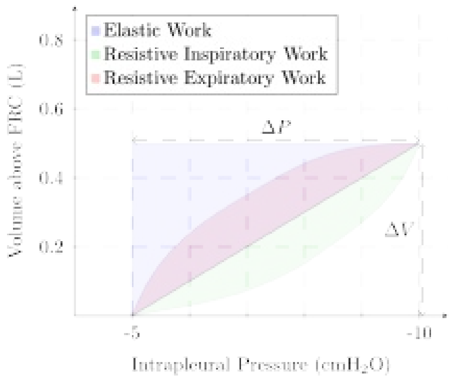
- Usually **negative**, typically **-5cmH$_2$O at rest**
  Balance between the:
  - Outwards recoil of the chest wall
  - Inwards recoil of the lungs (**P_{el}**)
- Varies with vertical distance in the lung
  - Gravity pulls the lung parenchyma inferiorly
  - Intrapleural pressure is therefore:
    - **More negative** in the **apex**
      Typically **-10cmH$_2$O** at FRC
    - **Less negative** in the **base**
      Typically **-3cmH$_2$O** at FRC
- This changes the degree of inflation at FRC
  - Apical alveoli are maximally inflated
  - Basal alveoli are relatively deflated
- During inspiration, the pleural pressure changes evenly throughout the lung, however the basal alveoli are better ventilated because their compliance is increased (due to lower resting volume)

Inspiration

- Diaphragmatic and external intercostal/accessory muscle contraction causes an increase in the volume of the thorax
- Intrapleural pressure becomes more negative, typically to **-8cmH$_2$O**
- When $P_{pl} > P_{el}$, the lungs expands
- Alveolar pressure (P_A) becomes sub-atmospheric, and inspiration occurs
- At end inspiration:
  - $P_{pl} = P_{el}$
  - $P_A = P_{atmospheric}$

Expiration

- Muscular relaxation causes the chest wall to passively return to their resting position
- Thoracic volume falls
- P_{pl} falls to -5cmH$_2$O
- The elastic recoil of the lung causes it to collapse until $P_A = P_{atmospheric}$



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Compliance

> Define compliance (static, dynamic and specific), its measurement, and relate this to the elastic properties of the respiratory system.

- Compliance is the **change in volume** for a **given a change in pressure**
  Compliance is measured in $ml.cmH_2O^{-1}$.
- It occurs due to the tendency of a tissue to resume its original position after removal of an applied force
- It is the inverse of **elastance**, which is the force at which the lung recoils for a given distension
- A decreased compliance means the transpulmonary pressure must change by a greater amount for a given volume, which increases elastic work of breathing

Compliance of the Respiratory System

- Compliance of the respiratory system is a function of both lung and chest wall compliance:
  $\frac{1}{C_T} = \frac{1}{C_L} + \frac{1}{C_W}$.
- The curve is not linear as compliance varies with lung volume In the normal range however, (-5 to -10cmH_2O) compliance of the lung and chest wall **independently** is typically stated as **~200$ml.cmH_2O^{-1}$**.
  - **Compliance of the respiratory system** as a whole is therefore **~100$ml.cmH_2O^{-1}$**

Measurement of Lung and Chest Wall Compliance

- Lung compliance is calculated form the alveolar-intrapleural pressure gradient
- Chest-wall compliance is calculated from the intrapleural-ambient pressure gradient
- Total compliance is calculated from the alveolar-ambient gradient

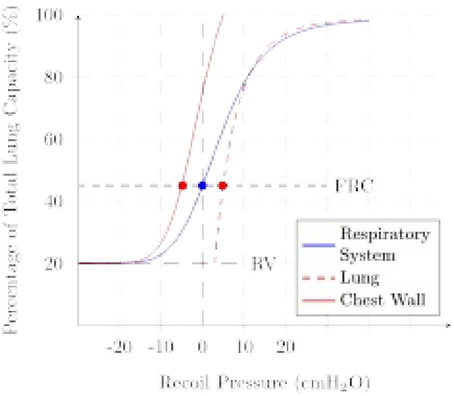
- Measuring ambient and alveolar pressure is straightforward, as is calculating compliance of the respiratory system
  - Alveolar pressure is measured by taking a plateau pressure
- Separating lung and chest wall compliance requires measurement of intrapleural pressure
  This is performed by measuring oesophageal pressure (using a balloon) with an **open glottis**, as oesophageal pressure approximates intrapleural pressure.

- Measurement of compliance of each system individually determines what proportion of plateau pressure is distributed to each
  - If the lung is significantly less compliant than the chest wall, a greater pressure is required to distend the lung
  - Therefore, the alveolar-intrapleural gradient will be much greater than the intrapleural-ambient gradient
  - This can be expressed by the equation:
    $$\Delta P_{Pl.} = P_{Plat.} \times \frac{C_L}{C_L + C_W}$$

Static Compliance

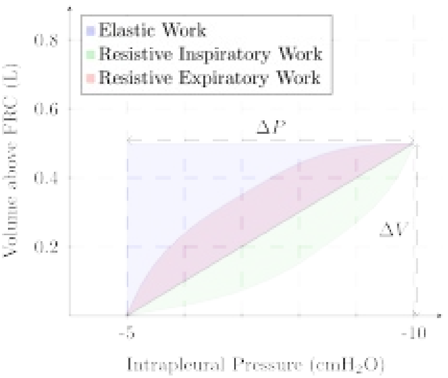
- **Static compliance** is the compliance of the system at a given volume when there is no flow
- Therefore there is no pressure component due to resistance
- A static compliance curve is made by measuring the pressure across a range of lung volumes, with patient taking incremental breaths
- Static compliance is a function of:

 - Elastic recoil of the lung
 - Surface tension of alveoli



Dynamic Compliance

- **Dynamic compliance** is the compliance measured during respiration, using continuous pressure and volume measurements
- Therefore, dynamic compliance **includes the pressure required to generate flow** by overcoming resistance forces
  - This means it is also a bit of misnomer
- **Dynamic compliance is always less than static compliance**, as there will always be a degree of airway resistance
- Dynamic compliance is a function of respiratory rate
  In normal lungs at normal respiratory rates it approximates static compliance.
- Reduced in in lung units with unequal time constants at high respiratory rates
  - Due to incomplete filling of alveoli - the portion of pressure that is used to overcome airways resistance is therefore proportionally greater



Specific Compliance

Specific compliance is the compliance per unit volume of lung, expressed as:

$$C_S = \frac{C_{Tot}}{FRC}$$

- Specific compliance is used to compare different lungs

Hysteresis

- In general, hysteresis refers to any process where **the future state of a system is dependent on its current and previous state**
- Specific to the lung, it means the compliance of the lung is different in inspiration and expiration

- There is hysteresis in both static and dynamic curves:
    - In dynamic compliance curves:
      Airways resistance is a function of flow rate. Flow rate (therefore resistance) is maximal at the beginning of inspiration and end-expiration.
    - In static compliance curves:
      There is no resistive component. Hysteresis is due to viscous resistance of surfactant and the lung.

Changes in Compliance

Respiratory system compliance can be affected by changes to either lung or chest wall compliance, and can be increased or decreased.

Increased Lung Compliance

- Normal ageing
- Asthma attack
- Emphysema

Decreased Lung Compliance

- Alterations in lung volume and consolidation
  Compliance is reduced at **extremes of lung volume**. It is **highest at FRC**.
    - Children
    - Pneumonectomy/lobectomy
    - Atelectasis/collapse
    - Pneumonia
    - ARDS
- Increased pulmonary blood volume/**venous congestion**
    - APO
- Increased surface tension
    - **Reduced surfactant**
        - Hyaline Membrane Disease
- **Impaired parenchymal compliance**
    - Pulmonary fibrosis

Increased Chest Wall Compliance

- Collagen disorders

Decreased Chest Wall Compliance

- **Chest wall restriction**/structural abnormalities
    - Obesity
    - Spastic paralysis of chest wall musculature
    - Ossification of costal cartilages
    - Kyphosis/scoliosis
    - Scarring/constriction (e.g. circumferential burns)
- **Position**
    - Prone (60% reduced compliance)/supine
      This is due to the effect of position on lung volume.

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Last updated 2019-07-20

Time-Constants

> Explain the concepts of time constants

A Refresher on Time Constants

The time-constant is:

- The **time** that a **process would take to complete *if*** its **initial rate of change** remained constant
- Relevant when modeling a process using exponential functions
  - Remember an **exponential function** is a curve where **the rate of change is proportional to the current value**

For a quantity that decreases[1] overtime, the general case is:

$y = y_0 e^{-kt}$, where:

- y_0 is the value of y at $t = 0$
- $-k$ is the rate constant (k plots a curve that **grows**)
- t is time

Importantly:

- k is the **reciprocal of the time constant**, τ
- In a negative exponential, **time-constant** is the time it would take for y to reach 0 if the original rate of change was maintained.
- Other fun facts about the time constant (for an exponential decay) include:
  - After 1 τ, y will be 37% ($\frac{1}{e}$) of its initial value
  - After 2 τ, y will be 13.5% ($\frac{1}{e^2}$) of its initial value
  - After 3 τ, y will be 5% ($\frac{1}{e^3}$) of its initial value
  - After 5 τ, y will be 1% ($\frac{1}{e^5}$) of its initial value

Physiological Significance

The time-constant is used in respiratory physiology in:

- Timing inspiration and expiration
- Elimination of inhalational anaesthetics
- The change in PaO_2 and $PaCO_2$ after changes in ventilation

In ventilation:

- The time constant is affected by:
  - Compliance
  - Resistance
  - Inflation pressure
    At a **constant inflation pressure**, the **time constant is equal to the product of resistance and compliance**, i.e.

$$\tau = C \times R.$$

- For two lung units of **equal compliance and resistance**
  - Inflation will occur as per the exponential growth function
  - Time-constants of each lung unit will be equal
  - No redistribution of gas will occur at end-inspiration as the pressure and volume of each unit is the same
- For two lung units, where **one has half the compliance but twice the resistance**
  - The time constants are equal, therefore both reach peak filling at the same time
    - However, the poorly compliant unit will only reach half the volume
  - No redistribution of gas will occur at end-inspiration as the pressure and volume of each unit is the same
- For two lung units, where one has **twice the resistance** of the other
  - The time-constants are unequal
  - The resistant unit will fill at half the rate of the other
    - If inspiration is prolonged both will reach the same volume
    - If inspiration his halted early, and expiration prevented, there will be a pressure gradient between the units (as compliance is the same), and gas will redistribute from the low-resistant unit to the high-resistant unit
- For two lung units where one has **half the compliance**
  - The time constants are unequal
  - The poorly compliant unit will fill at half the rate of the other
    - If inspiration is prolonged they will both reach the same pressure
      The volume in the poorly compliant unit will be half that of the more compliant unit.
  - During inspiration, the pressure rises more rapidly in the poorly compliant unit, and if inspiration is stopped and expiration prevented, this will result in redistribution into the more compliant unit until pressures are equal

In general:

- **Rate of filling is determined by time constants**
  - **High-resistance** lung units have **longer time constants** and take longer to fill
- **Final volume** (assuming an indefinite inspiration) **is a function of compliance**
  - Poorly compliant units with **empty and fill rapidly**
    This creates the concept of **fast** and **slow alveoli**, depending on their time constants.

- At a sustained inflation pressure:
  - A low-resistance unit shows initial greater volume change but rapidly approaches equilibrium volume
  - A high-compliance unit takes a greater overall volume over a longer period
- At end-inspiration:
  - Pressure in units with a shorter time-constant rises more rapidly and if a breath is held will result in redistribution to those units with a longer time-constant.

Clinical Significance

If time-constants are equal:

- The pressure in each unit is identical throughout inspiration and distribution
  Therefore, dynamic compliance will be independent of respiratory rate.

If time-constants are unequal:

- Long-time constant units may still be inhaling whilst the rest of the lung has stopped, or begun exhalation
  This is called **pendelluft**.
- In pendelluft, distribution of inspired gas is dependent on respiratory rate
  - As respiratory rate increases, the proportion of the tidal volume that is delivered to the region with a long time-constant decreases
    Fast alveoli are preferentially inflated, causing V/Q scatter or shunt in the unventilated slow alveoli.

- Dynamic compliance will decrease as respiratory rate rises and be markedly different from static compliance

Footnotes

> 1. For a curve that grows overtime, the time constant is the time it would take for y to reach **63% of its final value**, i.e. $1 - \frac{1}{e}$. ↩

References

1. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.

Last updated 2019-07-18

Resistance

> Explain the relationship between resistance and respiratory gas flow

> Describe the factors affecting airway resistance, and its measurement

Resistance (measured in $cmH_2O.L^{-1}.sec^{-1}$) comprises the energy lost as frictional and inertial impedance to gas flow, where energy is lost as heat. Flow is a function of pressure gradient, resistance, and type of flow.

Types of Flow

Flow can be either laminar or turbulent. In laminar conditions flow is proportional to driving pressure, whilst in turbulent conditions flow is proportional to the square root of driving pressure.

Reynolds' Number

Type of flow can be predicted by **Reynolds's Number**, a dimensionless index where:

$Reynolds'\ Number = \frac{2r.d.v}{\eta}$, where:

- r = Radius
- d = Gas density
- v = Velocity
- η = Gas viscosity

A Reynolds' Number of < 2000 is predominantly laminar flow, whilst >4000 is predominantly turbulent.

Laminar Flow

In laminar flow:

- Gas moves in a series of concentric cylinders which slide over one another
  - Gas in the centre moves **twice as fast** compared to the outside, where it is almost stationary
- Gas appears in cross-section as an **advancing cone**
  Gas may reach the end of the tube when the volume of flow is less than the volume of the tube.
  - This is the mechanism of alveolar ventilation when tidal volumes are less than anatomical dead space volume

In a straight unbranched tube, flow can be quantified by the **Hagen-Poiseuille Equation**:
$F = \frac{\Delta P \pi r^4}{8l.\eta}$, where:

- F = Flow
- ΔP = Driving pressure
- r = Radius
- l = Length
- η = Viscosity

However, as in laminar conditions flow is proportional to the driving pressure and inversely proportional to resistance, flow can be substituted and the equation solved for resistance:

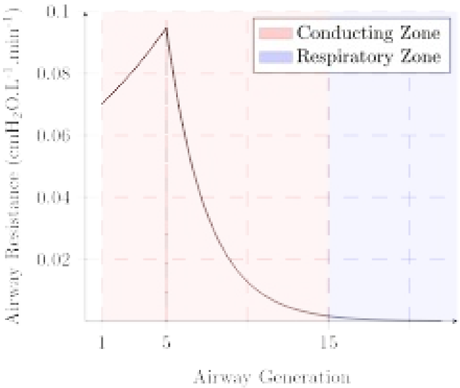
$$Resistance = \frac{8l.\eta}{\pi r^4}$$

This can be used to describe the factors affecting resistance:

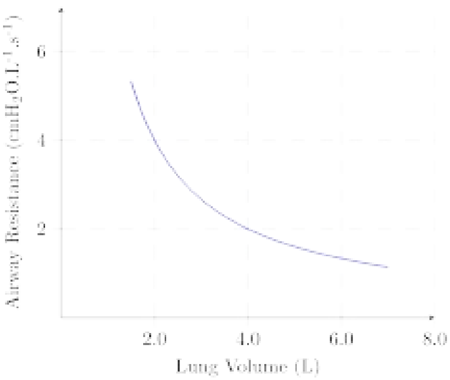
- Length
  Fixed constant.
- Viscosity
  Varies with the particular gas mixture being used.
- Radius
  Main determinant. May be divided into:
  - **Extraluminal factors**
    - Compression:
      - Haemorrhage, tumour, dynamic hyperinflation, atelectasis compressing airways, etc.
    - Lung volume:
      - Airway radius increases when lung volume expands due to radial traction on airways (until dynamic hyperinflation occurs, at which point airways are compressed again)
  - **Luminal constriction**
    Bronchospasm, bronchoconstriction.
  - **Intraluminal obstruction**
    Sputum plugging, aspiration.

Note that airway resistance:

- **Peaks** at the **5$^{\text{th}}$** generation
- Rapidly **decreases** with each airway division thereafter
  This is due to the total cross-sectional area increasing dramatically.



- Reduces with increasing lung volume, as radial tension distends airways, increasing their cross sectional area



Turbulent Flow

High flow rates and branching of airways disrupt disciplined laminar flow. Turbulent flow: is:

- Dominant in the upper airway (where velocity is high)
- Dominant in early-generation airways due to regular branching, changes in diameter, and sharp angles
- Reduces after the **11th generation** bronchioles
- Proportional to the square root of the driving pressure
  Therefore, **resistance is higher in turbulent flow** than in laminar flow.
  - Driving pressure is proportional to gas density, and independent of viscosity

Resistance in turbulent flow is managed by making flow less turbulent:

- Achieved by reducing Reynolds number
  - Helium mixtures reduce gas density
    Of greater benefit in upper airway than lower airway disease.

Transitional Flow

Transitional flow occurs at branches and angles in the airways, as occur in most of the bronchial tree.

References

1. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.

Last updated 2018-04-24

Surfactant

> Describe the properties, production and regulation of, surfactant and relate these to its role in influencing respiratory mechanics

Surface Tension

- Surface tension describes the tendency of a fluid to minimise its surface area
- It is related to the attraction between particles in the fluid relative to particles outside the fluid
- Surface tension is why:
  - Water scattered on a surface forms rounded droplets
  - Why multiple droplets will tend to coalesce into a single larger droplet
- This relationship is described by **La Place's Law**
  $P = \frac{2T}{r}$, where:
  - is pressure
  - is surface tension
  - is radius
- Alveoli obey Laplace's Law
- High surface tension causes three problems with alveoli
  - Compliance falls when the alveolus is empty
    As the radius falls, the pressure required to open it (at a given surface tension) will be increased. This increases work of breathing.
  - Smaller alveoli will preferentially empty into bigger alveoli
    Smaller alveoli require greater transmural pressures to remain inflated. This causes smaller alveoli to empty into larger ones.
  - Fluid transudation
    Surface tension draws fluid from interstitial spaces and contributes to pulmonary oedema.
- Overall, high surface tension is detrimental to the lungs

Surfactant

- Surfactant is a substance which substantially reduces work of breathing by reducing alveolar surface tension
- Surfactant is produced by type II alveolar cells in response to lung inflation and respiration
- It is composed of:
  - 85% phospholipid
  - 5% neutral lipid
  - 10% protein
- Surfactant is **amphipathic**
  Each component has a hydrophobic and hydrophilic end.
  - This causes the molecules to orient themselves along the air-liquid interface, disrupting the attractive bonds between water molecules
  - Surface tension is reduced in proportion to the concentration of molecules
- The concentration of surfactant changes throughout the respiratory cycle
  - During expiration alveoli collapse
    The decrease in alveolar radius is offset by the increase in surfactant concentration, so the fall in radius is mitigated by

the drop in surface tension.

References

1. CICM September/November 2012
2. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.

Last updated 2019-07-18

Volumes and Capacities

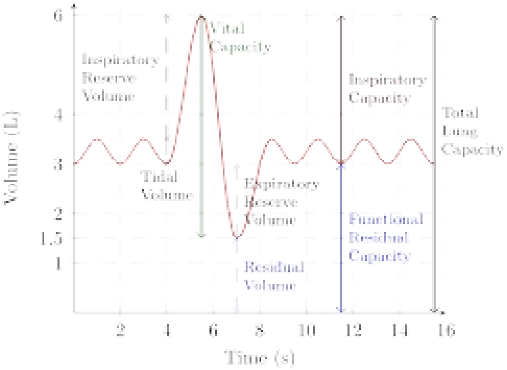
> Explain the measurement of lung volumes and capacities, and factors that influence them

> State the normal values of lung volumes and capacities

> Define closing capacity and its clinical significance and measurement

The lung has four volumes and four (main) capacities:

- A **volume** is measured directly
- A **capacity** is a **sum of volumes**



Volumes

- **Tidal volume** (V_T)
  Volume of air during normal, quiet breathing.
  - Normal is **7ml.kg^{-1}**, or 500ml

- **Inspiratory reserve volume** (IRV)
  Volume of air that can be inspired **above tidal volume**.
  - Normal is 45ml.kg^{-1}, or **2500ml**

- **Expiratory reserve volume** (ERV)
  Volume of air that can be expired following tidal expiration.
  - Normal is 15ml.kg^{-1}, or **1500ml**

- **Residual volume** (RV)
  Volume of air in the lungs following a maximal expiration.
  - Normal is 15-20ml.kg^{-1}, or **1500ml**

Capacities

- **Functional Residual Capacity** (FRC)
  FRC = RV + ERV.
  - Normal is **30ml.kg^{-1}** or 3000ml
  - FRC decreases 20% when supine, and a further 20% under general anaesthesia

- **Vital Capacity** (VC)
  VC = ERV + V_T + IRV.
  - Normal is 4500ml

- **Inspiratory Capacity** (IC)
  IC = V_T + IRV.
  - Normal is 3000ml

- **Total Lung Capacity** (TLC)
  TLC = RV + ERV + V_T + IRV.
  - Normal is 6000ml

Functional Residual Capacity

The FRC has many important physiological functions:

- **Gas exchange**
  The FRC allows blood in the pulmonary circulation to become oxygenated throughout the respiratory cycle (if there was no FRC, then at expiration the lungs would be empty and no oxygenation would occur).

- **Oxygen Reserve**
  FRC is the only clinically modifiable oxygen store in the body, and allows continual oxygenation of blood during apneic periods.

- **Minimise Work of Breathing**
  Work of breathing is a function of lung resistance and compliance.
  - The lung sits on the **steepest** part of the **compliance occurs** at FRC
    Compliance is optimised as:
    - Alveoli are open and minimally distended
      - Below FRC, some alveoli collapse and the volume of lung available to receive the tidal volume decreases
        Re-expansion of collapsed alveoli requires more work than expanding open alveoli.
      - Above FRC, some alveoli will become overdistended and their compliance will fall
  - **Airway resistance decreases** as airway radius increases as lung volume increases

- **Minimise RV Afterload**
  PVR is minimal at FRC.
  - Above FRC, compression of intra-alveolar vessels occurs and PVR increases
  - Below FRC, extra-alveolar vessels collapse and PVR increases

- **Maintain lung volume above closing capacity**
  If closing capacity (see below) exceeds FRC, then shunt will occur.

Factors affecting FRC:

- FRC is reduced by:
  - Supine positioning
    Falls by ~20%.
  - Anaesthesia
    Falls by ~20%.
  - Raised intra-abdominal pressure
  - Impaired lung and chest wall compliance
- FRC is increased by:
  - PEEP
    - Extrinsic
    - Intrinsic (gas trapping)
      - PEEP
  - Emphysema
  - Acute asthma
  - Age

May increase slightly.

Measurement of Lung Volumes and Capacities

- ERV, V_T, and IRV can all be measured directly using spirometry
  - A **spirometer** is a flow meter
    - The patient exhales as fast as possible through the flow meter
    - A flow-time curve is produced
    - This curve can be integrated to find volume
- Any capacity which is a sum of these (IC, VC) can therefore be calculated

- RV **cannot** be measured by spirometry, as it can't be exhaled
  - Therefore FRC and TLC cannot be calculated
- RV can be measured using:
  - Gas dilution
  - Body plethysmography

Gas Dilution

- Gas dilution relies on two principles:
  - Conservation of Mass
  - Helium has poor solubility and will not diffuse into circulation

- **Limitations** of gas dilution:
  - Only gas communicating gas can be measured - will underestimate FRC in gas-trapping

- Method:
  - Patient takes several breaths from a gas mixture containing a known concentration of helium (giving time for equilibration)
  - The concentration of expired helium is then measured

    From the law of conservation of mass:

    $C_1V_1 = C_2V_2$
    - V_2 is equal to the volume of the gas mixture the patient was breathing from (V_1) and the patients FRC
    - Therefore:

      $C_1V_1 = C_2(V_1 + FRC)$

      $FRC = V_1\frac{C_1 - C_2}{C_2}$

Body Plethysmography

- Body plethysmography relies on:
  - Boyle's law

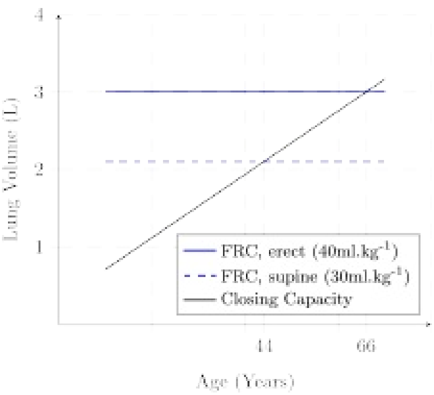
    Pressure and volume are inversely proportional at a constant temperature, i.e. ($P \times V = k$).

- Method:
  - Patient is placed in a closed box, with a mouthpiece that exits the box
  - The patient inhales against a closed mouthpiece:
    - When the patient inhales, the volume of gas in the box decreases (the patient takes up more space) and therefore the pressure increases
    - The change in volume of the box is given by:

- $P_1V_1 = P_2V_2$, where:
  - V_2 is the change in box volume, or $V_1 - \Delta V$
  - Therefore:
    $$P_1V_1 = P_2(V_1 - \Delta V)$$
    As ΔV is the only unknown value, it can be calculated.
- The change in volume of the lung must be the same as the volume of the box (ΔV)
  - In the case of the lung, the initial volume (V_1) is FRC
  - Therefore:
    $$P_1 \times FRC = P_2(FRC + \Delta V)$$
    $$FRC = \frac{P_2\Delta V}{P_3 - P_4}$$

Closing Capacity

- Closing capacity is **volume at which small airways begin to close**
  Closing capacity is the sum of residual volume and closing volume.
  - Because dependent lung is compressed by gravity, dependent (typically basal) airways are of smaller calibre than non-dependent (typically apical) airways
  - During expiration, these airways are compressed first
    Alveoli connected to these airways are isolated, and **V/Q scatter or shunt** occurs.
  - If **closing capacity exceeds FRC**, then airway closure occurs during normal tidal breathing
    This occurs when:
    - FRC is decreased
    - CC is increased
      - Increases with age
        - CC exceeds FRC in the supine patient at 44
        - CC exceeds FRC in the erect patient at 66
  - This is clinically relevant during **preoxygenation**, as it will limit the denitrogenation that can occur



Measurement of Closing Capacity

Closing capacity is measured using Fowler's Method, and is covered under Dead Space.

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

Last updated 2019-07-18

Spirometry

> Describe the pressure and flow-volume relationships of the lung, chest wall and the total respiratory system

> Describe the measurement and interpretation of pulmonary function tests, including diffusion capacity.

Pulmonary function tests are performed with a **spirometer**, which measures either volume or flow (integrated for time) to quantify lung function.

Basic spirometry can be used to quantify:

- Lung volumes and capacities
  All except residual volume (and therefore FRC and TLC).
- Dynamic measurements
  - FEV_1
    Volume of air forcibly exhaled in one second.
  - FVC
    Forced vital capacity.
  - PEFR
    Peak expiratory flow rate.
  - Flow-volume loop

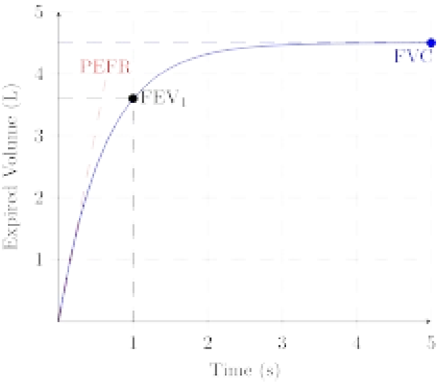
Additional testing can be performed to measure:

- Residual volume
  FRC and TLC can therefore be calculated.
- Diffusion capacity

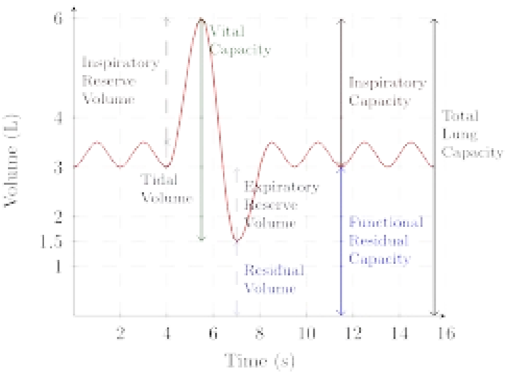
Basic Spirometry

Basic spirometry includes:

- Forced spirometry
  Patient forcibly exhales a vital capacity breath, producing a exponential (wash-in) curve. This calculates:
  - PEFR from the gradient at time 0 (assuming maximal effort)
  - FEV_1 is the volume expired in 1s
    Normal is > 80% of predicted.
  - FVC is the total volume exhaled.
  - The FEV_1/FVC ratio
    Normal is > 0.7.
  - These values also quantify disease severity:
    - In obstructive airways disease:
      - FEV_1 <80% predicted
      - FEV_1/FVC ratio
    - Restrictive disease:
      - FEV_1 <80% predicted
      - FVC
      - FEV/FVC ratio >0.7
        The ratio is normal as the FEV_1 and FVC fall proportionally.

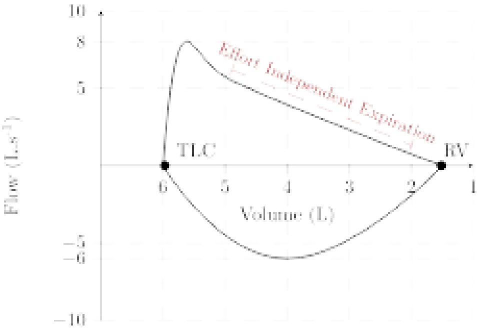


- Volume-Time Graph (also known as a spirograph or spirogram)
  Quantifies static lung volumes by having a patient perform:
  - Normal tidal breathing
  - Vital capacity breath
  - Vital capacity exhalation

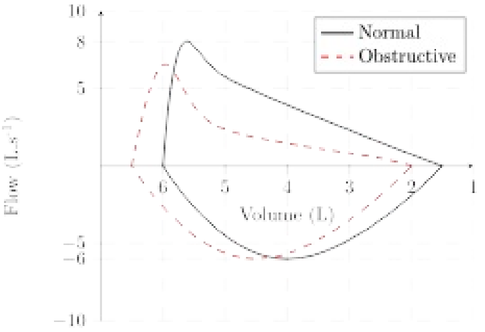


Flow-Volume Loops

- **Normal**
  - Peak expiratory flow of **~8L.s^{-1}**
    Initial flow is highest as the increased lung volume **increases the calibre** of lung airways, reducing airways resistance.
    - This is called the **effort dependent** part of the curve
  - Flow tails off later in expiration
    - Lungs collapse, and airway calibre falls
    - Small airways are compressed
      Any increase in expiratory pressure will increase airway resistance proportionally.
      - This is called **dynamic airways compression**, and results in a uniform flow rate that is **independent of expiratory effort***
        This is therefore labeled the effort independent** part of the curve.

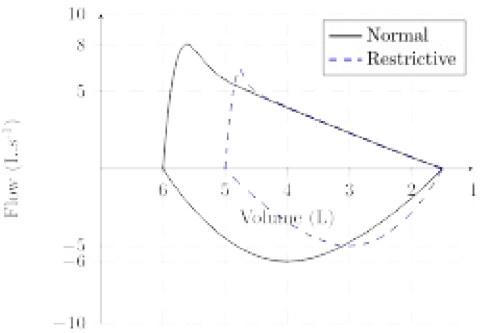


- **Obstructive lung disease**
  - RV and TLC are increased due to gas trapping
  - Peak flow is limited
  - Effort-independent portion becomes concave



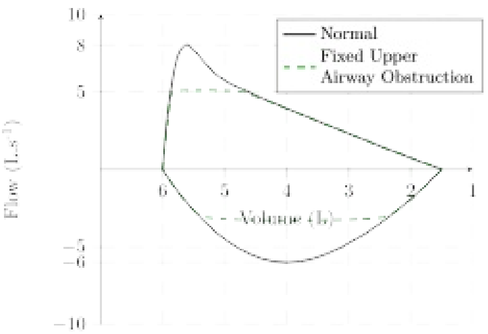
- **Restrictive lung disease**
  - TLC is reduced, but residual volume is unchanged
  - Peak flow may be reduced (as seen here)

    However, this reduction is **proportional** to the decrease in volume, such that the FEV_1:FVC ratio is normal. If peak flow is preserved, the FEV_1:FVC ratio will be increased.
  - Effort independent part is linear



- **Fixed upper airway obstruction**

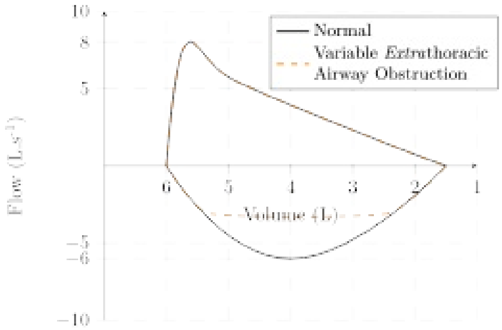
  Describes an upper airway obstruction that does not change calibre during the respiratory cycle.
  - Peak inspiratory and expiratory flow rates are limited by the stenosis



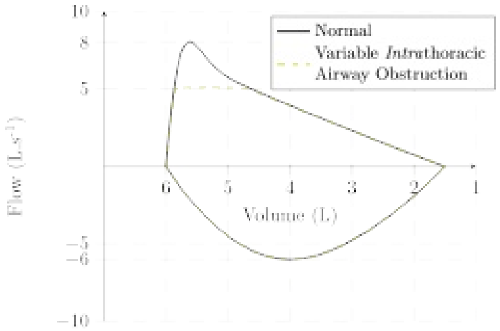
- **Variable *extrathoracic* obstruction**

  Variable as the obstruction changes during the respiratory cycle:
  - During (negative pressure) inspiration the lesion is pulled into trachea, reducing inspiratory flow
  - During expiration the lesion is pushed out of the trachea

    The way to remember this is an **extra**thoracic obstruction impedes **in**spiration
  - The reverse effect occurs in positive pressure ventilation



- **Variable *intrathoracic* obstruction**
  The opposite to extrathoracic obstruction.
  - During inspiration the airway calibre increases and inspiratory flow is unimpeded
  - During expiration the airway calibre falls and expiratory flow is reduced



References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Work of Breathing

> Describe the work of breathing and its components

Work of breathing is the energy used by the muscles for respiration. It is defined as:
$Work = Pressure \times Volume$, measured in Joules.

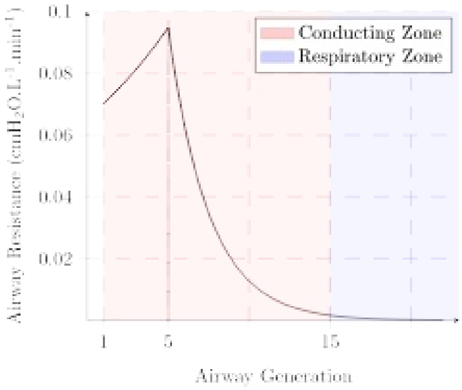
- This gives the work for a single respiratory cycle
  Energy expenditure over time is better described as the "power of breathing".
- It does not take into account **respiratory rate** or **flow rate**
  These factors have a significant effect on energy requirement.
  - This would be given by the **rate of work**, or **power**, where:
    $Power = \frac{Work}{Time}$, measured in Watts.
  - Tidal breathing is efficient and uses < 2% of BMR
- The oxygen requirement of breathing at rest is ~2-5% of VO_2, or ~3ml.min^{-1}

Determinants of Work of Breathing

Work of breathing is divided into:

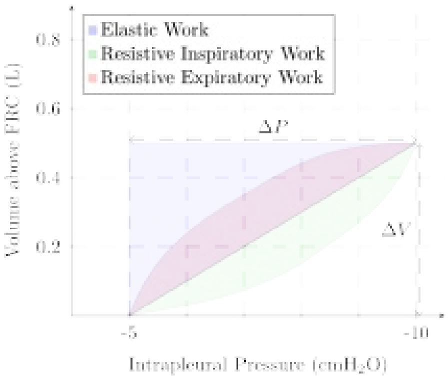
- **Elastic work**
  About 65% of total work, and is stored as elastic potential energy. Energy required to overcome elastic forces:
  - Lung elastic recoil
  - Surface tension of alveoli
- **Resistive work**
  About 35% of total work, and is lost as heat. This is due to the energy required to overcome frictional forces:
  - Between tissues
    - Increased with increased interstitial lung tissue
  - Between gas molecules
    - Increased at high flow rates
    - Increased with turbulent flow
      - High respiratory rates
      - Upper airway obstruction
      - Increased airway density
        - Hyperbaric
        - Diving
    - Increased with decreased airway radius
      - Low lung volume
        - Inadequate PEEP
        - Decreased respiratory muscle tone
      - Bronchoconstriction
      - Dynamic airway compression
        Effort-independent expiration.
      - Apparatus
        - Endotracheal Tube
        - HME filters
      - Airway resistance varies depending on airway division:
        - Resistance peaks at the 3rd airway division (lobar bronchi)

- Falls with increasing airway divisions due to increased cross-sectional area



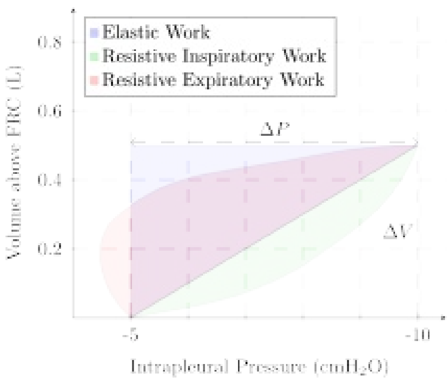
Graphing Work of Breathing

Work of breathing can be evaluated with a dynamic lung compliance curve:



- If there **were no resistive forces**, then this curve would be a straight line
  - The triangular area is the elastic work done
- The resistive work of breathing causes the deviation of the inspiratory and expiratory lines:
  - The area between the compliance line and the inspiratory line is additional **resistive inspiratory** work done
  - The area between the compliance line and expiratory line is additional **resistive expiratory** work done
    - This work is typically done by elastic recoil of the lungs
    - If this area falls within the area of elastic work of breathing, it is a purely passive process, using the stored elastic potential energy of inspiration
    - If part of this area falls outside the area of elastic work of breathing, it demonstrates additional **active work of expiration** which may occur in obstructive lung disease or when minute ventilation is high

Active expiratory work:



Minimising Work of Breathing

Work of breathing can be minimised by optimising the determinants:

- Elastic work
  - PEEP
    Keep lung volume at FRC and maximise number of ventilated alveoli.
  - Positioning
    Optimise lung volume.
  - Surfactant
    Minimising surface tension.
  - Optimise respiratory rate
    Elastic work of breathing typically decreases with increased respiratory rate.
- Resistive work
  - Decrease respiratory rate
    Respiratory rate is directly proportional to resistive work.
  - Increase laminar flow
    Laminar flow is more efficient than turbulent flow. Laminar flow can be increased by:
    - Reducing gas density
      Heliox.
  - Increase Radius
    - Increase lung volume
    - Bronchodilators

Derivation

Work is defined as:
$W = FD$, where:

- W = Work in Joules
- F = Force in Newtons
- D = Distance in Metres

Additionally, pressure is defined as:
$P = \frac{F}{A}$, where:

- P = Pressure in Pascal
- A = Area in Meters squared

Therefore:
$F = PA$

Substituting:
$W = PAD$
$W = PV$, where:

- V = Volume

Therefore:
$Work = Pressure \times Volume$

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
2. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.

Last updated 2019-07-18

Oxygen Cascade

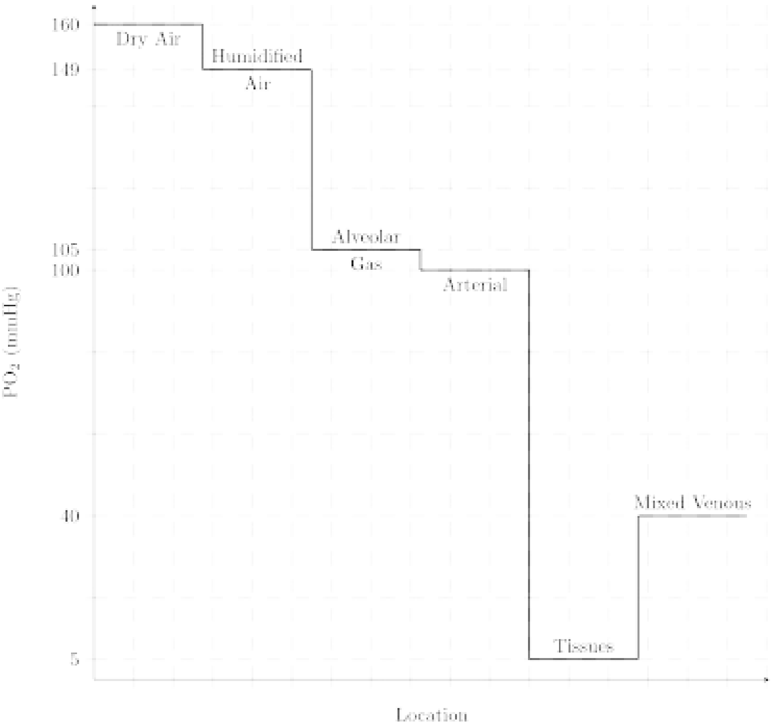
> Describe and explain the oxygen cascade

The **oxygen cascade** describes the transfer of oxygen from air to mitochondria.

- In each step of the cascade the PaO_2 falls
  It demonstrates that oxygen delivery to tissues relies on the **passive transfer** of gas down **partial pressure gradients**.
- The steps of the cascade are:
  - Dry atmospheric gas
  - Humidified tracheal gas
  - Alveolar gas
  - Arterial blood
  - Mitochondria
  - Venous blood

Remember:

- **Partial pressure** determines rate and extent of gas transfer
- Oxygen **content** is what is important for cellular function



Atmospheric Gas

Atmospheric partial pressure of oxygen is a function of barometric pressure and the FiO_2:

- $PO_2 = P_B \times FiO_2$, where:
  - is 760mmHg
  - is 0.21
- Therefore, PO_2 = **160mmHg**

Humidified Tracheal Gas

- Gas is humidified during inspiration
- Gas in the proximal trachea is **heated to 37°C** and has **100% relative humidity**
- The **saturated vapour pressure** of water at 37°C is **47mmHg**
- Therefore:
  $PO_2 = (P_B - P_{SVP\ of\ Water}) \times FiO_2$, where:
  - and FiO_2 are as above
  - is **149mmHg**

Alveolar Gas

Ideal alveolar PO$_2$ is calculated using the **alveolar gas equation**:

$P_AO_2 = P_iO_2 - \frac{P_aCO_2}{R} + F$, where:

- P_AO_2 is the alveolar partial pressure of oxygen
- P_iO_2 is the inspired partial pressure of oxygen
- P_aCO_2 is the arterial partial pressure of carbon dioxide
- R is the respiratory quotient, where $R = \frac{Volume\ of\ CO_2\ produced}{Volume\ of\ O_2\ consumed}$
  - R is used in the alveolar gas equation to correct for the change in inspired relative to expired volume
    As generally less CO$_2$ is produced than O$_2$ consumed, expired volumes are typically less than inspired volumes
  - R is dependent on the metabolic substrates used for metabolism:
    - Pure fat ≈ 0.7
    - Pure protein ≈ 0.9
    - Pure carbohydrate ≈ 1
    - The normal value for a Western diet is quoted as **0.8**
- F is a correction factor, usually equal to ~2mmHg, and is given by $F = P_ACO_2 . FiO_2 . \frac{1-R}{R}$

Alveolar oxygen is therefore dependent on:

- PiO$_2$, which is a function of:
  - FiO$_2$
  - Air pressure
- Alveolar ventilation
  As $P_aO_2 \propto \frac{1}{\dot{V}_A}$.

Arterial Blood

The difference in partial pressure of oxygen between alveolar and arterial blood is called the **A-a gradient**:

$$A - a\ gradient = PAO_2 - PaO_2 = PiO_2 - \frac{PaCO_2}{R} - PaO_2$$

- A normal A-a gradient is $\frac{Age}{4} + 4$

- Normal arterial PO_2 is 100mmHg
- It occurs due to:
  - Shunt/VQ scatter
    A small shunt is normal due to blood from the bronchial circulation and thebesian veins.
  - Diffusion abnormality

Mitochondria

- PO_2 varies with metabolic activity, but typically quoted as 5mmHg
- The **Pasteur point** is the partial pressure of oxygen at which oxidative phosphorylation ceases, and is **~1mmHg**

Venous Blood

- PO_2 is greater than mitochondrial PO_2
  Mixed venous blood typically quoted as 40mmHg.
- Higher than mitochondria as not all arterial blood travels through capillary beds

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References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
2. Brandis K. The Physiology Viva: Questions & Answers. 2003.

Last updated 2019-07-18

Diffusing Capacity and Limitation

> Explain perfusion-limited and diffusion-limited transfer of gases

> Define diffusing capacity and its measurement

> Describe the physiological factors that alter diffusing capacity

Rate of diffusion of gases is given by **Fick's Law**:
$Rate\ of\ Diffusion = \frac{\Delta P \times A \times s}{T \times \sqrt{MW}}$, where:

- ΔP is the pressure gradient across the membrane
- A is the area of the membrane
- s is the solubility of the substance
- T is the thickness of the membrane
- MW is the molecular weight of the substance

These can be divided into pressure, lung factors, and substance factors:

- **Pressure gradient**
  In the lung, this is a function of:
  - Partial pressure of the gas in the alveolus
    This is affected by:
    - Atmospheric pressure
    - Ventilation
      Alveolar hypoventilation will:
      - Increase $PACO_2$
      - Decrease PAO_2
  - Partial pressure of the gas in blood
    This is affected by:
    - Solubility of the gas in blood
      CO_2 is **~20** times as soluble as O_2 in blood.
    - Binding of gas to protein:
      - Particularly **haemoglobin**
        Affects the rate of uptake of O_2 and CO, and is why calculated DL_{CO} is corrected for haemoglobin.
        - The shape of the oxy-haemoglobin dissociation curve allows a large volume of oxygen to be bound before PaO_2 begins to rise substantially.
      - Formation of carbamino compounds
      - Anaesthetic agents to plasma contents
        e.g. albumin, cholesterol.

- **Lung factors**
  - Surface Area
    Affected by:
    - Parenchyma volume
      - Body size
      - Pathology
        Many lung diseases will reduce surface area for gas exchange.
    - V/Q mismatch
      Both shunt and dead space reduce the surface area available for gas exchange.

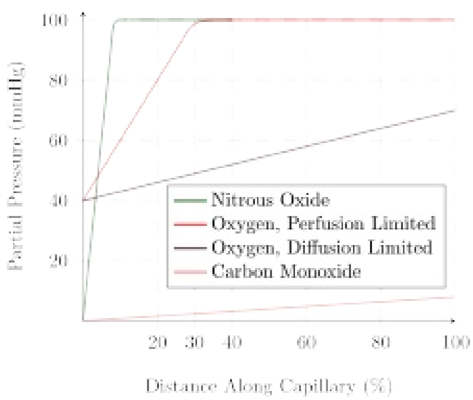
        - Pulmonary blood volume
          Vascular distension and recruitment also affects surface area. Factors affecting pulmonary blood volume include:
            - Cardiac output
                - Increased recruitment of vasculature in high output states
                - Decreased recruitment and increased V/Q mismatch in shock states.
            - Posture
              Increased surface area when supine relative to sitting or standing.
    - Thickness
      Increasing alveolar-capillary membrane thickness impedes gas exchange. Causes of this include:
        - Pathology
          e.g. Pulmonary oedema and cardiac failure.

- **Substance factors**
    - Solubility
      More soluble substances will diffuse more quickly.
    - Molecular weight
      Smaller substances will diffuse more quickly.

Diffusion and Perfusion Limitation

Limitation refers to what process limits gas uptake into blood:

- Gases which are **diffusion limited** fail to equilibrate, i.e. the partial pressure of a substance in the alveolus does not equal that in the pulmonary capillary
    - e.g. Carbon Monoxide
- Gases which are **perfusion limited** have equal alveolar and pulmonary capillary partial pressures, so the amount of gas *content* transferred is dependent on blood flow
    - e.g. Oxygen



Oxygen

- Oxygen diffusion takes **~0.25s**
- Pulmonary capillary transit time is **0.75s**
- Therefore, under normal conditions oxygen is a **perfusion limited** gas
- However, **oxygen may become diffusion limited** in certain circumstances:
    - **Alveolar-capillary barrier** disease
      Decreases the rate of diffusion.
        - Decreased surface area
        - Increased thickness
    - **High cardiac output**

    Decreases pulmonary transit time.
  - **Altitude**
    Decreases PAO_2.

Carbon Dioxide

- Carbon dioxide is ventilation limited, rather than diffusion or perfusion limited
- This is because it is:
  - 20x more soluble in blood than oxygen
  - Rapidly produced from bicarbonate and carbamino compounds
  - Present in far greater amounts than oxygen
    $1.8L.kg^{-1}$ exist in the body (though $1.6L^{-1}$ of this are in bone and other relatively inaccessible compartments).
- Impairment of diffusion capacity causes type 1 respiratory failure as oxygen is affected to a much greater extent than carbon dioxide

Other Gases

- **Carbon monoxide**
  Diffusion limited due to:
  - High affinity for haemoglobin
    Continual uptake into Hb results in a low partial pressures in blood.

- **Nitrous oxide** Perfusion limited as equilibrium between alveolus and blood is rapidly reached as it is:
  - Not bound to haemoglobin
  - Relatively insoluble

Diffusion Capacity

- Measurement of the ability of the lung to transfer gases
- Measured as DL_{CO} or diffusing capacity of the lung for carbon monoxide
  Carbon monoxide is used as it is a diffusion limited gas.
- Process:
  - Vital capacity breath of 0.3% CO
  - Held for 10s and exhaled
  - Inspired and expired CO are measured
  - Difference is the amount of CO which is now bound to Hb
  - DL_{CO} is corrected for:
    - Age
    - Sex
    - Hb
- DL_{CO} is decreased in:
  - Thickened alveolar-capillary barrier
    - Interstitial lung disease
  - Reduced surface area
    - Emphysema
    - PE
    - Lobectomy/pneumonectomy
- DL_{CO} is increased in:
  - Exercise
    Recruitment and capillary distension.
  - Alveolar haemorrhage

Hb present within the lung binds CO.
- Asthma (may be normal)
  Potentially due to increased apical blood flow.
- Obesity (may be normal)
  Potentially due to increased cardiac output.

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1. Brandis K. The Physiology Viva: Questions & Answers. 2003.
2. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.
3. ANZCA March/April 1999
4. Deranged Physiology - Carbon Dioxide Storage and Transport

Last updated 2017-10-04

West's Zones

> Describe West's zones of the lung and explain the mechanisms responsible for them

West's Zones take into account the effect of alveolar pressure on pulmonary blood flow. The lung is divided into **four zones**:

- **West Zone 1: $P_A > P_a > P_v$**
  Alveolar pressure exceeds arterial pressure.
  - The alveolus compresses the capillary, and no blood flow occurs
  - As there is ventilation but no perfusion, this can also be thought of as **dead space**
  - This occurs when:
    - Alveolar pressure is high
      - PEEP
    - Arterial pressure is low
      - Shock
        - Hypovolaemia

- **West Zone 2: $P_a > P_A > P_v$**
  Arterial pressure exceeds alveolar pressure, which exceeds venous pressure.
  - Blood flow occurs **intermittently** during the cardiac cycle
  - Alveolar pressure acts as a **Starling resistor**
    Flow is proportional to the P_a - P_A gradient.
    - When P_a falls below P_A (e.g. in diastole), then no blood flow will occur

- **West Zone 3: $P_a > P_v > P_A$**
  Arterial pressure exceeds venous pressure which exceeds alveolar pressure.
  - Blood flow occurs throughout the cardiac cycle
    Flow is proportional to the P_a - P_v gradient.
  - For an accurate measure of PCWP, a PAC must be placed in West Zone 3 (so there is a continual column of blood)
  - This tends to happen naturally as the majority of pulmonary flow is to this region

- **West Zone 4: $P_a > P_i > P_v > P_A$**
  Interstitial pressure acts as a Starling resistor for pulmonary blood flow.
  - It is seen when interstitial pressure is high (e.g due to pulmonary oedema).

References

1. Brandis K. The Physiology Viva: Questions & Answers. 2003.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Basics of V/Q Matching

Optimal gas exchange occurs when regions of lung are ventilated in proportion to their perfusion, i.e. V/Q = 1

- Uneven distribution of ventilation and perfusion causes inefficient gas exchange:
  - Excessive ventilation causes excessive work
  - Inadequate ventilation causes inadequate gas exchange

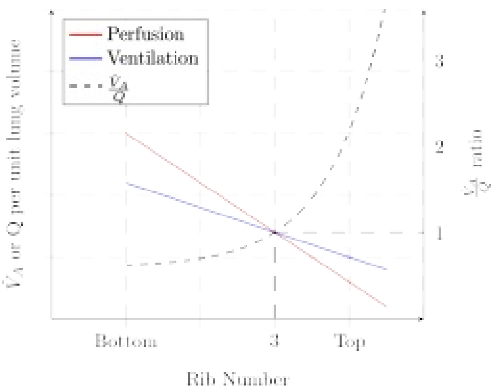
Distribution of Ventilation

- The right lung is slightly better ventilated than the left
- In an erect patient the bases of the lung are better ventilated
  The weight of lung above compresses the lung below, improving the compliance of dependent lung whilst stretching the non-dependent lung.
  - This is only significant at low inspiratory flow rates
  - The V/Q ratio in the bases is ~0.6
  - The V/Q ratio in the apices is >3
- In a lateral position:
  - The dependent lung is better ventilated in a spontaneously breathing patient
  - The non-dependent lung is better ventilated in a ventilated patient

Distribution of Perfusion

- The pulmonary circulation is a low pressure circulation
- Gravity therefore has a substantial effect on fluid pressure
- Consequently, the distribution of blood throughout the lungs is uneven:
  - The **bases perfused better than the apices**
    This is affected by lung volume, with the effect:
    - Becoming more pronounced at TLC (with apical perfusion falling precipitously)
    - Reversing slightly at RV

V/Q Ratios



- The global V/Q ratio for normal resting lung is **0.9**
- The global V/Q ratio improves to 1.0 during exercise

V/Q Mismatch and Etymology

- V/Q mismatch occurs when V/Q ≠ 1:
  - **V/Q >1** (Dead Space)
    Ventilation in excess of perfusion.
    - However, pulmonary blood is passing ventilated alveoli and PaO_2 is normal

  - **V/Q 0 to 1** (V/Q scatter)
    Perfusion in excess of ventilation.
    - Increasing in PAO_2 will increase PaO_2
    - This is commonly referred to by the general term of V/Q mismatch

  - **V/Q = 0** (Shunt)
    Mixed venous blood entering the systemic circulation without being oxygenated via passage through the lungs. PaO_2 falls.

References

1. West J. Respiratory Physiology: The Essentials. 9th Edition. Lippincott Williams and Wilkins. 2011.
2. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.

Last updated 2017-10-04

Dead Space

Dead space is the proportion of minute ventilation which does not participate in gas exchange.

Types of Dead Space

Dead space can be divided into:

- **Apparatus dead space**
  Dead space from equipment, such as tubes ventilator circuitry. Some apparatus dead space may actually *reduce* total dead space, as an ETT bypasses the majority of anatomical dead space of the patient (nasopharynx).
- **Physiological dead space**
  Dead space from the patient. Physiological dead space is divided into:
  - **Anatomical dead space**
    The volume of the conducting zone of the lung. Anatomical dead space is affected by:
    - Size and Age
      3.3ml.kg^{-1} in the infant, falls to 2.2ml.kg^{-1} in the adult
    - Posture
      Decreases when supine.
    - Position of the neck and jaw
      Increased with neck extension.
    - Lung volumes
      Increases by ~20ml per litre of additional lung volume.
    - Airway calibre
      Bronchodilation increases airway diameter and therefore V_D.
  - **Pathological/Alveolar Dead Space**
    Dead space caused by disease. Causes of pathological dead space include:
    - Erect posture
    - Decreased pulmonary artery pressure/impaired pulmonary blood flow
      - Hypovolaemia
      - RV failure/Increased RV afterload:
        - HPV
        - MI
      - PE
    - Increased alveolar pressure
      Increases West Zone 1 physiology.
      - PEEP
    - COAD

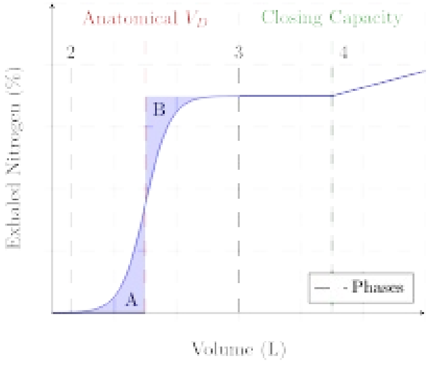
Calculation of Dead Space

Two methods exist to allow dead space volumes to be calculated:

- Physiological dead space may be measured with **Bohr's method**
- Anatomical dead space may be measured by **Fowler's method**
- Pathological dead space may be calculated by subtracting anatomical dead space (Fowler's method) from physiological dead space (Bohr's Method)

Fowler's Method

Fowler's Method is a **single-breath nitrogen washout test**, used to calculate **anatomical dead space** and **closing capacity**.



Method:

- At the end of a normal tidal breath (at FRC) a **vital-capacity breath of 100% oxygen** is taken
- The patient then exhales to RV
  Expired nitrogen concentration and volume is measured.
- A plot of expired nitrogen concentration by volume is generated, producing a graph with four phases:
  - Phase 1 (Pure Dead Space)
    Gas from the anatomical dead space is expired. This contains 100% oxygen - no nitrogen is present.
  - Phase 2
    A mix of anatomical dead space and alveolar (lung units with short time constants) is expired. The midpoint of phase 2 (when area A = area B) is the volume of the **anatomical dead space**.
  - Phase 3
    Expired nitrogen reaches a plateau as just alveolar gas is exhaled (lung units with variable time constants).
  - Phase 4
    Sudden increase in nitrogen concentration, which indicates **closing capacity**. This increase occurs because:
    - Basal alveoli are more compliant than apical alveoli
    - Therefore, during inspiration basal alveoli inflate more than apical alveoli
      The single 100% oxygen breath therefore preferentially inflates the basal alveoli. At the end of the vital capacity breath, the oxygen concentration in basal alveoli is greater than that of apical alveoli.
    - In expiration, the process is reversed:
      - Basal alveoli preferentially exhale
      - At closing capacity, small basal airways close and now only apical alveoli (with a higher concentration of nitrogen) can exhale
      - Measured expired nitrogen concentration increases

Bohr's Method

Physiological dead space is measured using the Bohr equation. This calculates dead space as a ratio, or proportion of tidal volume:

$$\frac{V_D}{V_T} = \frac{V_T - V_A}{V_T}$$

The Bohr equation is based on the principle that **all CO_2 exhaled must come from ventilated alveoli**.

$$\frac{V_D}{V_T} = \frac{PA_{CO_2} - P\bar{E}_{CO_2}}{PA_{CO_2}}$$

Note that:

- $P\bar{E}_{CO_2}$ is the mixed-expired carbon dioxide
  Partial pressure of CO_2 in an expired tidal breath.
- The Bohr equation requires alveolar PCO_2 to be measured
  As this is impractical, the **Enghoff modification** is typically used, which assumes that $PACO_2 \approx PaCO_2$. The equation then becomes:
  $$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}$$
- A **normal** value for physiological dead space during normal tidal breathing is **0.2-0.35**

Physiological Consequences of Increased Dead Space

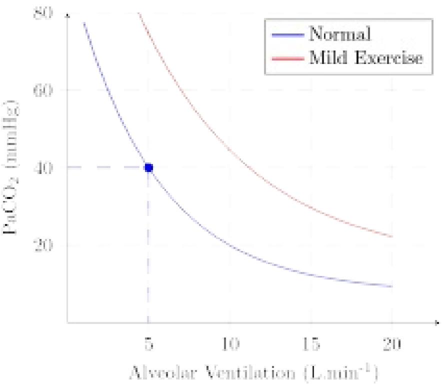
In dead space:

- The V/Q ratio approaches infinity as alveolar **perfusion** falls
- This results in a rise in $PaCO_2$
- In a spontaneously-ventilating individual, this stimulates the respiratory centre to increase minute ventilation to return alveolar ventilation (and therefore CO_2) to normal
- There is minimal effect on PaO_2, as in pure dead space all blood is passing through ventilated alveoli and therefore undergoes gas exchange

Relationship between Alveolar Ventilation and $PaCO_2$

Atmospheric air contains negligible CO_2. As MV increases, $PaCO_2$ will fall, as will the gradient for further CO_2 diffusion. This can be expressed by the equation:

$$PaCO_2 \propto \frac{1}{\dot{V}_A}$$



Note that this graph:

- Describes the change in $PaCO_2$ for a change in alveolar ventilation
  A doubling of alveolar ventilation will halve $PaCO_2$.
- Does not describe the change in ventilatory drive for a given change in $PaCO_2$
  This is covered under removal of CO_2.

Footnotes

Note that West Zone 1 (where PA > Pa > Pv) physiology is increased dead space.

The $PaCO_2$-$ETCO_2$ difference is a consequence of dead space, as dead space gas dilutes alveolar gas.

References

1. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.
2. West J. Respiratory Physiology: The Essentials. 9th Edition. Lippincott Williams and Wilkins. 2011.

Last updated 2019-07-18

Shunt

> Explain the concept of shunt and its measurement

Shunt is blood reaching the systemic circulation without being oxygenated via passage through the lungs.

Factors Contributing to Shunt

- Normal shunt
  - Anatomical shunt
    - Thebesian veins, which drain directly into the left cardiac chambers
    - Bronchial circulations, which drain into the pulmonary veins
  - Functional shunt
    Blood draining through alveoli with a V/Q between 0 and 1.
    - This may not be true shunt, as blood may have some oxygen content but not be maximally oxygenated
- Pathological shunt
  Pathological shunting can be anatomical (e.g congenital cardiac malformations), or physiological (e.g. pneumonia causing alveolar consolidation).
  - Intra-cardiac e.g. VSD
  - Extra-cardiac
    e.g. Pulmonary AVM, PDA

Calculation of Shunt

- Shunt cannot be directly measured
- This is because we cannot separate true shunt (V = 0) from V/Q scatter (V/Q < 1) when sampling blood entering the left heart
- **Venous admixture** is used instead
  Venous admixture is **the amount of mixed venous blood that must be added to pulmonary end-capillary blood to give the observed arterial oxygen *content***. Venous admixture:
  - Is a calculated, theoretical value
  - Assumes that alveoli have either complete shunt (no ventilation at all, i.e. V/Q = 0) or no shunt (V/Q = 1)
  - Is expressed as a ratio, or **shunt fraction**:
    $\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$, where:
    - $\dot{Q}_S$ = Shunt blood flow
    - $\dot{Q}_T$ = Cardiac output
    - C_cO_2 = Pulmonary end-capillary oxygen content, assumed to have an oxygen tension equal to PAO_2 (with the corresponding oxygen saturation)
    - C_aO_2 = Arterial oxygen content
    - C_vO_2 = Mixed venous oxygen content

Physiological Consequences of Shunt

Effect on Carbon Dioxide

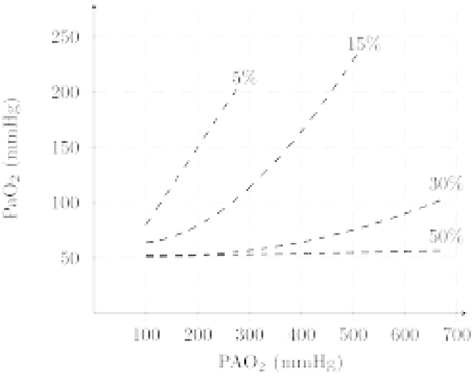
- No CO_2 can diffuse from shunted blood
- Therefore $PaCO_2$ might be expected to rise, however:
    - In a spontaneously breathing patient the increased $PaCO_2$ increases respiratory drive, and alveolar ventilation increases
        - Therefore, **shunt does not tend to increase $PaCO_2$** unless:
            - The shunt fraction is large and
            - The patient is unable to increase their alveolar ventilation to compensate
    - Additionally, the steepness of the CO_2 dissociation curve at the arterial point means that although CO_2 *content* increases, the increase in $PaCO_2$ is small

Effect on Oxygen

- **PaO_2 falls proportionally to shunt fraction**
- As shunted alveoli are perfused but not ventilated, **true shunt** is said to be **unresponsive to an increase in FiO_2**
  This is where technical definitions become important to avoid confusion.
    - For an alveoli with a V/Q between 0-1 (V/Q mismatch or V/Q scatter, but not true shunt):
        - There is perfusion, but *relatively less* ventilation
        - Therefore blood passing through this alveoli will be *partially* oxygenated
        - Increasing PAO_2 will improve oxygenation (assuming no diffusion limitation):
            - Administration of supplemental oxygen
            - Hyperventilation
            - As per the alveolar gas equation
    - For an alveoli with a V/Q of 0 (true shunt)
      There is no ventilation. Regardless of the increase in PAO_2, PaO_2 will not improve.

The Isoshunt Diagram

- Isoshunt diagram plots the relationship between FiO_2 and PaO_2 against a set of 'virtual shunt lines'
- These 'shunt fractions' are calculated from the above equation and so are actually V/Q admixture fractions



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3. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Oxygen Storage

> Describe the oxygen ~~and carbon dioxide~~ stores in the body

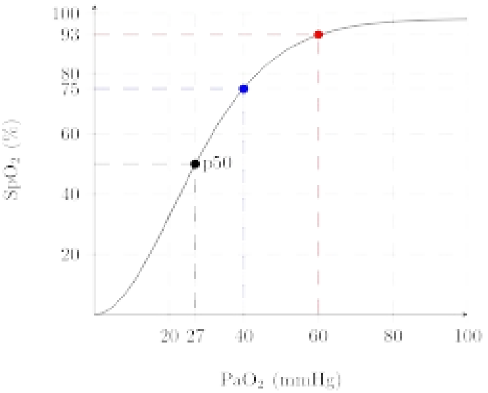
The standard textbook 70kg male contains **~1.5L** of oxygen, split between:

- ~850ml in blood
  There is 20.4ml of oxygen per 100ml of blood, divided up as:
  - 20.1ml bound to haemoglobin
  - 0.3ml dissolved
- ~250ml bound to myoglobin
- ~450ml contained in FRC (21% of 2.4L)
  This is why preoxygenation increases safe apnoea times, as the nitrogen washout increases the volume of oxygen stored.

Oxygen-Haemoglobin Dissociation Curve

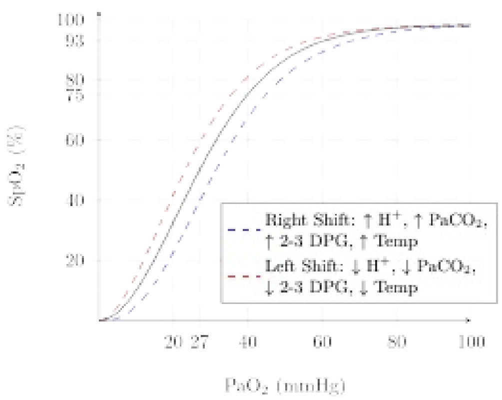
The sigmoid shape of the oxygen-haemoglobin dissociation curve offers many physiological advantages:

- Buffering in case of low PaO_2
  The plateau allows oxygen **content** to remain high, even if the PaO_2 falls
- Maintenance of diffusion gradient to tissues
  The steep section allows a large amount of oxygen to be delivered with only a small drop in PaO_2, which allows the rate of oxygen delivery to be maintained (as the blood-tissue partial pressure gradient is steep) with an increase in oxygen demand.



- The sigmoid shape exists due to **cooperative binding**
  Each oxygen which binds to Hb causes conformational changes which allow it bind additional oxygen molecules more easily.
  - When the fourth oxygen molecule has bound, Hb is said to be in the **relaxed conformation** (R state)
  - When no oxygen is bound, Hb is said to be in the **tense state** (T state)

- The curve can be right or left-shifted by changes in temperature, pH, CO_2, and 2-3 DPG



- Note that the **mixed venous point is not on the arterial curve** (unlike how it is displayed above), as the venous dissociation curve is right-shifted relative to the arterial curve

Haemoglobin Species

Haemoglobin is a four-tetramer molecule, and its species can be physiological or pathological:

- **Physiological**
  - **HbA**
    - Most common
    - 2 alpha and 2 beta subunits ($\alpha_2\beta_2$)
  - **HbA$_2$**
    - Less common
    - 2 alpha and 2 delta subunits ($\alpha_2\delta_2$)
  - **HbF**
    - Foetal Hb
    - Higher affinity for oxygen due to lack of 2,3-DPG
    - 2 alpha and 2 gamma subunits ($\alpha_2\gamma_2$)

- **Pathological**
  - **HbS**
    Sickle-cell disease.
    - Abnormal beta subunit
    - Unable to deform as they pass through capillaries
      - Increases blood viscosity, thrombus, and ischaemia through capillary occlusion
        - Often causes splenic infarction
      - Reduced red cell lifespan to 10-20 days

  - **MetHb**
    Methaemoglobinaemia.
    - Ferrous iron (Fe^{2+}) is oxidised to ferric iron (Fe^{3+})
    - Cannot bind oxygen, and left-shifts the oxyHb curve for normal Hb which reduces oxygen offloading at tissues
    - Normally prevented by:
      - Glutathione in red cell reduces oxidising agents
      - Methaemoglobin reductase enzyme uses NADH to reduce MetHb
    - Occurs due to:
      - Oxidising agents overwhelm capacity of glutathione system, e.g.:
        - SNP
        - NO
        - Amide local anaesthetics

- Sulfonamides
- Failure of the methaemoglobinaemia reductase enzyme
  - G6PD

- **COHb**
  Carboxyhaemoglobin.
  - Haemoglobin binds carbon monoxide with greater affinity than oxygen

- **CyanoHb**
  - Haemoglobin **irreversibly** binds cyanide molecules, causing a **functional anaemia**
  - Cyanide inhibits cytochrome oxidase in the electron transport chain, preventing oxidative phosphorylation occurring

Oxygen Saturation

Oxygen Saturation can be defined in two ways:

- **Functional Saturation**
  $$SpO_2\ (\%) = \frac{[HbO_2] \times\ 100}{[HbO_2] + [DeoxyHb]}$$
  However, additional haemoglobin species exist in varying amounts, and this definition may deceptively imply good oxygen delivery when this is not the case.

- **Fractional Saturation**
  $$SpO_2\ (\%) = \frac{[HbO_2] \times\ 100}{[HbO_2] + [DeoxyHb] + [MetHb] + [COHb]}$$
  Fractional saturation includes carboxy- and met-haemoglobin, and so is a more accurate estimator of oxygen saturation.

Note that pulse oximetry doesn't measure either of these and is dependent on the calibration, but will typically measure functional saturation.

Myoglobin

Muscle is highly metabolically active and has a large O_2 demand. Myoglobin serves as an O_2 store for muscle. It is similar to Hb in that it is a large O_2-binding iron-containing protein myoglobin, and is different because it:

- Contains one globin chain and one haeme group (binding one O_2 molecule), and so **does not exhibit cooperative binding**
  The myoglobin dissociation curve therefore has a **rapid upstroke** and an **early plateau**.
- Has a **P_{50} of 2.7mmHg**
  This allows it to take up oxygen from haemoglobin (as the partial pressure gradient favours diffusion into the cell), and unload it into the cell (so it can actually be used).
- Is found in skeletal and cardiac muscle

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Last updated 2019-07-18

Carbon Dioxide

> Describe the ~~oxygen and~~ carbon dioxide stores in the body

> Describe the carbon dioxide carriage in blood including the Haldane effect and the chloride shift

> Explain the carbon dioxide dissociation curve

> Describe the movement of carbon dioxide from blood to the atmosphere

CO_2 is produced in the mitochondria during the citric-acid cycle as a product of metabolism.

- There is **~120L** of carbon dioxide in the body
  A total of $1.8L.kg^{-1}$, $1.6L.kg^{-1}$ of which is in relatively inaccessible compartments.
- Normal elimination (and, at steady state, production) of carbon dioxide is **200ml.min^{-1}**

Carbon Dioxide in Blood

In blood, CO_2 is stored as:

- Bicarbonate (90%)
- Dissolved gas
- Carbamino compounds

Form	Arterial Blood	Additional CO_2 in venous blood
Bicarbonate	90%	60%
Dissolved	5%	10%
Carbamino compounds	5%	30%

Bicarbonate

- CO_2 diffuses freely into erythrocytes, where it can be catalysed by carbonic anhydrase to produce bicarbonate:
  $CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$
- To maintain bicarbonate production, the products (H^+ and HCO_3^-) are then removed:
  - **H^+** ions are **buffered** to **haemoglobin**
    $HbO_2 + H^+ \Leftrightarrow HHb + O_2$
  - Intracellular **HCO_3^-** is then exchanged with extracellular **Cl-** via the BAND3 membrane protein
    - This is called the Hamburger, or **Chloride Shift**
    - Chloride entering the cell draws water in along its osmotic gradient, **increasing the haematocrit of venous blood** relative to arterial blood

Dissolved Gas

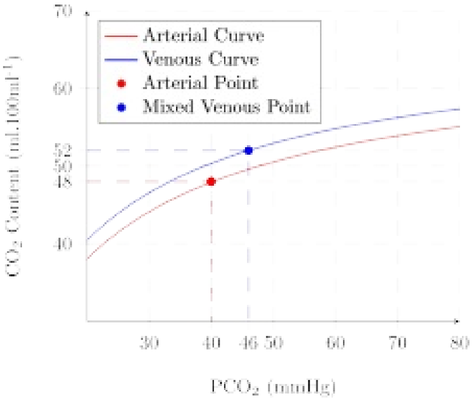
- As per **Henry's Law**, the amount of carbon dioxide dissolved in blood is proportional to the $PaCO_2$
- As carbon dioxide is 20x as soluble as oxygen in water, dissolved carbon dioxide contributes much greater proportion of carbon dioxide *content* than dissolved oxygen does to oxygen content

Carbamino Compounds

- CO_2 can bind directly to proteins (predominantly haemoglobin), which displaces a H^+ ion:
  $Hb + CO_2 \Leftrightarrow HbCOO^- + H^+$
  - The H^+ ion is then buffered by another plasma protein (also predominantly haemoglobin)
    $Hb + H^+ \Leftrightarrow HHb$
- Bound CO_2 does not contribute to the partial pressure gradient
- Carbamino compounds are only a small contributor to overall CO_2 carriage, but contribute about one third of the arterio-venous CO_2 difference due to the **Haldane effect**
  The Haldane effect states that deoxyHb binds CO_2 more effectively than oxyHb. This is because:
  - DeoxyHb is a **better buffer** of **H^+**
    pKa of deoxyHb is 8.2, compared to that of oxyHb which is 6.6.
    - Enhanced buffering contributes ~30% of the Haldane effect
  - DeoxyHb forms carbamino compounds more easily Deoxy-Hb has 3.5x the affinity for CO_2 than Oxy-Hb.
    - This forms ~70% of the Haldane effect

CO_2 Dissociation Curve

This curve plots PCO_2 against blood CO_2 content in $ml.100ml^{-1}$.



Key points:

- Mixed venous CO_2 content is $52ml.100ml^{-1}$, at a PCO_2 of 46mmHg
- Arterial CO_2 content is $48ml.100ml^{-1}$, at a PCO_2 of 40mmHg
- Approximately 50% of the arterial-mixed venous difference occurs due to the upwards shift of the curve, which is due to the Haldane effect
  This is the mechanism for changes in PO_2 affecting the CO_2 dissociation curve.

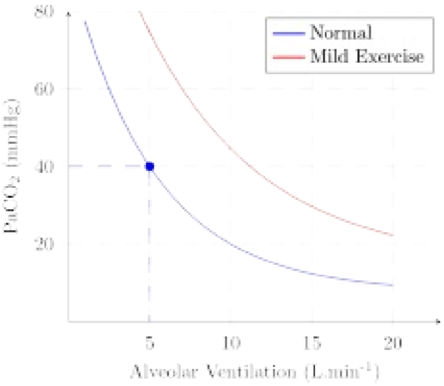
Removal of CO_2

CO_2 dissolves from pulmonary arterial blood into the alveolus down a concentration gradient. As inspired CO_2 is negligible, $PACO_2$ is a function of alveolar ventilation and CO_2 output, given by the equation:

$$PACO_2 = \frac{CO_2\ output}{\dot{V}_A}$$

Simplified, $PaCO_2$ is inversely proportional to alveolar ventilation:

$$PACO_2 \propto \frac{1}{\dot{V}_A}$$



Distribution of Carbon Dioxide

CO_2 in the body can be considered as a three-compartment model:

- Well-perfused (blood, brain, kidneys)
- Moderately-perfused (resting muscle)
- Poorly-perfused (bone, fat))

- Each of these tissues has a different time-constant, such that a mismatch of ventilation with metabolic activity may take **20-30 minutes** to equilibrate across compartments

- Therefore hypoventilation and hyperventilation have different effects on PCO_2:
  - **Hyperventilation** causes a rapid decrease in PCO_2 in blood, subsequent (slower) redistribution from peripheral compartments
  - **Hypoventilation** causes a rise in $PaCO_2$, the rate of which is determined both by production and distribution into plasma
    - With **no ventilation**, PCO_2 rises at **3-6mmHg.min^{-1}**
      - Due to the Haldane effect the $PaCO_2$ will rapidly increase during passage through the pulmonary capillary (despite the fact that carbon dioxide *content* is unchanged) as the proportion of OxyHb increases
    - Therefore:
      - PaO_2 is more sensitive at detecting early hypoventilation provided PAO_2 is normal
      - Steady-state PCO_2 gives the best indication of adequacy of ventilation
        - In acute hypoventilation, produced CO_2 is preferentially stored in tissues, decreasing CO_2 elimination
        - In acute hyperventilation, CO_2 is mobilised from tissues resulting in increased CO_2 elimination

CO_2 Cascade

Region	Value (mmHg)
Mixed Venous	46
Alveolar	40
(Arterial)	40
Mixed-expired	27

- Venous CO_2 diffuses into the alveolus, reaching equilibrium with arterial PCO_2
- Alveolar CO_2 is then diluted by dead space gas, resulting in a lower $ME'CO_2$

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Last updated 2018-04-24

Positive Pressure Ventilation

> Describe the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure.

Physiological effects of positive pressure ventilation are mostly related to the **increased mean airway pressure**. This is a function of:

- Ventilation mode
- Tidal volume and peak (and plateau) airway pressure
- Respiratory rate
- I:E ratio
- **PEEP**
  PEEP has a much larger effect than the other factors.
  - PEEP is defined as a positive airway pressure at the end of expiration
  - PEEP is distinct from positive airway pressure (which is not confined to a phase of the respiratory cycle) and CPAP (which is a mode of ventilation)
  - iPEEP refers to **intrinsic PEEP**, auto PEEP or dynamic hyperinflation
    iPEEP is PEEP generated by the patient, and occurs when expiration stops before the lung volume reaches FRC.
    - Application of external PEEP may limit the generation of iPEEP by maintaining airway patency in late expiration

Respiratory Effects

- Decreased work of breathing
  - Decreased VO_2
    More important when work of breathing is high.
- Alteration in anatomical/apparatus dead space
  - Intubation typically reduces dead space, as the additional apparatus dead space is of smaller volume than the anatomical dead space it replaces
  - Non-invasive ventilation masks cause a large increase in dead space
- Increases lung volume (and FRC, for PEEP) by an amount proportional to the compliance of the system
  - Improves oxygenation via alveolar recruitment
  - Improves lung compliance via alveolar recruitment, reducing work of breathing
  - Elevated airway pressures may increase the proportion of West Zone 1 physiology and alveolar dead space
    In healthy lungs an increase in the $\frac{V_D}{V_T}$ ratio is seen when PEEP exceeds 10-15cmH_2O.
- Reduces airway resistance
  Airway resistance decreases as lung volume increases.

Cardiovascular Effects

- Alteration in cardiac output
  - PEEP and IPPV generally decrease CO via decreasing VR due to the increase in intrathoracic pressure.
    Leads to reduction in RV filling pressure, LV filling, and CO.
    - This is the predominant reason why CO falls with the application of PEEP
      In a well patient, CO falls by:
      - 10% with IPPV and ZEEP
      - 18% with IPPV and 9cmH_2O of PEEP
      - 36% with IPPV and 16cmH_2O of PEEP

        - These changes are:
            - More marked in hypovolaemia
              Changes are reversed with volume expansion.
            - Less severe with poor lung compliance
              Reduced compliance greatly reduces the effect of PEEP and IPPV on the vasculature, as the change in intrapleural pressure is reduced.
    - LV preload may also be reduced due to increased RV afterload
        - Increased RV afterload may increase RV EDV, displacing the interventricular septum into the LV
        - The bulging septum decreases LVEDV, causing LV diastolic function and reduced LV filling
          This is an example of **ventricular interdependence**.
    - Reduced LV afterload due to reduced LV transmural pressure
      In some cases, IPPV augments circulatory function by reducing LV afterload to a greater extent than preload.
        - Effects in a well patient are minimal, as PEEP is relatively small in magnitude compared to systemic arterial pressures
        - In patients generating highly negative intrathoracic pressures, the LV transmural pressure can increase markedly, increasing LV afterload and reducing cardiac output

- Reduction in MAP
  MAP decreases as PEEP increases.

- Changes to oxygen flux
  PEEP will tend to improve PO_2 whilst reducing CO.

- Changes to pulmonary vascular resistance and RV afterload
    - If lung volume is lower than FRC, then PVR will reduce as PEEP stretches open extra-alveolar vessels
        - Alveolar recruitment will reduce hypoxic-pulmonary vasoconstriction, further reducing PVR
    - If lung volume is higher than FRC, then PVR will increase as PEEP compresses alveolar vessels
    - Therefore, PEEP has *variable effects* on RV afterload depending on how it changes lung volume with respect to FRC

End-Organ Effects

- Reduced urine output due to:
    - Reduced CO and renal blood flow
    - ADH release as a consequence of reduced atrial stretch and ANP release
      May worsen oedema in patients with prolonged periods of ventilation.

- Reduced hepatic blood flow due to:
    - Increased CVP and decreased CO lowering the pressure gradient for hepatic flow
        - May result in circulation only intermittently throughout the cardiac cycle

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Last updated 2017-09-22

Hypoxia

> Explain the physiological effects of hyperoxia, **hypoxaemia**, hypercapnia, hypocapnia, and carbon monoxide poisoning.

- **Hypoxaemia** is a low partial pressure of oxygen in blood
- **Hypoxia** is an oxygen deficiency at the **tissues**, due to:
  - Impaired **oxygen delivery**
  - Impaired **oxygen extraction**

Oxygen delivery is given by the equation:
$DO_2 = HR \times SV \times (1.34 \times [Hb] \times SpO_2 + PaO_2 \times 0.003)$, where:

- 1.34 is Hüfner's constant
  This is the oxygen carrying capacity of haemoglobin, in ml.g^{-1} (of Hb).
  - The theoretical maximum is 1.39
  - *In vivo* it is 1.34 due to the effect of carboxyhaemoglobin and methaemoglobin compounds, which limit O_2 binding
- 0.03 is the solubility coefficient of O_2 in water at 37ºC, in mls.mmHg^{-1}
  Can also be expressed as 0.003 mls.dL^{-1}.mmHg^{-1} (mls per deciliter per mmHg). Different texts use different values, depending on whether haemoglobin is reported in g.L^{-1} or g.100ml^{-1}.

Classifications and Causes of Hypoxia

Hypoxia can be categorised into four types:

- Hypoxic hypoxia
- Anaemic hypoxia
- Ischaemic hypoxia
- Histotoxic hypoxia

Hypoxic Hypoxia

Hypoxic hypoxia, or **hypoxaemia**, is hypoxia due to low PaO_2 (and therefore low SpO_2), typically defined as a PaO_2<60.

Causes of hypoxaemia can be further classified based on their A-a gradient:

- Causes of hypoxaemia with a **normal A-a gradient**:
  - Low PiO_2
  - Decreased alveolar ventilation
- Causes of hypoxaemia with a **raised A-a gradient**:
  - Diffusion limitation
  - Shunt
  - (Increased oxygen extraction)

Low FiO_2

Hypoxaemia occurs at high altitudes when the PO_2 is decreased.

Decreased alveolar ventilation

A fall in alveolar ventilation ($\dot{V}_A = Respiratory\ Rate \times (V_T - V_D)$) causes a rise in $PACO_2$, and therefore decreases PAO_2. Decreased V_A can occur with:

- Respiratory centre depression:
  - Drugs
  - Head injury (Raised ICP, closed head injury)
  - Encephalopathy
  - Fatigue
- Nerve dysfunction:
  - Spinal cord injury
  - GBS
  - MND
- NMJ dysfunction:
  - Paralysis
  - MG
- Muscular dysfunction:
  - Myopathy
  - Fatigue
  - Malnutrition
  - Dystrophy
- Chest wall abnormalities:
  - Kyphoscoliosis
  - Ankylosing Spondylitis
  - Pleural fibrosis

Diffusion Limitation

Impaired diffusion of O_2 across the membrane results in a lowered PaO_2. Diffusion limitation occurs due to:

- Decreased alveolar surface area
- Increased alveolar capillary barrier thickness
  - Pulmonary fibrosis
  - ARDS

Shunt

Shunt occurs when **blood reaches the systemic circulation without being oxygenated via passage through the lung**. As the alveolus is **perfused** but **not ventilated**, thus the **V/Q ratio is 0**.

- Administration of 100% O_2 has less effect on PaO_2 as shunt fraction increases
  - Oxygen content of shunted alveoli is identical to mixed venous content
  - Oxygen content of non-shunted alveoli does not increase appreciably at high partial partial pressures as haemoglobin is already fully saturated

Shunt physiology is explored in more detail under shunt.

Increased Oxygen Extraction

- Increased oxygen extraction (VO_2) will not typically cause hypoxia
- This is because:
  - Normal VO_2 is 250ml.min^{-1}
  - Normal DO_2 is 1L.min^{-1}

  - Maximal oxygen extraction ratio is ~70% (though it varies between organs)
    Therefore VO_2 can increase until it reaches 70% of the DO_2, a point called critical DO_2.
- However, it may worsen hypoxia in the presence of a supply-side (DO_2) pathology

Anaemic Hypoxia

- Impaired oxygen delivery due to low Hb
- Typically asymptomatic at rest but limits exercise tolerance
- Compensation occurs by increasing levels of 2,3-DPG, causing a right-shift in the Hb-O_2 dissociation curve to favour oxygen off-loading at tissues

Carbon Monoxide Poisoning

- CO poisoning is classified as a subset of anaemic hypoxia as carboxyhaemoglobin **reduces** the **effective** amount of **haemoglobin** in solution
- CO has 210 times the affinity for Hb than O_2
  - CO rapidly displaces O_2 from Hb and is liberated slowly
- CO poisoning causes headache and nausea, but no increased respiratory drive since the PaO_2 is unchanged

Ischaemic Hypoxia

- Ischaemic hypoxia is due to impaired cardiac output resulting in impaired oxygen delivery

Histotoxic Hypoxia

- Histotoxic hypoxia is due to impaired tissue oxidative processes, preventing utilisation of delivered oxygen
- Most common cause of histotoxic hypoxia is cyanide poisoning, which inhibits cytochrome oxidase and prevents oxidative phosphorylation
- Managed by using methylene blue or nitrites, which form methaemoglobin, in turn reacting with cyanide to form the non-toxic cyanmethaemoglobin

Effects of Hypoxia

- With a normal $PaCO_2$, PaO_2 must fall to 50mmHg before an increase in ventilation occurs
- With a rising $PaCO_2$, a fall in PaO_2 below 100mmHg will stimulate ventilation via action on carotid and aortic body chemoreceptors
  - The effects of each stimuli are synergistic, and greater than what is seen with either effect alone
- Prolonged hypoxaemia will also lead to cerebral acidosis (via anaerobic metabolism), which will stimulate central pH receptors and stimulate ventilation

Acid-Base Changes

- Hypoxia results in both fixed and volatile acid-base disturbances
- Anaerobic metabolism results in **lactate** production
- Production of fixed acid results in a **base deficit**, and a low bicarbonate
- Hypoxia and metabolic acidosis stimulate ventilation and hypocarbia

CO_2 retention

- In chronic hypercarbia the CSF pH normalises (as bicarbonate is secreted into CSF), with a raised CO_2

- Fall in PaO_2 becomes the predominant stimulus for ventilation

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1. West J. Respiratory Physiology: The Essentials. 9th Edition. Lippincott Williams and Wilkins. 2011.
2. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
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Last updated 2019-07-18

Hypo and Hypercapnea

> Explain the physiological effects of ~~hyperoxia, hypoxaemia~~, hypercapnia, hypocapnia~~, and carbon monoxide poisoning~~

Carbon dioxide is lipid soluble and can rapidly cross membranes, allowing it affect acid-base status in any compartment.

Hypercapnea

- **Respiratory Effects**
  - Increased respiratory drive via chemoreceptor stimulation
- **CVS effects**
  - Peripheral vasodilation
    - May cause tachycardia from sympathetic stimulation
  - Pulmonary vasoconstriction
  - Myocardial depression
    Intracellular acidosis.
  - Arrhythmogenic
- **CNS effects**
  - Increased CBF
  - Increased ICP secondary to increased CBF
  - SNS activation
  - CNS depression
    When $PaCO_2$ > 100mmHg

Hypocapnea

- **Respiratory Effects**
  - Left-shift of oxyhaemoglobin dissociation curve
  - Respiratory depression
- **CVS effects**
  - Myocardial depression
    Intracellular alkalosis.
- **CNS effects**
  - Decreased cerebral blood flow
- **Electrolyte effects**
  - Decreased serum K^+
  - Decreased serum Ca^{2+}
    Leads to paresthesias and twitches.
    - Ca^{2+} binds to H^+ binding site on albumin

References

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Last updated 2019-07-18

Position and ventilation

> Explain the effect of changes in posture on ventilatory function

Altered patient position can cause significant changes to V/Q matching.

Lateral Decubitus

In the lateral position in a **spontaneously ventilating** patient:

- Dependent lung ventilation improves by ~10%
  Due to impaired compliance of the non-dependent lung (it hyperinflates) and improved compliance of the dependent lung (it is less expanded).
    - Dependent lung corresponds more to West Zone 3
    - Non-dependent lung corresponds more to West Zone 2
- Dependent lung perfusion improves by ~10%
  Due to the effect of gravity.

In the lateral position in a **positive-pressure ventilated** patient:

- The majority (~55%) of the tidal volume is delivered to the non-dependent lung
- The majority of pulmonary blood flow is delivered to the dependent lung
- The compliance of the dependent lung falls due to compression from the:
    - Mediastinum
    - Abdominal organs
      These move cephalad in a paralysed patient.
- The dependent lung typically receives greater blood flow due to the effect of gravity
    - This may worsen V/Q matching
    - Blood flow is also affected by:
        - HPV
        - Anatomical factors
          Blood flow is greater in central than peripheral portions.
        - Lung volume
          Alterations is extra-alveolar and intra-alveolar pressures at FRC may alter regional blood flow.
- When both lungs are being ventilated, V/Q matching can be improved with selective application of PEEP to the dependent lung, which improves compliance

Thoracotomy

Opening of a non-dependent hemithorax causes:

- Increased compliance and FRC of the non-dependent lung
- Reduced compliance and FRC of the dependent lung

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Last updated 2017-09-20

Humidification

> Define humidity and give an outline of the importance of humidification

Humidification describes the amount of water vapour present in air:

- **Absolute Humidity** is the amount of water vapour in a given volume of air ($g.m^{-3}$)
- **Relative Humidity** is the ratio between the amount of water vapour in a sample of air (absolute humidity) and the amount of water required to fully saturate that sample at its current pressure and temperature

- **Moisture** is the water produced by condensation when relative humidity exceeds 100%.

- Humidification of inspired air is important to avoid drying out mucosa and sputum, which leads to tissue damage and failure of the mucociliary elevator
- Optimal function requires a relative humidity of **greater than 75%**

Mechanism

The nose is:

- Optimised for humidification
  The **septum** and **turbinates** increase contact of air with mucosal surfaces by:
  - Increasing **surface area**
  - Generating **turbulent flow**
- The preferred orifice for breathing unless airways resistance becomes a significantly limiting factor
  This is relevant in:
  - Airway obstruction (e.g. polyps)
  - At high minute ventilations (> $35L.^{-1}$)
- Humidifies inspired gas to 90%, compared to **60%** for the mouth

Method of humidification:

- Fluid lining the airway acts as a heat and moisture exchanger
- In inspiration:
  - Relatively dry air is evaporates water from the airway lining
  - Relative humidity is increased to 90% in the nasopharynx and 100% BTPS by the second generation of bronchi
    This gives a water vapour pressure of **47mmHg** at BTPS, with an absolute humidity of **$44g.m^{-3}$**.
- In expiration:
  - Air cools in the upper airway
    As cooler air has a lower saturated vapour pressure, moisture condenses on the airway.
  - Moisture is reabsorbed
    This reduces potential water losses from the airway from **$300ml.day^{-1}$** to **$150ml.day^{-1}$**.

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Last updated 2018-09-21

Cough Reflex

> Explain the pathways and importance of the cough reflex

Coughing:

- Is an airway protection reflex
- Involves deep inspiration followed by **forced expiration against a closed glottis**
  The sudden opening of the cords causes a violent rush of air at **>900km.h^{-1}**, removing irritants and secretions from the airways.

Sensation

Vagus afferents have exquisitely sensitive light touch and corrosive chemical receptors in the larynx, carina, terminal bronchioles, and alveoli.

Integration

Vagal afferents synapse in the medulla, which coordinates the effector response.

Effector

A series of processes occur in three phases:

- Inspiratory phase
  A close to vital capacity breath is taken.
- Compressive phase
  Effort closure of the epiglottis to seal the larynx, followed by a violent contraction of abdominal musculature and internal intercostals, causing a rapid rise in intrapleural pressure to >100mmHg.
- Expulsive phase
  Wide-opening of the cords and epiglottis, causing a violent expiration.
  - Compression of the lungs causes narrowing of the noncartilaginous airways and increases turbulent flow, removing adherent material from the tracheobronchial tree

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References

1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.

Last updated 2019-07-18

Non-Respiratory Functions

> Outline the non-ventilatory functions of the lungs

The lungs are a unique organ as:

- The entire cardiac output passes though the pulmonary circulation
- They have a huge capillary bed which blood is in contact with
- They have a large interface with the external environment

Consequently they are adapted to a number of non-respiratory functions, which include:

- **F**iltration
- **I**mmune defence
- Blood **r**esevoir
- **M**etabolism
- Drug Delivery
  - (**T**aking up drugs)
  - **I**nhalational Anaesthetics
- **S**ynthetic
  - Endocrine

Filtration

The entire cardiac output passes through the 7μm pulmonary capillaries, which act as an effective sieve for particulate matter. This function may be impaired by intra-cardiac shunting (e.g. PFO) or pre-capillary anastomoses.

Complementing this role, the lungs are able to clear thrombi more rapidly than other organs as pulmonary endothelium has a high concentration of plasmin activator and heparin.

Metabolism

The pulmonary endothelium has a variety of effects on drugs and endogenous hormones:

Class	Activated	Inactivated
Amines		5-HT, Noradrenaline
Peptides	Angiotensin I (via ACE)	Bradykinin, ANP
Arachidonic acid derivatives	Arachidonic acid	Many prostaglandins
Other Drugs		Lignocaine, fentanyl

Blood Reservoir

The highly compliant pulmonary circulation contains a resevoir of ~500ml of blood which acts as a **volume reserve** for the LV.

Defence

The large surface area required for gas exchange leaves the lung vulnerable to invasion by airborn substances. This is attentuated by:

- Mucous
  A mucous layer protects large airways, as large (>8μm) particles impact into the mucous.
  - Mucous is exocytosed by goblet cells in response to noxious stimuli including chemical irritation as well as inflammatory and neuronal stimulation
  - The efficacy of the mucous-cilia system is enhanced by bronchoconstriction, which reduces flow velocity and causes particulate matter to settle
- Cilia
  Cilia are projections from epithelium which beat rhythmically at ~12Hz to propel mucous out of the airway at a rate of ~4mm.min^{-1}.
  - Ciliary function can be impeded by pollutants, smoke, and infection
  - Ciliary function is stimulated by anaesthetic agents
- Inhaled particles which reach the respiratory zone are not trapped by mucous, but instead phagocytosed by alveolar macrophages
- Bronchoconstriction reduces flow velocity and causes particulate particles to settle in the mucous

Drug Delivery

The same properties that optimise the lung for gas exchange optimise it for delivery of inhaled agents. Drugs absorbed in the pulmonary circulation are:

- Lipophilic
- Alkaline (pKa >8)

Endocrine

Important endocrine functions of the lung include:

- Release of inflammatory mediators such as histamine, endothelin, and eicosanoids
- Release of nitric oxide to regulate smooth muscle
- ACE metabolises angiotensin I to angiotensin II

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
2. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.

Last updated 2019-07-18

Altitude Physiology

Altitude causes a number of physiological effects, related to:

- Reduce atmospheric pressure
- Reduced temperature
- Reduced relative humidity
- Increased solar radiation

Pressure Effects

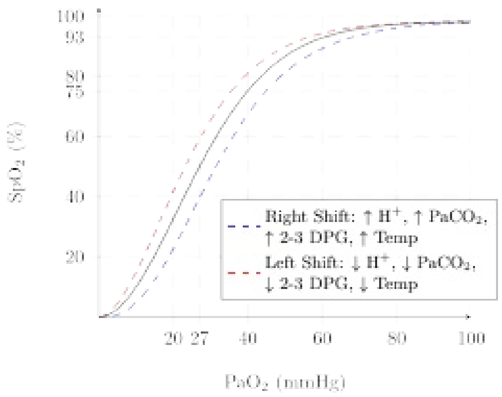
Reduced air pressure results in a proportional decrease in PO_2:

- At 3,000m, alveolar PO_2 is 60mmHg
- At 5,400m, consciousness is lost in unacclimatised individuals
- At 10,400m, air pressure is 187mmHg
  With 47mmHg of water vapour and an alveolar PCO_2 of 40, breathing 100% O_2 gives an alveolar PO_2 of 100mmHg.
- At 14,000m, consciousness is lost despite 100% O_2
- At 19,200m, the ambient pressure is so low that the boiling point of water is 37°C
  This is the **Armstrong limit**.

Respiratory

- Fall in PaO_2 is compensated by increasing minute ventilation, which decreases $PACO_2$ and therefore increases PAO_2
  - Limits of compensation are reached on 100% oxygen at 13,700m
- Effective compensation is limited by the respiratory alkalosis, this is known as the **braking effect**:
  - Peripheral chemoreceptors detect hypocapnea
  - Central chemoreceptors detect alkalosis
- The subsequent respiratory alkalosis generates a compensatory metabolic acidosis
  This acidosis relaxes the braking effect and allows further hyperventilation, and is therefore am important part of acclimatisation.

- There is an **initial left-shift** of the oxygen-haemoglobin dissociation curve due to alkalosis
- This stimulates a compensatory increase in 2,3-DPG to right-shift the curve and improve oxygen offloading at the tissues



Cardiovascular

- PVR increases due to HPV
- Heart rate increases due to increased SNS outflow

- Stroke volume falls (cardiac output remains the same) due to decreased preload:
  - Plasma volume falls due to:
    - Pressure diuresis
    - Insensible losses from hyperventilation and reduce relative humidity
- Myocardial work increases
  - Increased HR
  - Increased viscosity of blood due to high haematocrit
  - Increased RV afterload from high PVR

    Increased pulmonary capillary hydrostatic pressures lead to fluid transudation and pulmonary oedema

Haematological

- Increased risk of thrombotic events to due increased haematocrit
- Increased red cell mass due to EPO secretion

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

Last updated 2019-07-18

Respiratory Changes with Obesity

> Discuss the effect of morbid obesity on ventilation

Obesity is a multisystem disorder defined by an elevated body mass index (BMI):

- Normal: BMI < 25
- Overweight: BMI 25 - 30
- Obese: BMI > 30
- Morbidly Obese:
  - Obesity related disease and a BMI > 35
  - BMI > 40

Characteristics of obesity include:

- Complex genetic and environmental causes
- Increased caloric intake
- Increased metabolic rate (normal for BSA)

Morbid obesity causes several changes to the respiratory system:

- Airway
  - Increased risk of OSA
  - Increased risk of GORD and aspiration
  - Increased risk of difficult bag-mask ventilation
  - Increased risk of difficulty laryngoscopy

- Changes to respiratory pattern
  - Increased minute ventilation
    - Secondary to increased VO_2 and VCO_2
      Due to the increase in LBW and adiposity.
    - Increased airway reactivity
      Central adiposity increases circulating cytokines, including TNF-α, IL-6, leptin.

- Changes to volumes and capacities
  - Reduced respiratory system compliance
    - Decreased chest wall compliance
      Due to abdominal and chest wall fat.
      - Fat distribution may be more important than absolute BMI
    - Decreased lung compliance
      Basal atelectasis due to abdominal compression and reduced respiratory compliance.
  - Decreased ERV and FRC
    - Note that RV is generally relatively unchanged
  - Increased airway resistance
    Due to decreased airway radius at lower lung volumes.
  - Increased work of breathing
    Due to reduced respiratory compliance and increased airway resistance.
  - Closing capacity encroaches on FRC
    As FRC falls, closing capacity becomes closer to FRC.
    - If closing volume exceeds expiratory reserve volume, then small airways will collapse during normal tidal breathing, causing shunt

- Changes to blood gases

    - Increased A-a gradient
      Occurs when closing capacity exceeds FRC.
- Changes to respiratory circulation
    - PVR increases due to reduced FRC causing increased HPV
      May lead to secondary PHTN and right heart dysfunction.

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1. Alvarez A, Brodsky J, Lemmens H, Morton J. Morbid Obesity: Peri-operative Management. Cambridge: Cambridge University Press. 2010.
2. Lotia S, Bellamy MC. Anaesthesia and morbid obesity. Contin Educ Anaesth Crit Care Pain 2008; 8 (5): 151-156.

Last updated 2017-09-21

Respiratory Changes in Neonates and Children

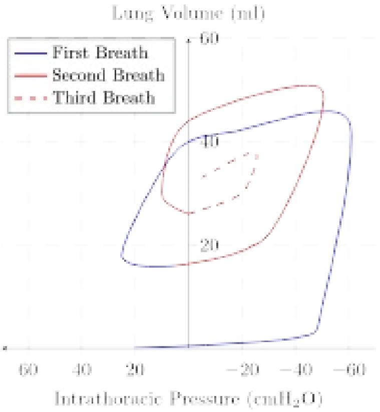
Transition at Birth

Transition from placental gas exchange to pulmonary gas exchange occurs within 20s after birth:

- Compression of the thorax through the vaginal canal expels foetal lung water
- Elastic recoil, combined with cooling of the skin and mechanical stimulation (which stimulate the respiratory centre), facilitate first breath

- The rapid drop in pulmonary vascular resistance with spontaneous breathing drives the changes in the cardiac circulation

- The **first three breaths** establish functional residual capacity
  Large changes in intrathoracic pressure in the first three breaths pressure drive alveolar amniotic fluid into the circulation, and establish FRC.



Neonates and Children

- **Compliance**
  Neonatal chest walls are highly compliant relative to their lungs (due to both a reduced lung compliance and increased chest wall compliance), as compared to adults where lung and chest compliance is equal. Therefore elastic work of breathing is largely determined by the lungs.

- **Oxygenation**
  - O_2 consumption is ~10ml.kg^{-1}.min^{-1} in neonates, and 6ml.kg^{-1}.min^{-1} in children
  - There is a ~10% shunt after birth which contributes to a greater A-a gradient

- **Ventilation**
  - Obligate nose breathers
  - Increased CO_2 production due to higher metabolic rate
  - Increased minute ventilation, which is due to increased respiratory rate (25-40 breaths per minute)

- **Neurological control of breathing**
  Respiratory patterns change following birth, and complete change to adult respiratory patterns may take some weeks. Patterns include:
  - **Periodic breathing** is a slowly oscillating respiratory rate and V_T
  - **Periodic apnoea** is intermittent apnoea interspersed with normal breathing.

- **Volumes and capacities**

    - Closing capacity is increased relative to adults, causing shunt
    - Functional residual capacity is unchanged
    - Tidal volume and dead space are unchanged

- **Laryngeal anatomy**
    - Large head
    - Large tongue
    - Large, stiff, U-shaped epiglottis
    - Elevated larynx
      Glottis is at C-3C4 (C6 in adults).
    - Upper airway is narrowest at the cricoid ring (rather than the glottis).
    - Trachea is shorter and narrower
      4-5cm long, 6mm diameter in the neonate.

- **Small airways**
    - Reduced bronchial smooth muscle so bronchospasm is uncommon
    - Bronchioles contribute 50% of airways resistance
      Bronchiolitis much more distressing in neonates and children.

References

1. Lumb A. Nunn's Applied Respiratory Physiology. 7th Edition. Elsevier. 2010.
2. CICM March/May 2013

Last updated 2018-07-14

Anti-Asthma Drugs

> Describe the pharmacology of anti-asthma drugs.

- **Oxygen**
  Increases FiO_2 and improves saturation.
- **Heliox**
  Reduces specific gravity of inhaled gas mixtures, improving laminar flow.
- **β_2-agonists**
  Acts on a G-protein coupled receptor to ↑ cellular levels of adenylyl cyclase, ↑ cAMP, which results in smooth muscle relaxation and bronchodilatation.
- **Corticosteroids**
  Glucocorticoids are steroid hormones that bind to specific intracellular receptors and translocate into the nucleus, where they regulate gene expression in a tissue-specific manner. They are used in asthma as they cause:
  - Bronchodilatation by increasing bronchial smooth muscle response to circulating catecholamines
  - Decreased airway oedema by decreasing inflammatory responses and transudate production
- **Muscarinic antagonists**
  Anti-muscarinics are synthetic quaternary ammonium compounds which competitively inhibit M3 muscarinic receptors on bronchial smooth muscle, antagonising the bronchoconstrictor action of vagal impulses.
- **Methylxanthines**
  Methylxanthines are phosphodiesterase inhibitors, reducing levels of cAMP hydrolysis and increased intracellular levels of cAMP (via a different mechanism, so they are synergistic with β_2 agonists) and causing smooth muscle relaxation.
- **Ketamine**
  Increases sympathetic outflow and relaxes bronchial smooth muscle.
- **Volatile Anaesthetic Agents**
  Volatile anaesthetic agents reduces bronchial smooth muscle constriction where this is preexisting (such as asthma).
- **Leukotriene Antagonists**
  Selectively inhibits the cysteinyl leukotriene receptor, increased activity of which is involved in airway oedema and bronchial smooth muscle constriction.

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1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

Last updated 2019-07-18

Cardiac Anatomy

> Describe the anatomy of the heart, the pericardium and coronary circulation

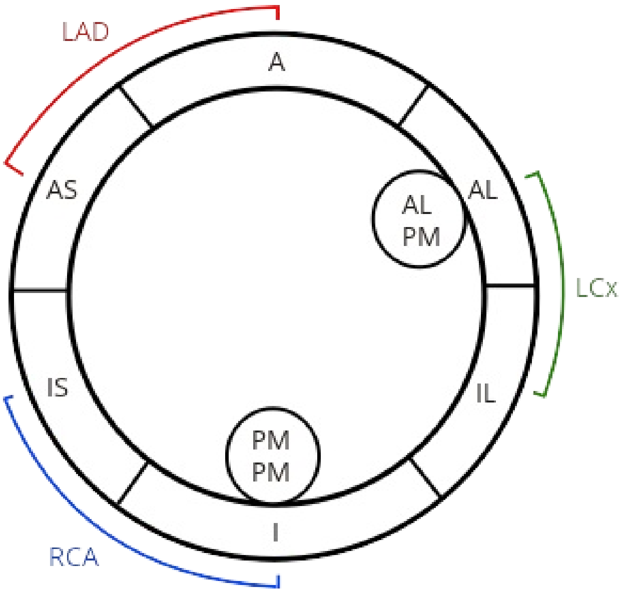
Echocardiographic Anatomy

The left ventricle is:

- Divided into four parts
  From base to apex, in **equal thirds** along the long axis of the ventricle:
  - Basal
  - Mid-cavity
    Identified by presence of the papillary muscles.
  - Apical
  - Apex
    Tip of the ventricle, beyond where the cavity ends.
- Each part is divided into segments
  Total of **seventeen segments** between:
  - 6 basal and mid-cavity segments
    - Inferior
      Mid-cavity contains the postero-medial papillary muscle.
    - Inferoseptal
    - Inferolateral
    - Anterior
    - Antero-septal
    - Antero-lateral
      Mid-cavity contains the anterolateral papillary muscle.
  - 4 apical segments
    - Inferior
    - Anterior
    - Lateral
    - Septal
  - Apical cap

Coronary Supply

The segments of the basal and mid-cavity parts are supplied by all three vessels:



In the apical part, the:

- LAD
  Supplies:
  - Anterior
  - Septal
- LCx
  Supplies:
  - Lateral
- RCA
  Supplies:
  - Inferior

The apical cap is supplied by the **LAD**.

References

1. Alfred Anaesthetic Department Primary Exam Tutorial Series
2. AHA 17 Segment Model. PMOD.

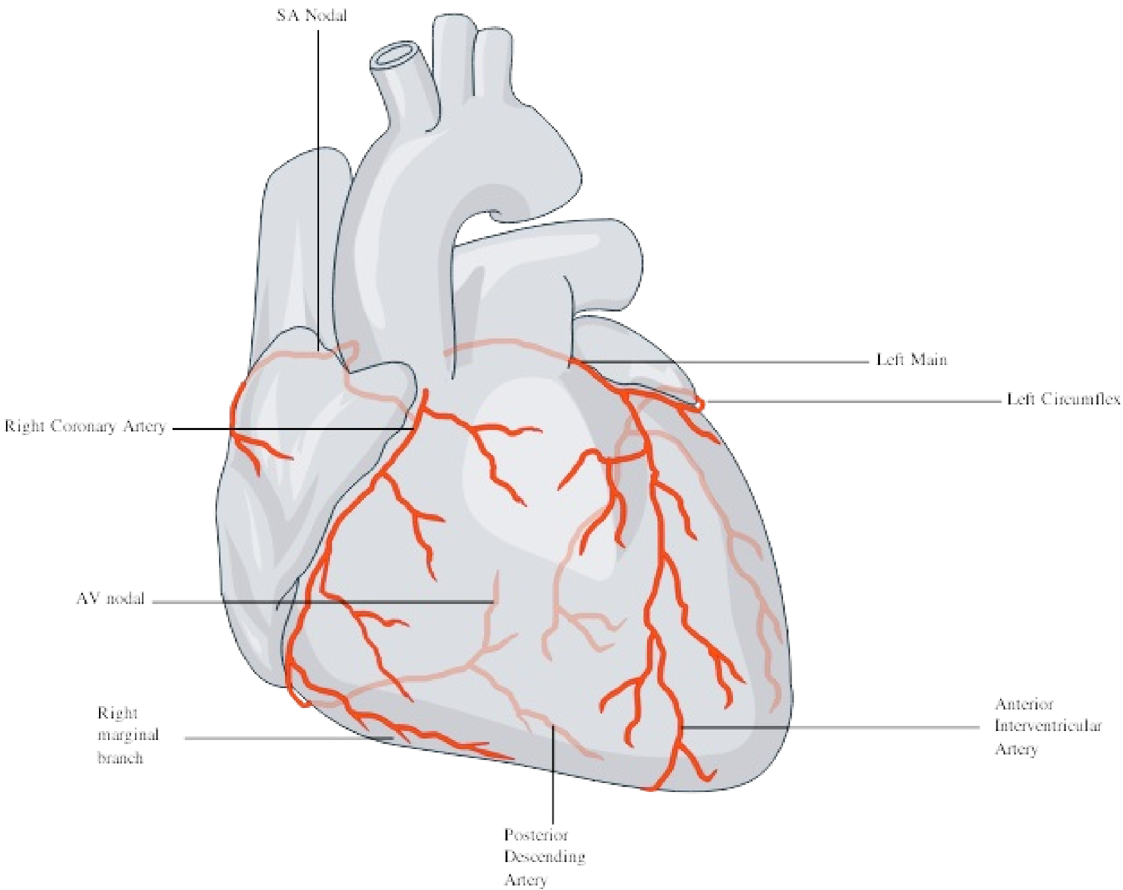
Last updated 2018-08-01

Coronary Circulation

> Describe the anatomy of the ~~heart, the pericardium and~~ coronary circulation

Vascular Anatomy

Coronary Artery Anatomy



The **left main** coronary artery:

- Arises from the posterior aortic sinus superior to the left coronary cusp of the aortic valve
  Eddy currents produced in the **sinuses of Valsalva** (outpouchings of the aortic wall) prevent the valves occluding the os of the LM and RCA during systole, so they remain patent throughout the cardiac cycle.
- The **left main** is 5-10mm long, and bifurcates to form the LAD and LCx

The **LAD**:

- Courses along the **anterior interventricular groove** to the apex of the heart
  Here, it anastomoses with the posterior descending artery from the RCA.
- **Supplies** the **anterolateral myocardium** and **anterior 2/3** of the interventricular **septum**
- **Branches** of the LAD include:
  - **Diagonal** vessels
    Branches are named successively from proximal to distal, i.e. $LADD_1$, $LADD_2$, etc.

  - **Septal perforators**

The **LCx**:

- Courses along the **left atrioventricular** groove between the LA and LV in the epicardial fat pad
- **Supplies** the **inferolateral wall** of the **LV**
- Gives off three **obtuse marginal** branches (OM_1, OM_2) which follow the left margin of the heart
- Runs in close approximation with the coronary sinus for much of its course

The **RCA**:

- Arises from the anterior aortic sinus, superior to the right coronary cusp of the aortic valve
- Courses vertically downwards in the **right atrioventricular groove**
- Supplies the RA and RV

The **posterior descending artery**:

- Arises from either the LCx or RCA
  These vessels travel in opposite directions around the atrioventricular groove.
- Descends in the posterior interventricular groove before coursing along the base to anastomose with the LAD at the apex of the heart
- Is also known as the posterior interventricular artery

Coronary Dominance

Coronary dominance refers to which vessel gives rise to the PDA:

- In a **right-dominant** circulation the PDA is supplied by the **RCA**
- In a **left-dominant** circulation the PDA is supplied by the **LCx**

Additionally:

- The **SA node** is supplied by the **RCA in 60%** of individuals
- The **AV node** is supplied by the **RCA in 90%** of individuals

Venous Anatomy

- 85% of venous drainage occurs via the **coronary sinus**, which is formed from the cardiac veins:
  - The **great cardiac vein** runs with the LAD
  - The **middle cardiac vein** follows the PDA
  - The **small cardiac vein** runs with the RCA
  - The **oblique vein** follows the posterior part of the LA
- Most of the remainder is via **anterior cardiac veins** which drain directly into the RA
- A small proportion of blood from the heart is drained via the **thebesian veins** directly into four the cardiac chambers
  Most into the right atrium, and least into the left ventricle. The portion of blood draining into the left side of the circulation contributes to **physiological shunt**.

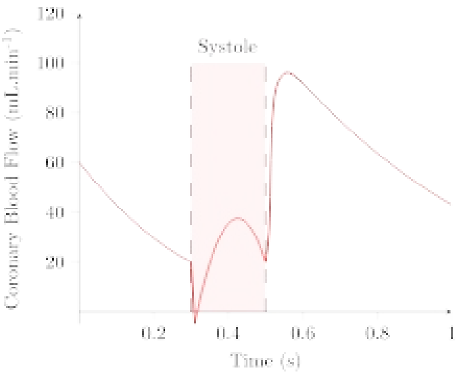
Coronary Blood Flow

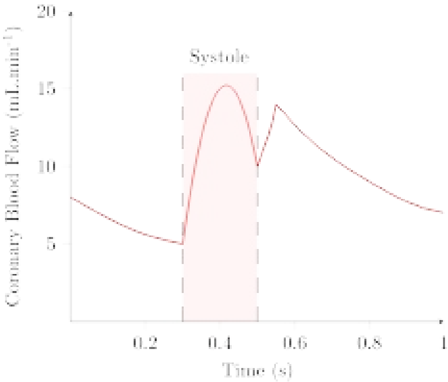
Coronary Blood Flow:

- Normal is **~250ml.min^{-1}** (~5% of resting CO)
- May increase 4x during strenuous exercise
  Myocardial *work* may increase up to 9x, though as myocardial oxygen extraction is unchanged efficiency is actually improved during exercise.

CBF is dependent on:

- Coronary vascular resistance
- Coronary perfusion pressure
  The difference between aortic root pressure and the greater of RAP or intracavity pressure: i.e.
  $$CBF = \frac{P_{Aorta} - P_{Cavity}\ or\ RAP}{CVR}$$
  - Note that the pressure gradient is usually Aorta-Cavity rather than Aorta-RA
    This is because the pressure in the ventricle acts as a Starling resistor - coronary flow is independent of RAP whilst $RAP < P_{Cavity}$
- Heart rate
  LV CBF is affected in systole due to the changes in perfusion pressure, and compression of intramuscular vessels (causing an increase in CVR).
  - RV CBF is less affected, as the force of contraction is significantly smaller and a pressure gradient is maintained
  - Tachycardia reduces diastolic time and subsequently LV CBF





Control of Coronary Blood Flow

CBF is **autoregulated**:

- **Myogenic autoregulation**
  This is common to many organ systems, and occurs within the coronaries.
  - Increasing transmural pressure increases the leakiness of smooth muscle membranes, depolarising them
  - Resistance increases proportionally to pressure, such that flow remains constant
- **Metabolic autoregulation**
  Anaerobic metabolism results in production of vasoactive mediates such as **lactate** and **adenosine**, which stimulate vasodilation and therefore increase flow (and oxygen delivery).
  - This is the predominant means for autoregulation in the heart
  - Typical **myocardial oxygen extraction is 70%** and raising this further is difficult
    Therefore, increasing oxygen supply requires an increase in blood flow.

Autonomic mechanisms also control some aspects of coronary blood flow:

- **Direct** effects include:
  - Parasympathetic and sympathetic innervation of coronary vessels, with release of ACh or NA and A decreasing or increasing coronary blood flow
- **Indirect** effects
  - Are more important than direct effects
  - Are related to autoregulation occurring with changing levels of myocardial work in response to parasympathetic or sympathetic stimuli

References

1. Hall, JE, and Guyton AC. Guyton and Hall Textbook of Medical Physiology. 11th Edition. Philadelphia, PA: Saunders Elsevier. 2011.
2. CICM July/September 2007
3. McMinn, RMH. Last's Anatomy: Regional and Applied. 9th Ed. Elsevier. 2003.
4. Coronary Artery Graph based on Coronary Arterial Circulation - es. 2/3/2013. (Image). By Addicted04 (Own work) CC BY 3.0, via Wikimedia Commons.

Last updated 2019-07-18

Cardiac Cycle

> Describe the normal pressure and flow patterns (including velocity profiles) of the cardiac cycle

The cardiac cycle:

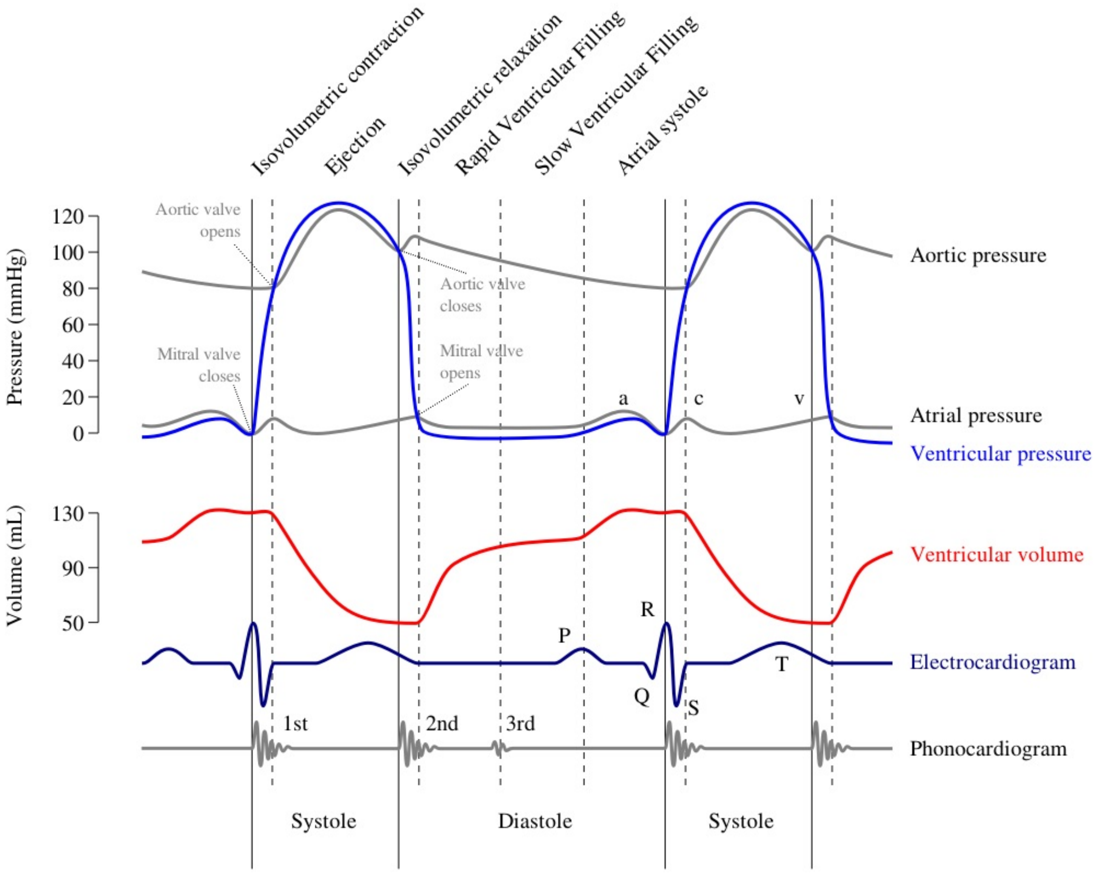
- Describes sequence of events that occur in the heart over one beat
- Consists of **two phases** divided into **six stages**
- Typically is descried as beginning in **late diastole** when the myocardium is relaxed and the ventricles are passively filling

Phases of the cardiac cycle:

- Diastole
    - Isovolumetric Ventricular Relaxation
    - Rapid Ventricular Filling
    - Slow Ventricular Filling
      (The cycle begins here).
    - Atrial Contraction
- Systole
    - Isovolumetric Ventricular Contraction
    - Ejection

Phases of the Cardiac Cycle

Events during each phase of the cardiac cycle are represented on **Wigger's Diagram**:



Slow Ventricular Filling (Diastasis)

In slow ventricular filling:

- The AV valves are open and the semi-lunar valves are closed
- The ventricle is **relaxed completely** and fills slowly
  The ventricles have been mostly filled during rapid ventricular filling and so the pressure gradient is reducing.
  - The pressure in each ventricle is almost zero
- **Arterial pressure is falling**, as it is end-diastole
- **CVP is slowly rising** as the ventricle and atria fill
  This period occurs **after the y descent**.
- The **ECG** will show the beginnings of a **P-wave** at the end of this phase

Atrial Contraction

The atria contract, and remaining blood in the atria is ejected into the ventricle. This supplies **10%** of the ventricular **filling at rest**, but up to **40% in tachycardia**.

In atrial contraction:

- **Arterial pressure** is still **falling**
- The **CVP** waveform demonstrates the **a** wave as atrial contraction also causes blood to reflux into the SVC
- The **ECG** will show the **PR interval**

Isovolumetric Ventricular Contraction

Once the action potential passes through the AV node and bundle of His, ventricular contraction begins.

In isovolumetric contraction:

- Ventricular pressure rises, and the **AV valves close**
  This gives rise to the first heart sound, S_1.
  - As ventricular pressure is still less than systemic vascular pressure, the semilunar valves remain closed
- **Arterial pressure** is still **falling**
- The **CVP** waveform shows the **C** (closure) wave, as the tricuspid valve herniates back into the RA during ventricular contraction
  There is a similar spike in LA pressure as the mitral valve also bulges back into the LA.
- The **ECG** will show the remainder of the QRS or the start of the QT interval
  - Atrial repolarisation occurs at this stage, but is typically masked by ventricular depolarisation

Ejection

When ventricular pressure exceeds arterial pressure, the semilunar valves open and ejection occurs. **Initial ejection is rapid**, but as ventricular pressure falls and systemic pressure rises the gradient falls ejection becomes slower.

During ejection:

- **Arterial pressure rises rapidly**, and is slightly less than ventricular pressure during this stage
- The **CVP** waveform shows the **x descent**, as the shortening RV pulls the RA down, rapidly lowering CVP
- The **ST segment** shows on the ECG as the ventricles are fully depolarised, though the **T wave** may appear in late ejection

Isovolumetric Relaxation

When contraction is complete, the ventricles begin to relax. **Inertia** means that ejection continues for a short time.

During isovolumetric relaxation:

- The **semilunar valves close**
  This gives rise to the second heart sound, S_2, and marks the beginning of isovolumetric relaxation.
  - This occurs when ventricular pressure falls below vascular pressure
- **Arterial pressure begins to fall**, interrupted by the **dicrotic notch** which is a brief increase in arterial pressure as the semilunar valves close
- The **v wave** is visible on the CVP waveform
  Due to atria filling against closed AV valves.
- The **end of the T wave** is visible on the ECG as ventricular repolarisation occurs

Rapid Ventricular Filling

Most of ventricular filling occurs in this phase. This is because in early ventricular diastole the ventricle is **still relaxing** and so a **pressure gradient is maintained** between the atria and ventricle.

During rapid ventricular filling:

- The **AV valves open** and ventricular filling occurs
  This occurs when atrial pressure exceeds ventricular pressure.
- **Arterial pressure is falling**
- The **y descent** occurs when the AV valves open, causing a rapid drop in CVP as the ventricles fill
- No electrical activity is produced - the ECG shows the TP interval

References

1. Hall, JE, and Guyton AC. Guyton and Hall Textbook of Medical Physiology. 11th Edition. Philadelphia, PA: Saunders Elsevier. 2011.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
3. Wigger's Diagram (with some modifictions) from Wigger's Diagram. 21/3/2012. (Image). By DanielChangMD (revised original work of DestinyQx); Redrawn as SVG by xavax. CC BY 3.0 , via Wikimedia Commons.

Last updated 2019-07-18

Cardiac Action Potential

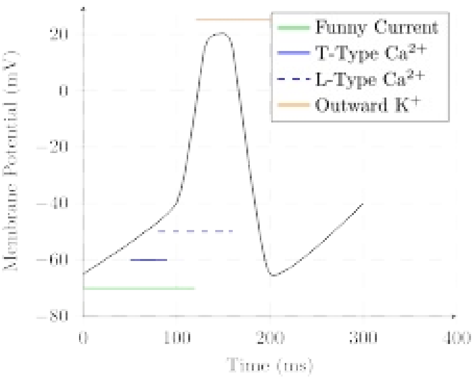
> Explain the ionic basis of spontaneous electrical activity of cardiac muscle cells

> Describe the normal and abnormal processes of cardiac excitation and electrical activity

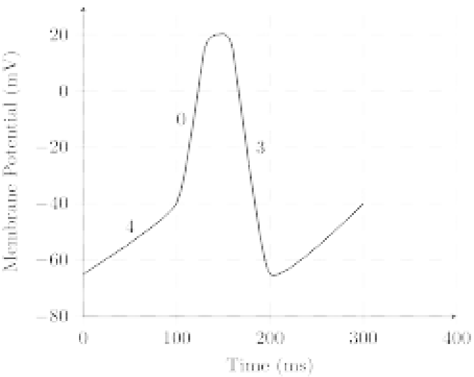
An action potential is a propagating change in the membrane potential of an excitable cell, used in cellular communication and to initiate intracellular processes. It is caused by altering the permeability of a membrane to different ions.

Pacemaker Potential

This pattern of electrical activity is seen in the SA and AV nodes. It **has no resting state**, and is continually depolarising.

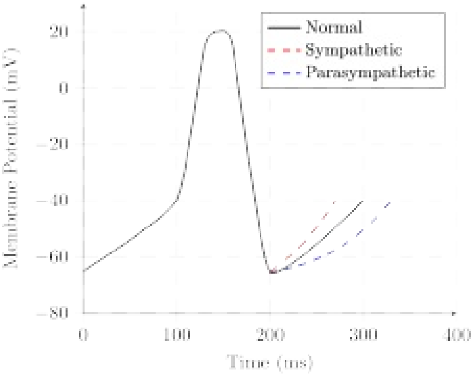


Phases of the Pacemaker Potential



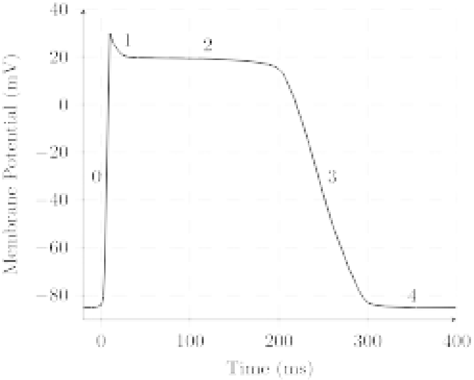
- **Phase 0**
  Begins at the threshold potential of **-40mV**, with a peak membrane potential of **20mV**. Driven predominantly by the voltage-gated L-type (long-lasting) Ca^{2+} channels causing an influx of calcium ions.
- **Phase 3**
  Repolarisation phase, which occurs as K^+ channels open and Ca^{2+} channels close. The nadir is called the **maximum diastolic potential** and is **-65mV**.
- **Phase 4**
  Phase 4 consists of:
  - The **funny current**
    A steady influx of Na^+/K^+ which gradually depolarises the cell.
    - Sympathetic stimulation increases the funny current, increasing the rate of depolarisation.
    - Parasympathetic stimulation increases K^+ permeability, hyperpolarising the cell and flattens the gradient of phase 4.

- Calcium current
  In phase 4, this is the transient calcium current, driven by T-type calcium channels. They open when the membrane potential reaches ~-50mV, also causing depolarisation.



Ventricular Action Potential

To prevent tetanic contraction (which would be bad) ventricular muscle has a long plateau prior to repolarisation, which lengthens the absolute refractory period to 250ms. The relative refractory period is 50ms.



Phases of the Ventricular Action Potential

- **Phase 0**: Depolarisation
  At the threshold potential, voltage-gated **fast-Na$^+$** channels open briefly, causing depolarisation. The membrane potential peaks at **30mV**.
- **Phase 1**: Partial Repolarisation
  The closure of Na$^+$ channels results in K$^+$ fleeing the cell down its electrochemical gradient, causing a slight drop in voltage called partial repolarisation.
- **Phase 2**: Plateau
  L-type Ca^{2+} channels open, causing a slow inward Ca^{2+} current which maintains depolarisation and facilitates muscle contraction.
- **Phase 3**: Repolarisation
  Membrane permeability normalises, and outward potassium current returns the membrane potential to normal.
- **Phase 4**: Resting Potential
  Membrane potential returns to its resting **-85mV**.

Propagation of the Cardiac Action Potential

Pacemaker cells:

- Are responsible for automaticity and rhythmicity of the heart
- The fastest pacemaker is the focus for myocardial conduction
  This is typically the SA node.
  - Should the SA node fail, the next fastest pacemaker will take over
  - This provides an element of redundancy

Conduction pathway:

- **Atrial Conduction**
  From the SA node, the impulse travels at ~1m.s^{-1}, depolarising the atria.
  - Current travels down **Bachmann's Bundle**, which connects the right atrium to the left atrium

- **AV node**
  The AV node is the only (normal) site of connection between the atria and ventricles. AV nodal cells:
  - Transmits with a delay of 0.1s
    This allows time for atrial contraction to finish before ventricular contraction begins.
  - Have a prolonged refractory period and cannot conduct more than **220** impulses per minute
    - This period is prolonged by vagal stimulation, which increases potassium permeability and hyperpolarises the cell
    - Conversely, sympathetic stimulation increases calcium permeability and allows more rapid transmission
  - Conducts via three pathways:
    - Bachmann Pathway
      Also conducts to the LA.
    - Wenckebach pathway
    - Thorel pathway

- **Ventricular Conduction**
  From the AV node, the signal propagates:
  - Initially via the **Bundle of His** to the right and left bundles
  - Secondly via the **Purkinje fibres** which conduct at 1-4m.s^{-1}
    Purkinje fibres have a long refractory period, and spontaneously depolarise with an intrinsic rate of 30-40 bpm.
  - Lastly, ventricular muscle is depolarised
    Endocardium, papillary muscle and septum contract first, followed by apex, followed by the chambers.

Autonomic Control

- **Parasympathetic Innervation**
  - SA node by the right vagus
    There is continual PNS input ("Vagal tone") via inhibitory ACh GPCR, reducing the SA node from its intrinsic rate of 90-120bpm to a more sedate 60-100bpm.
  - AV node by the left vagus
  - The atria are innervated by parasympathetic neurons, whilst the ventricles are only minimally innervated
    PNS stimulation therefore has little effect on inotropy, but does affect chronotropy.
    - PNS stimulation may have no direct effect on inotropy, instead acting indirectly via changes in chronotropy

- **Sympathetic Innervation**
  - SNS activity causes release of noradrenaline (at post-ganglionic synapse) and adrenaline from adrenal medulla which stimulate cardiac β_1 receptors causing:
    - Positive chronotropy at the SA node
    - Positive inotropy at ventricular muscle
    - Positive lusitropy
    - Shorter action potential duration (due to opening of rectifying K^+ channels
    - Increased AV conduction

Cardiac Transplant

The transplanted heart has no vagal/parasympathetic innervation but still expresses β_1 receptors, so it:

- Defaults to a resting heart rate of ~100bpm
- Becomes highly preload dependent as it cannot respond quickly to changes in SVR
- Not responsive to parasympatholytics (atropine, glycopyrrolate) or ephedrine (as this is indirectly-acting) to increase chronotropy - isoprenaline may be used
- Gradual response to demands in exercise (lacks local SNS innervation, but will still respond to circulating catecholamines)
- Increased sensitivity to catecholamines due to increased expression of β_1 receptors

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Last updated 2019-07-18

Determinants of Cardiac Output

> Define the components and determinants of cardiac output

Cardiac output a function of Heart Rate (HR) and Stroke Volume (SV):
$CO = HR \times SV$.

- **Heart rate** is fairly intuitive
- **Stroke volume** is defined as the difference between ESV and EDV, i.e. $SV = EDV - ESV$
  Stroke volume is a function of three factors:
  - **Preload**
  - **Afterload**
  - **Contractility**
- Preload and afterload have almost as many definitions as there are textbooks
- For the purpose of the exam, it's good to have both a laboratory and a clinical definition
- These definitions are those which have appeared in old examiner reports, or given to me by cardiac anaesthetists

Preload

Preload is defined as the **myocardial sarcomere length just prior to contraction**.

- As this is not measurable without removing the heart and cutting it into tiny pieces, clinically it is usually **approximated by EDV** or, less appropriately, by EDP
  - EDV is typically calculated on echocardiography
  - EDP is typically measured using a CVC or PAC
    - CVP ≈ RVEDP
    - PCWP ≈ LVEDP

Determinants of Preload

Preload is a function of:

- **Venous Return**
  - Intrathoracic Pressure
  - MSFP
    - Venous compliance
      A decrease in venous compliance will increase LVEDP.
    - Volume state
- **Ventricular compliance**
  Reduced in diastolic dysfunction.
- **Pericardial compliance**
- **Valvular disease**
  - AV valve disease will **impair** preload
  - Semilunar valve disease will **increase** preload
- **Atrial kick**
- **Wall thickness**
  Increased ventricular wall thickness decreases preload.
  - HOCM/Hypertrophy

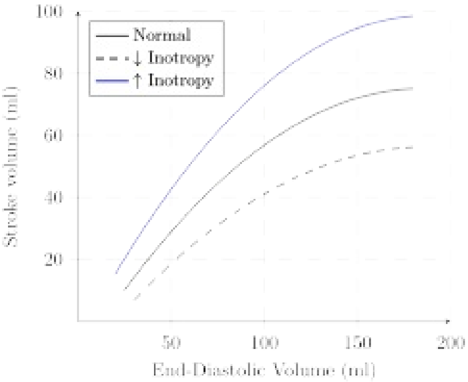
Preload and the Respiratory Cycle

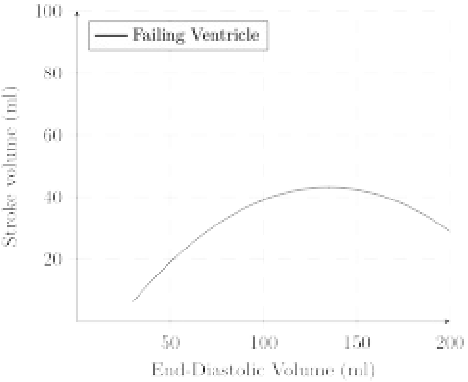
- Negative intrathoracic pressure causes RAP and PCWP to fall
- This increases RA filling, so and RVEDP and RVEDV increase relative to the pleural pressure (though absolute pressure is still low)
- LV effects are more variable
  Negative intrapleural pressures:
  - Increase LV transmural pressure
    This impairs ejection.
  - Cause bowing of the interventricular septum into the LV
    This reduces LVEDV.

Frank-Starling Mechanism

- The **Frank-Starling Law of the Heart** states that the **strength of cardiac contraction is dependent on initial fibre length**
- At a cellular level, additional stretch increases:
  - The number of myofilament crossbridges that can interact
  - Myofilament Ca^{2+} sensitivity

- This law is represented by the **ventricular function curve**
  Plot of preload against stroke volume (or cardiac output, assuming a constant heart rate).
  - Right shift of the curve demonstrates negative inotropy
  - Left shift of the curve demonstrates positive inotropy





The failing ventricle:

- In cardiac failure, the ventricle becomes overstretched
  This reduces the number of overlapping crossbridges, reducing contractility.
- This is limited in the acute setting by constriction of the pericardium, which prevents excessive ventricular dilation

Afterload

Afterload is **the sum of forces, both elastic and kinetic, opposing ventricular ejection**

- This definition is a bit wordy but avoids using the words "resistance" and "impedance", which are strictly defined in physics (and crudely applied in medicine), and may be leapt on by the cruel examiner

Determinants of Afterload

Afterload is equal to **ventricular wall stress**, which is given by the equation:

$\theta \propto \frac{P \times r}{T}$, where:

- θ is ventricular wall stress
- P is ventricular transmural pressure
- r is ventricular chamber radius
- T is ventricular wall thickness

Each of these factors are in turn influenced by:

- **Ventricular transmural systolic pressure**
  Transmural pressure is the difference between intrathoracic pressure and the ventricular cavity pressure during ejection.
  - Intrathoracic Pressure
    Negative intrathoracic pressure will increase afterload, as the ventricle has to generate a greater change in pressure to achieve ejection.
    - PEEP reduces LV afterload
    - Negative-pressure ventilation with a high work of breathing increases afterload
      This is why APO deteriorates - increased work of breathing increases LV afterload and worsens LV failure, increased pulmonary oedema, causing increased work of breathing...

  - **Ventricular cavity pressure**
    To facilitate ejection, the ventricle must overcome:
    - **Outflow tract impedance**
      - Valvular disease
        - e.g. aortic stenosis
      - HOCM
    - **Systemic arterial impedance**
      Determined by resistance (SVR), **inertia, and** compliance:
      - Determinants of **resistance** are stated in the Poiseuille Equation:
        $R = \frac{8.\eta.l}{\pi.r^4}$, where:
        - η = **Viscosity**
          Affected by **haematocrit** (e.g. increased in polycythaemia)
        - l = Vessel length
          Essentially fixed.
        - r = Vessel **radius**
          - Greatest determinant
          - Function of **degree of vasoconstriction** of resistance vessels
      - **Inertia**
        - Given by the mass of blood in the column
        - Affected by **heart rate**
      - Arterial **compliance**
        Decreased arterial compliance increases afterload.
        - During ejection, the aorta and large arteries distend, reducing peak systolic pressure (impedance to

further ejection)
        - Decreased arterial compliance increases the change in pressure for any given volume, increasing afterload during ejection
        - Decreased arterial compliance increases the speed of propagation of **reflected pressures waves** returning to the aortic root
            - Wave arrival in diastole augments coronary blood flow
            - Wave arrival during systole further increases afterload
    - In diastole the arteries recoil and blood pressure and flow are maintained - the **Windkessel effect**.

- **Ventricular chamber radius**
    - End-Diastolic Volume
      Increased EDV increases ventricular radius and therefore wall tension.

- **Myocardial wall thickness**
  Increasing wall thickness (seen clinically as ventricular hypertrophy) *decreases* afterload by sharing wall tension (the product of pressure and radius) between a larger number of sarcomeres.

Contractility

Contractility describes the **factors other than heart rate, preload, and afterload that are responsible for for changes in myocardial performance**.

Determinants of Contractility

Contractility is primarily dependent on **intracellular Ca^{2+}**. Determinants include:

- Drugs
- Disease
    - Ischaemia
      Reduced ATP production secondary to hypoxia, which impairs sarcoplasmic reticulum Ca^{2+} function. Further exacerbated by intracellular acidosis from anaerobic metabolism.
    - Heart Failure
      Impaired **contractility reserve**, i.e. minimal increase in contractility with sympathetic stimulation.
        - Reduced peak Ca^{2+} and sarcoplasmic reticulum uptake of Ca^{2+}
- Autonomic Tone
- Bowditch Effect
  Contractility improves at faster heart rates. This is because the myocardium does not have time to remove calcium, so it accumulates intracellularly.
- Anrep Effect
  Contractility increases as afterload increases.

Measuring Contractility

- As with the other determinants of cardiac output, there has been some difficulty in developing measurable indices for contractility
- All measures of contractility are affected by preload or afterload to some extent

- **dP/dt_{max}** ($\frac{\Delta P}{\Delta T}$)
  The **rate of rise** of LVP, assuming a constant preload and afterload
    - This index is **preload dependent** but **afterload independent**
    - Typically, the dP/dt_{max} in isovolumetric ventricular contraction is used

- A greater rate of rise indicates a more forceful contraction
- Measurement requires LV catheterisation

- **End-Systolic Pressure-Volume Relationship**
  - Uses the ventricular Pressure-Volume Relationship
  - Line plotted at the tangent to the curve from the **end-systolic point** (when isovolumetric ventricular relaxation begins)
    - The steeper the gradient the greater the contractility

- **Ejection Fraction**
  Most common method used clinically is **ejection fraction**:
  $EF\ (\%) = \frac{SV}{EDV} \times 100 = \frac{EDV - ESV}{EDV} \times 100$

Footnotes

- The use of wall stress for preload and afterload comes from the Cardiovascular Haemodynamics text, but is not used in the CICM texts
- This site has a nice overview of wall tension, and the relationship of pressure to radius
- This article discusses the wall stress definition for preload and afterload
- Changes with ventilation are described with pretty graphs here

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Last updated 2019-07-18

Venous Return

> Define the components and determinants of cardiac output

The venous system has two key cardiovascular functions:

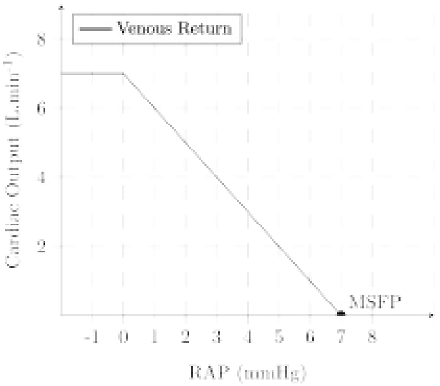
- Blood reservoir
  Contains 65% of blood volume.
- Conduit for return of blood to the heart

Venous return is the rate at which blood is returned to the heart (in L.min^{-1}). **At steady state**, venous return is equal to cardiac output, and can be expressed as:

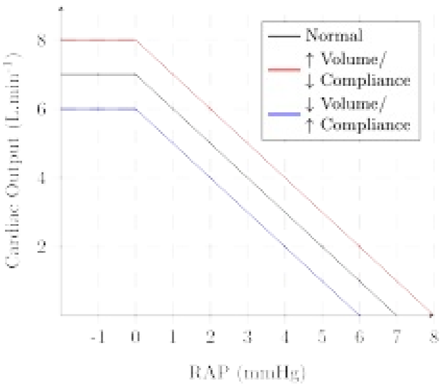
$VR = \frac{MSFP - RAP}{RVR}$, where:

- VR is venous return
- $MSFP$ is the **mean systemic filling pressure**
  This is the mean pressure of the circulation when there is no flow. It is an indicator of circulatory filling, and is a function of circulating volume and vascular compliance.
  - Normal mean systemic filling pressure is **~7mmHg**
- RAP is the right atrial pressure
  An elevated RAP reduces venous return.
- RVR is the resistance to venous return

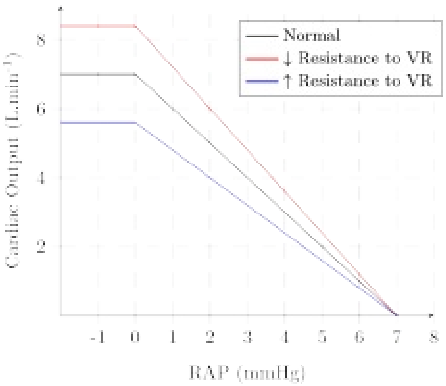
This relationship can be expressed graphically:



- When venous return is 0, the measured right atrial pressure is an indication of mean systemic filling pressure



- Alterations to circulating volume and compliance affect both venous return and mean systemic filling pressure



- Alterations to the resistance to venous return affect venous return but mean systemic filling pressure is unchanged

Factors Affecting Venous Return

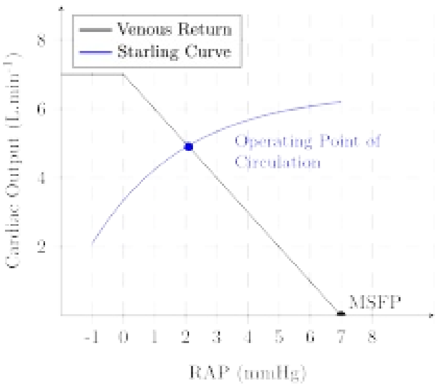
Venous return will be altered by any of the variables in the above equation:

- MSFP
  - Volume
    e.g. Haemorrhage, resuscitation.
  - Compliance
- RAP
  - Respiratory pump
    Negative intrathoracic pressure reduces RAP, improving venous return.
  - Positive pressure ventilation
  - Pericardial compliance
    - Constriction
    - Tamponade
- Resistance to Venous Return
  - Posture
  - Vascular compression
    - Obesity
    - Pregnancy
    - Laparoscopy

- Other factors affecting venous return
  - Skeletal muscle pump
    Contraction of leg muscles in combination with an intact venous system propels blood back towards the heart.

Interaction between Venous Return and Cardiac Function Curves

Guyton's curve can be superimposed on Starling's curve to examine the interaction between venous and cardiac function over a range of conditions:



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Myocardial Oxygen Supply and Demand

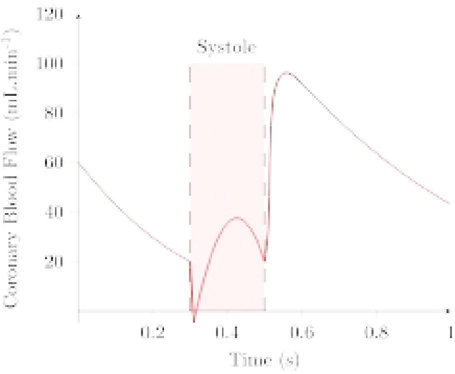
> Describe myocardial oxygen demand and supply, and the conditions that may alter each

- Myocardial oxygen supply is a function of coronary blood flow
- Myocardial oxygen demand is determined by myocardial work
- Myocardial ischaemia occurs when demand exceeds supply

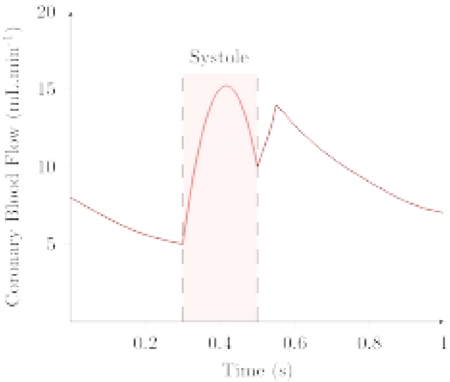
Myocardial Oxygen Supply

- Myocardial oxygen supply is dependent on:
    - **Coronary artery flow**
    - Oxygen content of blood
    - Oxygen extraction
- Functionally, **coronary artery flow is the determinant**. This is because:
    - Oxygen content in individuals without pulmonary disease is maximal
    - Resting myocardial oxygen extraction is near-maximal (**~70%**)
      This high ER makes the heart **less tolerant of anaemia** than organs with a low ER.
- Therefore coronary blood flow is the limiting factor
    - Coronary blood flow is given by the equation:
      $$CBF = \frac{P_{Aortic\ Root} - P_{Cavity}}{Coronary\ Vascular\ Resistance}$$
        - Aortic *root* pressure is the driving pressure for coronary flow
        - Cavity (ventricular) pressure acts as a **Starling resistor** for coronary flow
            - Note that if RAP exceeds cavity pressure, RAP will be the pressure opposing coronary flow (due to downstream pressure at the coronary sinus)
        - Note that **cavity and aortic root pressure change throughout the cardiac cycle**, therefore:
            - The flow to each ventricle is different during the cardiac cycle
            - The left ventricle is **best perfused in diastole**
              Therefore **heart rate** is an important determinant of coronary blood flow, as **tachycardia will decrease coronary blood flow**
- Flow to each ventricle is a function of how relationships change over the cardiac cycle

Left Ventricular Coronary Blood Flow:



Right Ventricular Coronary Blood Flow:



Myocardial Oxygen Demand

Normal myocardial oxygen consumption (MVO_2) is 21-27ml.min^{-1}. The **three major determinants** are:

- **Heart rate**
  A change in heart rate will change the number of tension-generating cycles, causing a proportional change in MVO_2.
- **Contractility**
  Refers to the **rate** of tension development as well as its **magnitude**. Changing $\frac{\Delta P}{\Delta t}$ will change MVO_2.
- **Ventricular wall tension**
  Ventricular wall tension is **pressure work**, or the work done by the ventricle to **generate pressure but not to eject volume**.
  - Wall tension is given by the **Law of LaPlace**
    $Wall\ Tension = \frac{P.r}{2}$, where:
    - P = Pressure during contraction
    - r = Radius
  - Wall tension is therefore a function of:
    - **Afterload**
      Increasing afterload will increase the pressure during contraction.
    - **Preload**
      Increasing preload will increase radius, but to a **lesser extent than increasing afterload**.
      - This is because *volume* and *radius* are *not directly proportional*

Minor determinants of myocardial work are:

- **External work**
  External work can also be thought of as **volume work**, or the energy expended to eject blood from the ventricle.
  - This is encompassed by the area enclosed by the pressure-volume loop
    - Conversely, internal work is defined as the work required to change the shape of the ventricle and prepare it for ejection
      On the pressure-volume loop internal work is represented by a triangle between the point of 0 pressure and volume, the end systolic point, and the beginning of rapid ventricular filling.
  - This is a minor determinant because the majority of ventricular work is generating the pressure required to eject blood, not actually move volume
  - External work is of greater importance at high CO
  - External work is used to calculate **cardiac efficiency**, given by the equation:
    $$Cardiac\ Efficiency = \frac{External\ Work}{Myocardial\ O_2\ Consumption}$$
- **Basal oxygen consumption**

-1 -1

Basal oxygen consumption (~8ml.min^{-1}.100g^{-1}) comprises ~25% of MVO_2.

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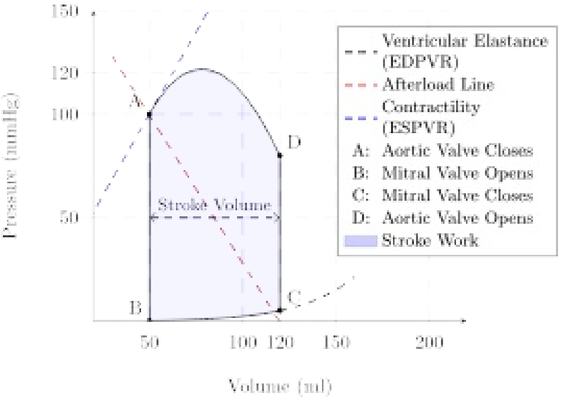
Last updated 2017-10-04

Pressure-Volume Relationships

> Describe the pressure-volume relationships of the ventricles and their clinical applications

Left Ventricular P-V Loop:



- Plot of left ventricular volume versus pressure
- Time is *not* directly demonstrated on this graph, but the stages of the cardiac cycle can be inferred:
    - A-B is isovolumetric relaxation
      Ventricular pressure is less than aortic pressure but greater than atrial pressure, so both mitral and aortic valves are closed.
    - B-C is rapid and slow ventricular filling, followed by atrial systole
      Atrial systole is sometimes demonstrated by a sharp 'bump' towards C, as ventricular pressure will briefly rise out of proportion to ventricular volume
    - C-D is isovolumetric contraction
      The ventricle contracts. As ventricular pressure is greater than atrial pressure but less than aortic pressure, the mitral valve closes (point C) and the aortic valve remains closed. Pressure increases without a change in volume.
        - This slope of this line is known as the **dP/dt$_{max}$** ($\frac{\Delta P}{\Delta T}$), and is an index of contractility
    - D-A is ventricular ejection
      When ventricular pressure exceeds aortic pressure, blood is ejected into the aorta and ventricular volume decreases.
- The slope of the line B-C gives the elastance of the ventricle
  This is also known as the **End-Diastolic Pressure Volume Relationship (EDPVR)**, and is often (erroneously) referred to as ventricular compliance.
    - **Elastance** of the ventricle **increases as it is filled**
      This is demonstrated by the dashed line.
        - The ventricle only overfills at high filling pressures
    - Increased elastance (such as in **diastolic dysfunction**) is demonstrated by an **increased slope** of this line, such that ventricular pressure will be higher at any given volume
      Both ventricular and arterial elastance are low in normal circumstances (a state known as ventricular-arterial coupling), as this allows the ventricle to achieve a wide range of volume transfers in ejection with minimal change in filling pressure.
- The horizontal distance between point B (ESV) and C (EDV) give the stroke volume
  Ejection fraction can then be calculated.
- **Preload** is given by the EDV
- **Afterload** is:
    - *Technically given* by the pressure-volume relationship throughout the entirety of ejection
      i.e. the slope D-A.

        - This comes from La Place's law:
          $$Afterload = \frac{P_{ejection} \times Radius_{ejection}}{2 \times Wall\ Thickness}$$
    - Usually *assumed to given* by the slope of a line drawn from the EDV (on the x-axis) to the **end-systolic point** (point A)
      This is also known as the arterial elastance line.
        - The gradient of the arterial elastance line can be worked out from the loops $E_A = \frac{Pressure_{End-Systole}}{Stroke\ Volume}$
        - This is different from the above formula because it only considers the pressure-volume relationship at end-systole, not throughout the entirety of ejection
        - E_A is a good substitute for afterload because it is relatively independent of preload and contractility, and will vary with changes in afterload

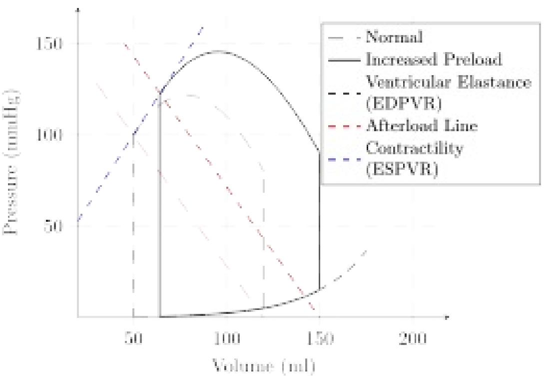
          i.e. For a given stroke volume, an increase in E_a leads to an increase in SBP. Similarly, if the ventricle is unable to maintain a given stroke volume as E_a increases, then SBP will fall.
- **Contractility** is given by the slope of the end-systolic pressure volume-relationship
  Also known as elastance at end-systole, or E_{es}, and is given by the tangent to the curve at end-systole.
    - This measurement is not entirely independent of other factors, as it is influenced by afterload

Basic Pressure-Volume Loops

These loops:

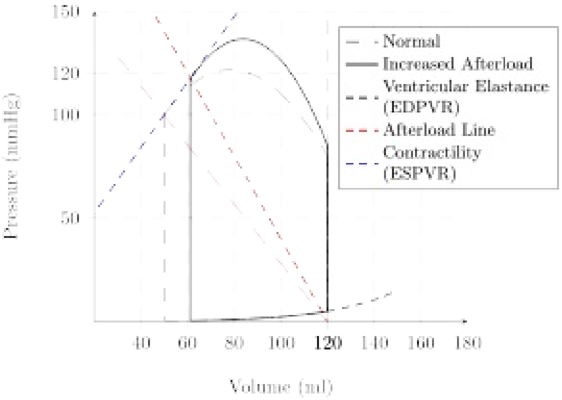
- Show isolated changes to one factor only
- Are not accurate of real-world physiology
  In reality:
    - Changing one factor will influence other factors
    - These values change beat-to-beat

Left Ventricular P-V Loop - Increased Preload:



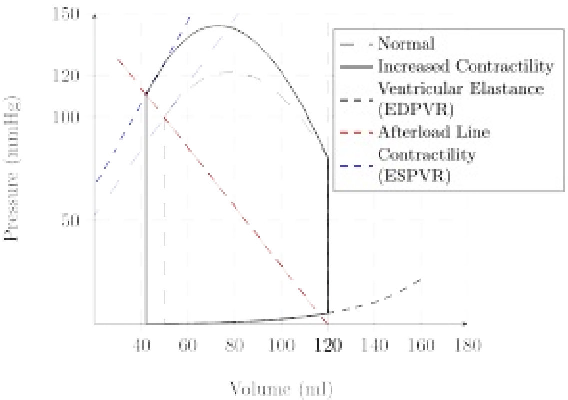
- EDV is increased, by definition
- The slope of the ESPVR remains unchanged (as contractility is unchanged)
- The slope of the afterload line (E_{ea}) is unchanged (as afterload is unchanged), but it is right-shifted due to the increased end-diastolic volume
- ESV is increased, though less than EDV, such that stroke volume increases

Left Ventricular P-V Loop - Increased Afterload:



- EDV is unchanged (as preload is unchanged)
- The slope of the ESPVR remains unchanged (as contractility is unchanged)
- The slope of the afterload line (E_{ea}) has increased, but its x-intercept is unchanged
  Note that the pressure-volume relationship throughout ejection is also steeper, and diastolic pressure has increased.
- ESV is increased, causing a reduction in stroke volume

Left Ventricular P-V Loop - Increased Contractility:



- EDV is unchanged (as preload is unchanged)
- The slope and x-intercept of the afterload line (E_{ea}) is unchanged (as afterload is unchanged)
- The slope of the ESPVR has increased, though its x-intercept is the same
- ESV is decreased, causing an increase in stroke volume

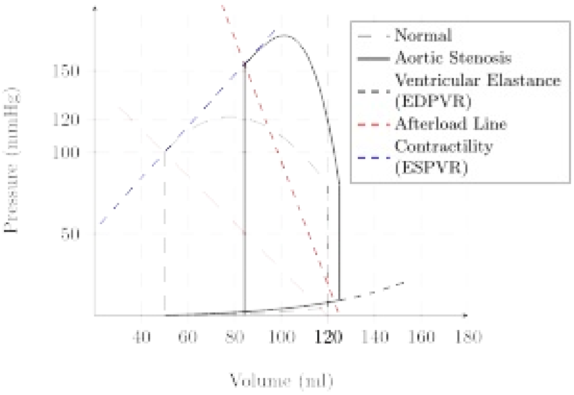
Advanced Pressure Volume Loops

The easiest way to approach more complicated pressure-volume loops is to address each of the basic factors before trying to draw the curve:

- How is preload changed?
- How is afterload changed?
- How is contractility changed?
- How are isovolumetric contraction and isovolumetric relaxation changed?

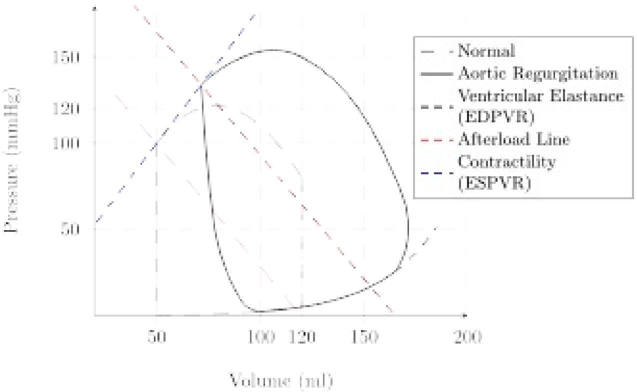
These show the loop for the primary physiological change, *without compensatory responses*:

Left Ventricular P-V Loop - Aortic Stenosis:



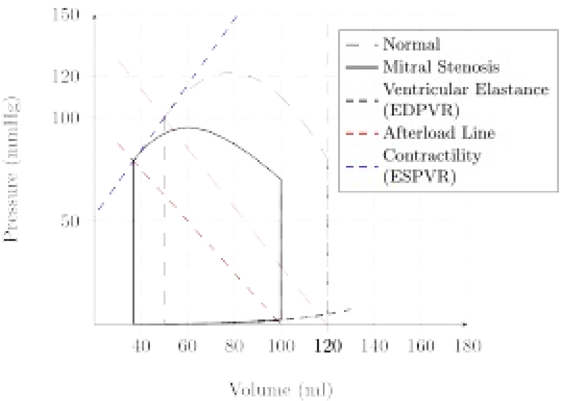
- Preload is increased due to the higher ESV, as the ventricle starts filling from a higher point
- Outflow tract impedance increases ventricular wall stress and therefore afterload
  This leads to the decrease in stroke volume.
- Contractility is unchanged

Left Ventricular P-V Loop - Aortic Regurgitation:



- Preload is dramatically increased as the ventricle fills from both the aorta and atria during diastole
- Afterload is increased due to the greater wall stress during ejection
- Contractility is unchanged
- There is no true isovolumetric relaxation, as the ventricle will begin to fill from the aorta at the completion of ejection
- Diastolic pressure is decreased and so the period of isovolumetric contraction is brief

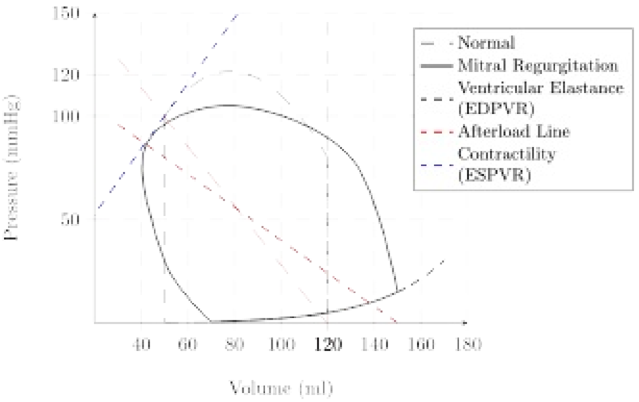
Left Ventricular P-V Loop - Mitral Stenosis:



- Preload is reduced due to the increased gradient across the mitral valve
  The effect of this is heart rate dependent, and will worsen as heart rate increases.
- Afterload is unchanged
  Afterload may fall due to the reduction in ventricular wall stress.

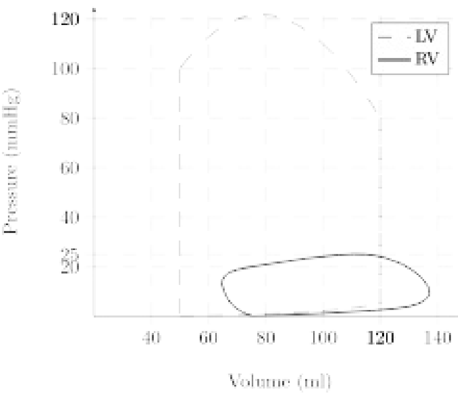
- Contractility is unchanged
- ESV decreases (due to the reduced preload), though less than EDV, such that stroke volume is reduced

Left Ventricular P-V Loop - Mitral Regurgitation:



- Preload is increased as the regurgitant volume increases left atrial pressure and therefore ventricular filling pressure
- Afterload is reduced as blood is ejected into the low-pressure atrial system
- Contractility is unchanged
- There is no true isovolumetric contraction phase as blood is ejected into the atria while ventricular pressure exceeds atrial pressure
- There is no true isovolumetric relaxation phase, as once atrial pressure exceeds ventricular pressure the ventricle will begin to fill
- *Apparent* stroke volume is increased due to the large difference between EDV and ESV, however *effective* stroke volume is reduced as only a portion of this is forward flow

Right Ventricular P-V Loop:



- The right ventricular curve is very different to the left ventricular curve
- RV preload is increased relative to LV preload

  Note that stroke volume is the same (as both sides should have the same cardiac output).
- RV afterload is dramatically reduced due to the low-resistance pulmonary circulation
  - Much of the RV ejection occurs after systolic pressure is reached
  - The right ventricle is very sensitive to changes in afterload
- Contractility is reduced

  Right heart contractility is partially dependent on coordinated contraction with the LV (particularly the septum), and therefore is decreased with LV systolic failure or conducting system disease (such as bundle brach block).

Footnotes

The Khan Academy series Changing the Pressure-Volume Loop is a fantastic introduction to the topic.

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Cardiac Reflexes

> Describe the cardiac reflexes

Cardiac reflexes are fast-acting reflex loops between the CVS and CNS which contribute to the maintenance of cardiovascular haemostasis.

They include:

- **Baroreceptor reflex**
  Aortic arch and carotid sinus reflexes.
- **Bainbridge reflex**
  Atrial stretch receptor reflexes.
- **Chemoreceptor reflex**
  Decreased PaO_2 < 50mmHg or decreased pH sensed by peripheral chemoreceptors causes subsequent tachycardia and hypertension.
- **Cushing reflex**
  Brainstem compression causes ischaemia of the vasomotor centre leading to Cushings' Triad:
  - Hypertension
    May have a wide pulse pressure.
  - Bradycardia
    Due to baroreceptor response from hypertension.
  - Irregular respirations
- **Bezold-Jarisch reflex**
  Stimulation of C fibres of the vagus nerve in the cardiopulmonary region.
  - This causes:
    - Significant bradycardia
    - Hypotension
    - Apnoea, followed by rapid shallow breathing. These fibres can be stimulated by a number of substances, including:
  - Capsaicin
  - Serotonin
  - Those produced in myocardial ischaemia
- **Oculocardiac reflex**
  Pressure on the globe or traction on ocular muscles causes a decrease in heart rate. This is mediated by the:
  - Trigeminal nerve (afferent limb)
  - Vagus nerve (efferent limb)
    Increased vagal tone reduces SA nodal activity.

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Last updated 2019-07-18

Starling Forces

> Describe the essential features of the micro-circulation including fluid exchange (Starling forces) and control mechanisms present in the pre- and post-capillary sphincters

Interstitial fluid is an ultrafiltrate of plasma, with the net filtration pressure determined by the net effect of opposing hydrostatic and oncotic pressures:

$$NFP = P_{Capillary\ Hydrostatic} - P_{Interstitial\ Hydrostatic} - (P_{Capillary\ Oncotic} - P_{Interstitial\ Oncotic})$$

These four variables are known as **Starling's forces**.

Actual fluid movement is (of course) more complicated. **Hydrostatic pressure falls along the capillary**, and movement of solute and water are affected by other factors. Some of these are described by the:

- **Reflection coefficient** (σ)
  This describes the fact that a small amount of protein leaks from the capillary, slightly increasing interstitial oncotic pressure and slightly decreasing capillary oncotic pressure. It is dependent on the interstitial protein content, and has a value between 0 and 1.
- **Filtration coefficient** (Kf)
  Encompasses membrane permeability (to water) and membrane surface area. Varies between tissues:

The **Starling Equation** becomes:

$$Net\ Fluid\ Movement = K_f(P_{CH} - P_{IH} - \theta(P_{CO} - P_{IO})$$

Typical Values for Pressures (mmHg)

	Arteriolar end	Venous end
Capillary hydrostatic pressure	25	10
Interstitial hydrostatic pressure	-6	-6
Capillary oncotic pressure	25	25
Interstitial oncotic pressure	5	5

Organ-Specific Values

In the glomerulus:

- Reflection coefficient is close to 1 due to the impermeability of the glomerulus to protein
- Kf is high due to both high permeability and a large surface area.
- Hydrostatic pressure is high
- Glomerular oncotic pressure is essentially 0

In the liver:

- Reflection coefficient is close to 0 in hepatic sinusoids as they are very permeable to protein

In the lungs:

- Reflection coefficient of ~0.5 in the lungs due to significant leak of protein
  - Protein leak decreases as interstitial oncotic pressure rises, limiting further oedema formation
- The oncotic pressure gradient is small, and favours reabsorption

- Hydrostatic pressure gradient is small, but favours extravasation of fluid
  - Interstitial hydrostatic pressure becomes more negative closer to the hilum, drawing fluid into the pulmonary lymphatics

Causes of Oedema

Oedema can be localised or generalised, and in both cases caused by:

- **Increased Filtration Pressure**
  Occurs when capillary hydrostatic pressure exceeds interstitial hydrostatic pressure. Causes:
  - Increased Venous pressure
    This includes an increase in CVP:
    - CCF
    - TR
    - Increased venoconstriction
    - Increased MSFP
  - Impaired venous return
    - Obstruction
    - Respiratory muscle pump
    - Skeletal muscle pump
  - Positioning
- **Decreased Oncotic Pressure Gradient**
  - Decreased plasma protein
    - Hepatic failure
    - Critical Illness
  - Increased interstitial oncotic pressure
    - Mannitol/starch extravasation
- **Increased capillary permeability**
  - Inflammatory proteins
    - Substance P
    - Histamine
    - Kinins
- **Inadequate Lymph Flow**

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Last updated 2017-09-22

Variations in Blood Pressure

> Describe the physiological factors that may contribute to pulse variations in blood pressure

Blood pressure is not uniform throughout the circulation. Ventricular ejection generates two waves:

- A **blood flow wave**
  Travels at **~20cm.s^{-1}**.
- An **arterial pressure wave**
  Distends the elastic walls of the large arteries during systole, which then recoil during diastole to facilitate continual blood flow. This is the **Windkessel effect**.
  - This wave travels at **4m.s^{-1}**
  - **This is** what is **felt** when **pulses** are **palpated**, and what is **seen** on the **arterial line** waveform

Key pressures measured are:

- **Systolic blood pressure**
  Maximal pressure generated during ejection.
  - Determined by:
    - Stroke volume
    - Systolic time
    - Arterial compliance
    - Reflected pressure wave
  - Relevant for:
    - Bleeding
      - Clot disruption
      - Aneurysmal wall pressure
- **Diastolic pressure**
  Pressure exerted by the circulation upon the aortic valve.
  - Determined by:
    - Circulatory compliance
    - Circulating volume
    - Aortic valve (in)competence
  - Relevant for:
    - Coronary perfusion
- **Mean arterial pressure**
  Average pressure in the circulation throughout the cardiac cycle, as measured by the **area under the curve** of the arterial line waveform.
  - Determined by:
    - Systolic blood pressure
    - Diastolic blood pressure
    - **Heart rate**
      Increasing HR will tend to increase MAP, as overall systolic time (and therefore time spent at higher pressure) is increased.
    - Shape of the arterial waveform/diastolic runoff
      The slow decrease in pressure after peak systolic pressure represent elastic recoil of large arteries, increasing the pressure driving blood into the peripheral circulation. A longer diastolic runoff period leads to a larger area under the curve, and a higher MAP.
  - Relevant for:
    - Organ perfusion

Changes by Site of Measurement

Measured pressure changes predictably at more distal sites:

- All gradients are increased
  Arterial upstroke and falloff are both steeper.
- The SBP increases
- DBP decreases
- **MAP is constant**
- The dicrotic notch occurs later and becomes less sharp
  This occurs due to reflections in arterial pressure waves.

Respiratory Variation

Ventilation causes variation in peak systolic pressure due to dynamic changes in cardiac loading conditions:

- **Negative pressure respiration** (i.e. regular breathing) generates a negative intrathoracic pressure during inspiration
  Leads to increased VR, but also pooling of blood in the pulmonary circulation and relative underfilling of the LV, leading to a decrease in SV and peak systolic blood pressure.
- **Positive pressure ventilation** causes the reverse
  Increased intrathoracic pressure during inspiration results in a decreased venous return but increases LV filling via compression of the pulmonary circulation.
- When this change is **>10mmHg**, it is known as **pulsus paradoxus**
- The magnitude of this effect varies with:
  - Magnitude of intrathoracic pressure change
    Large changes in intrathoracic pressure cause correspondingly larger changes in ventricular filling.
  - Other factors affecting cardiovascular function
    - Preload
      - Volume state
    - Compliance
      - Pericardial compliance
        - Constriction
        - Tamponade
      - Cardiac compliance
        - Diastolic dysfunction
    - Afterload
      - PE
      - Raised intrathoracic pressure
        - PEEP
        - Tension PTHx
- These differences can be measured:
  - Qualitatively
    By looking at respiratory swing on an arterial line or plethysmograph; or by palpation.
  - Quantitatively
    Using **pulse pressure** or **stroke volume variation**.

Pulse Pressure Variation

Describes the variation in pulse pressure over the course of a respiratory cycle. Pulse pressure variation is:

- Mathematically defined as:

$$PPV = \frac{Pulse\ Pressure_{maximum} - Pulse\ Pressure_{minimum}}{Pulse\ Pressure_{mean}} \times 100$$

- Therefore, it is calculated as a **percent**
- Used as an indicator of **fluid responsiveness**
  - Patients higher on the **Frank-Starling curve** will have less change in stroke volume with an increase in preload, and therefore:
    - Reduced PPV
    - Be less fluid responsive
  - A PPV of **>12%** suggests volume responsiveness.
  - Note that this does not necessarily mean a fluid responsive patient needs fluid.
- Reliant on several assumptions:
  - Regular sinus rhythm
    Irregular heart rates (particularly AF) lead to significant alterations in ventricular filling and therefore pulse pressure, independent of the respiratory cycle.
  - Controlled mechanical ventilation
    No spontaneous efforts.
  - Adequate tidal volumes
    Must be $>8ml.kg^{-1}$.
  - Normal chest wall compliance
    Requires a closed chest.

Stroke Volume Variation

SVV is:

- Alternately defined as:
  - The percent change in stroke volume during inspiration and expiration over the previous **20 seconds**
  - Variation of beat-to-beat SV from the **mean value** over the previous 20 seconds
    $$SVV = \frac{SV_{max} - SV_{min}}{SV_{mean}} \times 100$$
- Calculated by specialised devices from an invasive arterial waveform Calculation incorporates:
  - Pulse pressure
  - Vascular compliance
    Estimated from nomograms based on patient age, gender, height, and weight.
  - Vascular resistance
    Estimated from arterial waveform shape.
- An alternative to PPV in measuring fluid responsiveness
  Relies on similar principles.
- Probably less specific but more sensitive than PPV for identifying fluid responders

Circulatory Factors

Changes in circulatory function:

- **Inotropy**
  The rate of systolic upstroke is related to $\frac{\Delta P}{\Delta t}$, and therefore contractility.
- **SVR**
  The gradient between the peak systolic pressure and the dicrotic notch gives an indication of SVR. E.g., a steep downstroke suggests a low SVR, as the pressure in the circulation rapidly falls when ejection ceases.
- **Preload**

A beat-to-beat variation is seen with the respiratory cycle, due to the change in preload occurring with changes in intrathoracic pressure.

Pathological Changes

Some pathological causes include:

- **Aortic Stenosis**
  Causes a reduction in:
  - Pulse pressure
    Due to reduced stroke volume.
  - Gradient of upstroke
    Due to reduced stroke volume.
- **Aortic Regurgitation**
  - Wide pulse pressure
    Combination of:
    - Increased SBP due to the increased force of ejection due to increased preload (Starlings Law), which occurs due to high ESV
    - Decreased DBP due to part of the stroke volume flowing back into the ventricle through the incompetent valve

---

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Pulmonary Circulation

> Outline the anatomy of the pulmonary and bronchial circulations

> Describe the physiological features of the pulmonary circulation and its resistance

> Understand the differences between the pulmonary and systemic circulation

The pulmonary circulation is:

- A **low-pressure**, **high-flow**, high-pulsatility circulation
- Supplied by the pulmonary trunk (pressure 25/8 mmHg), driven by the RV (pressure 25/0 mmHg)
    - Arteries and veins run with the bronchi as far as the terminal bronchioles, dividing at the same points
    - Beyond this, they form a capillary bed so thin it is essentially sheet of flowing blood punctuated by alveoli

The **bronchial circulation**:

- Arises from the systemic circulation, and supplies blood to the conducting zone of the lung
- A third drains back to the systemic circulation
- The remainder drains into the pulmonary vessels - this is a **physiologic shunt**
    - Supply to tumours is predominantly from the bronchial circulation (rather than the pulmonary circulation) as these vessels respond to angiogenic factors.

Differences between Pulmonary and Systemic Circulations

Blood Pressure

Pulmonary arterial pressure is 25/8 mmHg (MAP 15 mmHg) compared to 120/80 mmHg (MAP 100 mmHg) in the systemic circulation. This is because the systemic circulation must:

- **Regulate flow** to different organs at different times
  It therefore contains resistance vessels which allow it to allocate cardiac output accordingly.
- **Maintain flow** to organs far above the heart

Conversely, the pulmonary circulation must:

- **Accept the entirety of cardiac output**, with little capacity to regulate flow (hypoxic vasoconstriction being the exception)
- **Minimise extravasation** of fluid
    - As per Starlings Law, fluid movement out of the capillary is given by the difference in hydrostatic gradients and oncotic gradients
    - The net oncotic gradient is small (but favours reabsorption), however the pulmonary interstitium has **no hydrostatic pressure**
    - Increased pulmonary capillary pressure therefore causes extravasation of large volumes of fluid

- Consequently, pulmonary vessels are thin walled and contain minimal smooth muscle
- This makes the pulmonary circulation **highly compliant** - the volume of blood is able to change substantially with minimal change in pressure

Pulmonary Vascular Resistance

Vascular resistance follows Ohms law, i.e.:

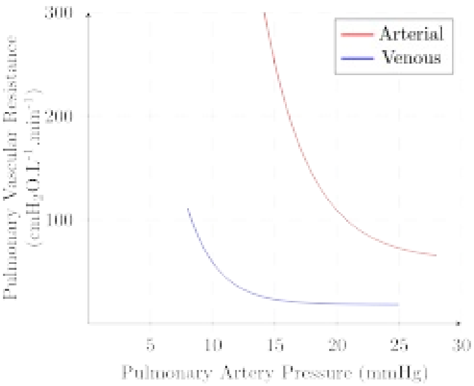
$$Vascular\ Resistance = \frac{P_{In} - P_{Out}}{Flow}$$

.

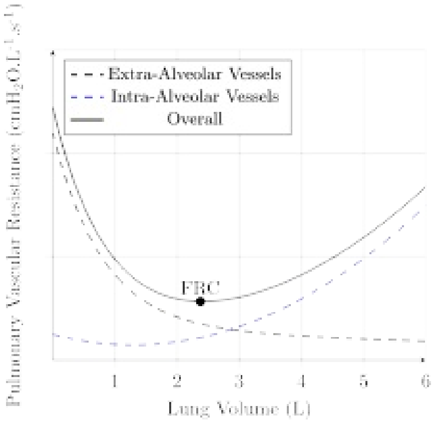
- Pulmonary vascular resistance is ~1/10th that of the systemic circulation
    - This is because the pressure drop across the pulmonary circulation is 10mmHg (MPAP - LAP), ~1/10th that of the systemic circulation, and flow is the same

Determinants of pulmonary vascular resistance are:

- **Pulmonary Artery Pressure**
  Increased PAP causes a decrease in PVR. This occurs because:
    - Previously closed pulmonary capillaries are recruited when their **critical opening pressure** is reached
      This is more important when MPAP is low.
    - Vessels distend at higher pressures
      This is more important when MPAP is high.



- **Lung volume** Lung volume has a variable effect on PVR.
    - At large lung volumes:
        - Resistance in large extra-alveolar vessels decreases as the vessels are pulled opening by distension of elastic tissues
        - Resistance in small intra-alveolar vessels increases as they are compressed by the high lung volumes
    - At small lung volumes, the reverse occurs



- **Hypoxic Pulmonary Vasoconstriction**
  Low **PAO_2** causes a vasoconstriction in the vessels supplying that alveolus, increasing PVR and directing blood to better ventilated alveoli.
    - Low alveolar PO_2 is the primary determinant
    - Low mixed venous PO_2 also contributes
    - Constriction begins when P_AO_2 falls below 100mmHg, and becomes dramatic below 70mmHg
    - This is important in:
        - Foetal circulation
        - Alveolar consolidation
            - Pneumonia
            - Cardiogenic pulmonary oedema

Raised LVEDP increases pulmonary venous pressures. Basal alveoli are more affected. HPV causes constriction of basal vessels, increasing blood flow to apical alveoli and resulting in **upper lobe diversion** seen on chest x-ray.

    - High altitude
  - HPV is attenuated by:
    - Elevated LAP
      Greater than 25mmHg.
    - High CO

- **Minor factors** which affect PVR:
  - **Increase** PVR:
    - Hypercarbia
    - Hypothermia
    - Acidaemia
    - Pain
  - **Decrease** PVR:
    - Bronchodilators
    - Volatiles

Response to Substances

Oxygen:

- The pulmonary circulation constricts when PO_2 falls, whilst the systemic circulation dilates

Carbon Dioxide:

- The pulmonary circulation constrictions when PCO_2 rises, whilst the systemic circulation dilates

Distribution of Pulmonary Flow

Gravity has a significant effect on pulmonary blood flow:

- In the upright lung, flow decreases almost linearly with height
- In the supine lung, flow to posterior regions exceeds that of anterior regions
  This occurs due to the low driving pressure of the pulmonary circulation, which means gravity has a much more significant affect on pulmonary blood flow than systemic blood flow.

West's Zones

The lung is divided into four zones, based on the relationship between alveolar and vascular pressures:

- **West's Zone 1**
  In West's Zone 1, PA > Pa > Pv.
  - This should not occur in normal conditions, because a normal pulmonary artery pressure is normally (just) sufficient
    This is because in the upright lung, the hydrostatic pressure difference will be about 30cmH_2O.
  - However, if alveolar pressure is raised (e.g. IPPV), or arterial pressure falls (shock), there may be a region where **alveolar pressure exceeds arterial pressure**

- **West's Zone 2**
  In West's Zone 2, **Pa > PA > Pv**.
  - Here, flow is determined by the arterial-alveolar pressure gradient rather than the arterial-venous gradient
    Alveolar pressure acts as a **Starling Resistor**, where **flow is independent of downstream pressure**.

- **West's Zone 3**
  Occurs when alveolar pressure falls below venous pressure, i.e. **Pa > Pv > PA**. Flow is dependent on the arterial-venous pressure gradient. Capillary pressure increases along their length, increasing transmural pressure and mean width.

- **West's Zone 4**
  Occurs at low lung volumes, as extra-alveolar vessels collapse and shunt occurs. The interstitium is acting as a Starling resistor, which can be expressed as: **Pa > Pint > Pv > PA**.

Hypoxic Pulmonary Vasoconstriction

As discussed above, HPV allows redirection of blood flow from poorly ventilated regions of the lung, and so improve V/Q matching. HPV is relevant in disease states, as well as specific physiologic circumstances:

- At high altitude, the PAO_2 is globally reduced, leading to high pulmonary artery pressures
- In utero, PAO_2 is negligible, and PVR is therefore very high
  This diverts blood from the pulmonary circulation into the left side of the heart via the foramen ovale. When the first breath is taken, pulmonary vessels dilate and the right-to-left shunt is reversed.

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Last updated 2019-07-18

Cerebral Blood Flow

> Describe the distribution of blood volume and flow in the various regional circulations and explain the factors that influence them, including autoregulation. These include, but not limited to, the cerebral and spinal cord~~, hepatic and splanchnic, coronary, renal and utero-placental~~ circulations

With respect to cerebral blood flow:

- Normal is **~750ml.min^{-1}** or ~15% of resting cardiac output
  Note that the brain makes up only ~2% of body weight.
  - A relatively high blood flow is required due to the high **cerebral metabolic rate for oxygen** ($CMRO_2$) of **50ml.min^{-1}**
- The brain is sensitive to interruptions in flow as it has:
  - A high metabolic rate
  - No capacity to store energy substrates

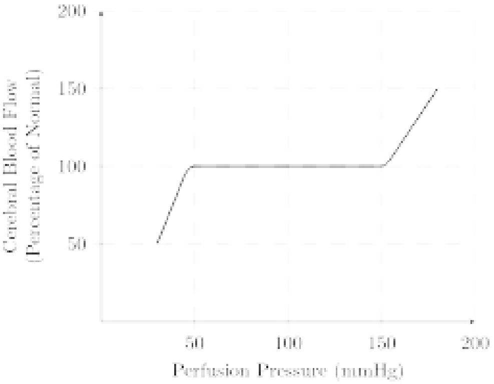
The factors affecting cerebral blood flow can be classified by the factors in the **Hagan-Poiseuille Equation**:

$CBF \approx \frac{\Delta P \pi R^4}{8 \eta L}$, where:

- ΔP is the pressure difference driving flow, i.e. CPP
- R is the radius of the blood vessels
- η is the blood viscosity
  These are also called rheologic factors.
- L is the length of the tube, a fixed quantity

Factors Affecting Perfusion Pressure{#cpp)

- Cerebral Perfusion Pressure is the difference between mean arterial pressure and intracranial pressure:
  $CPP = MAP - ICP$
- A **normal CPP** is **~80mmHg**
- In normal individuals, CBF is classically thought to be autoregulated over a **CPP range** of **60-160mmHg**
  - This occurs by **myogenic means**, similar to the kidney
  - In normal circumstances, this is dependent on MAP (i.e., with a normal ICP < 10mmHg, CBF is regulated over a MAP range of 50-150mmHg).
- Note that more **recent evidence** would suggest that CBF is autoregulated over a much narrower range of perfusion pressures, and has a greater capacity to buffer an increased rather than decreased perfusion pressure



- At the lower limit, the reduced perfusion pressure means flow cannot be maintained even with maximal vasodilation

- At the upper limit, the high perfusion pressure overcomes maximal vasoconstriction
  - Additionally, the increased CBF may result in damage to the blood-brain barrier
- The curve is **left-shifted in neonates and children** (due to lower normal MAP)
- The curve is **right-shifted in chronic hypertension**
- The curve is probably inaccurate in the pathological conditions where it would otherwise be useful, such as malignancy, subarachnoid haemorrhage, CVA, or TBI
  - This may be due to damage to either the feedback mechanisms, or the effectors (vasculature)
  - **Flow may become pressure-dependent**, and small changes in MAP can have large changes in CBF

Factors Affecting Vessel Radius

Vasodilation and constriction affect both cerebral blood flow and ICP, as vasodilatation increases cerebral blood volume and therefore may increase ICP through the Monroe-Kellie doctrine.

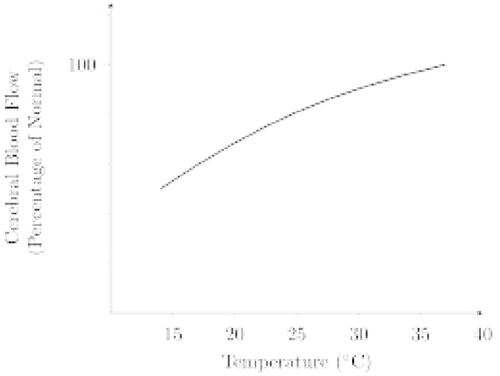
Vessel calibre is affected primarily by four factors:

- Cerebral metabolism
- **$PaCO_2$**
- **PaO_2**
- Neurohormonal factors
- Temperature

Cerebral Metabolism

Cerebral metabolism (typically given by the cerebral metabolic requirement for oxygen, $CMRO_2$) has a linear association with cerebral blood flow - this is known as **flow-metabolism coupling**. This is controlled locally through the release of vasoactive mediators, such as H^+, adenosine, and NO. Determinants of cerebral metabolism include:

- **Drugs**
  Cerebral metabolism may be decreased by use of drugs such as benzodiazepines, barbiturates, and propofol.
- **Temperature**
  $CMRO_2$ decreases linearly by ~7% per degree centigrade, allowing prolonged periods of reduced CBF without ischaemic complications.

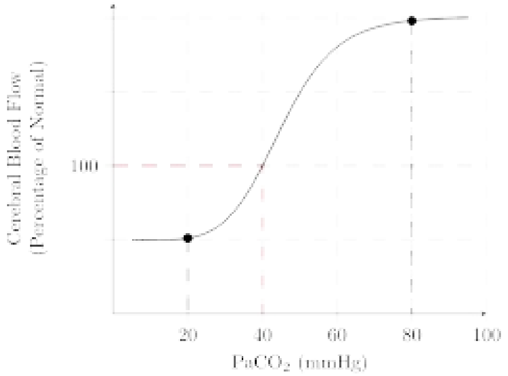


$PaCO_2$

Carbon dioxide acts as a cerebral vasodilator.

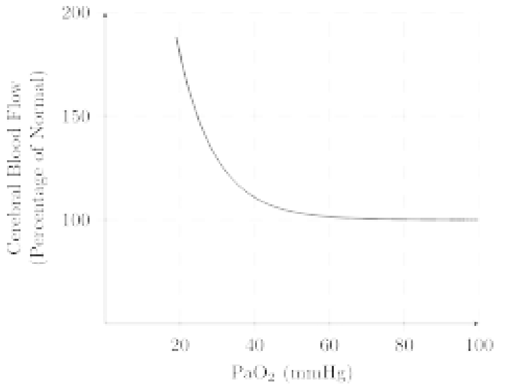
- CBF is almost linear between **20mmHg and 80mmHg**
  - Above 80mmHg, the circulation is maximally dilated
  - Below 20mmHg, the circulation is maximally constricted
    Additionally, the alkalosis causes a left-shift of the oxyhaemoglobin curve. This reduces offloading of oxygen, causing

hypoxia and subsequent vasodilation.
- There is a right-shift in chronic hypercapnea
  The mechanism of action is complex, but involves local increase in H^+ ions.
- Changes to CBF with CO_2 are dependent on current arteriolar tone - vasodilatory effects of CO_2 are significantly reduced when the perfusing pressure is low.



PaO_2

- CBF increases rapidly when PaO_2 falls below 60mmHg so that cerebral oxygen delivery is maintained
  Hypoxia causes a release of adenosine and reduced calcium uptake, with subsequent vasodilation



Neurohormonal

- Autonomic control of cerebrovascular tone is limited, though is responsible for the right-shift in the autoregulation curve with sustained hypertension

Factors Affecting Blood Viscosity

- Blood viscosity is dependent on haematocrit
- Reduced haematocrit is associated with increased CBF, but reduced O_2-carrying capacity
  The optimal haematocrit is ~0.3-0.35, which provides the best balance between reduction of viscosity to improve cerebral blood flow, without reducing DO_2.

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Hepatic Blood Flow

> Describe the distribution of blood volume and flow in the various regional circulations and explain the factors that influence them, including autoregulation. These include, but not limited to, ~~the cerebral and spinal cord~~, hepatic and splanchnic, ~~coronary, renal and utero-placental~~ circulations

The liver serves as a blood reservoir (30ml per 100g, half of which may be mobilised in hypovolaemia), and receives **25%** of cardiac output from a unique dual blood supply:

- Hepatic arterial system, which supplies about **one-third** of blood, but 40-50% of O_2
  Hepatic arterial blood has an **SpO_2** of **~98%**, as would be expected. It is a high-pressure, high-resistance, high-flow system (average velocity $18cm.s^{-1}$), with the capacity to autoregulate.

- Portal venous system, which supplies the remaining **two-thirds** of blood.
  It is a low-resistance, low-pressure, low-velocity system (average flow $9cm.s^{-1}$), with no capacity to autoregulate.
  The **SpO_2** of **portal venous blood varies** depending on gut activity:
  - In the **resting gut**, SpO_2 is **~85%**
  - In the **active gut**, SpO_2 is **~75%**

Regulation of Flow

As with other organs, blood flow is autoregulated via intrinsic and extrinsic mechanisms, and may be affected by external factors.

Intrinsic Autoregulation

- Myogenic autoregulation
- Hepatic arterial buffer response
  This is also known as the "hepatic artery-portal venous semi-reciprocal interrelationship".
  - Hepatic arterial resistance is proportional to portal venous blood flow, such that a reduction in portal venous flow causes a decrease in hepatic arterial resistance and increases hepatic arterial flow
    This is probably mediated by adenosine.

Extrinsic Autoregulation

- Autonomic Nervous System
  Both the hepatic and portal vasculature have sympathetic innervation:
  - The hepatic artery has dopamine receptors, as well as β- and α-adrenoreceptors
  - The portal vein has only α-adrenoreceptors
    Activation of these receptors causes venoconstriction, reducing the compliance of the hepatic vasculature and mobilising up to **250ml** of blood in times of sympathetic stress.

- Endocrine and hormonal effects
  A number of substances affect portal flow:

Hormone	Portal Vein Effect	Hepatic Artery Effect	Overall Effect on Flow
Adrenaline	Constriction	Constriction (α), then dilation (β)	Reduced
Glucagon	Dilation	-	Increased
Secretin	-	Dilation	Increased
Angiotensin II	Constriction	Constriction	Reduced

Vasopressin	Constriction	Constriction	Reduced
PCO_2	Constriction	-	Reduced

External Factors

Flow in the hepatic vein is dependent on venous return:

- Increased venous return (e.g. negative-intrathoracic pressure) increases hepatic flow
- Decreased venous return (e.g. positive-pressure ventilation, tamponade, haemorrhage), reduces hepatic flow, and in extreme cases flow may only occur intermittently throughout the cardiac cycle

- **Exercise** reduces both portal vein and hepatic arterial flow

Microvasculature

Hepatic arterioles and portal venules form the **hepatic triad** with a bile canaliculi. Hepatic arterioles and venules anastomose to form **sinusoids**, which create a specialised low-pressure (~2mmHg) capillary system which drains into the central veins of the hepatic acinus.

This arrangement:

- **Optimises hepatic O_2 extraction**
  Increased hepatic O_2 demand is met by increasing O_2 extraction, rather than by increasing flow (as occurs in the heart).
- **Prevents shunting and retrograde flow**

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1. CICM March/May 2013
2. Leslie RA, Johnson EK, Goodwin APL. Dr Podcast Scripts for the Primary FRCA. Cambridge University Press. 2011.
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Last updated 2019-07-18

Baroreceptors

> Describe the function of baroreceptors and to relate this knowledge to common clinical situations.

Baroreceptors are **stretch receptors** which monitor changes in arterial pressure. **Arterial pressure** is monitored by receptors in the:

- **Aortic arch**
    - Innervated by CNX
- **Carotid sinus**
  Small dilation of the ICA at the level of the bifurcation.
    - Innervated by CNIX
    - Remember the carotid *sinus* is a baroreceptor, the carotid *body* is a chemoreceptor

Low-pressure stretch receptors:

- Respond to increased venous return
- Are inhibited by positive pressure ventilation
- Act by stretch and typically described as **volume receptors**
- Are located in the:
    - **Atrial walls**
    - **SVC and IVC**
    - **Pulmonary circulation**

Baroreceptor Control

Afferent fibres from CNIX and CNX travel to the NTS in the **medulla**. Effector neurons from the RVLM are GABAergic and therefore inhibitory, i.e. increased baroreceptor discharge *reduces* tonic sympathetic tone and increases vagal tone.

Increased baroreceptor activity therefore **results in:**

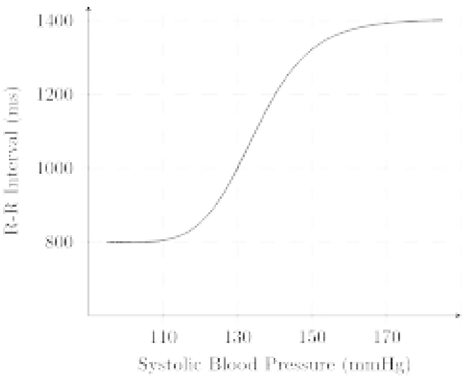
- Arterial and venous vasodilation
- Hypotension
- Bradycardia
- Decreased cardiac output
- Decreased respiratory rate

Conversely, **increased** activity of **low-pressure** stretch receptors results in an **increase** rather than a decrease in **heart rate**.

Baroreceptor Activity

Baroreceptors are:

- **More sensitive to pulsatile pressure** than constant pressure
  A decrease in pulse pressure without a change in MAP will decrease baroreceptor firing.
- Active throughout the cardiac cycle
  Rapid compensatory responses are vital in the short-term control of blood pressure, e.g. with posture.
- Active over the range from 50mmHg to 200mmHg



- This curve is left-shifted in children and neonates, and right-shifted in chronic hypertension, though this is reversible

Hormonal control

Activation of atrial/ventricular stretch receptors stimulates ANP/BNP release respectively, which act to reduce blood pressure in the following ways:

- Increased GFR
  Act to constrict the efferent arteriole and dilates of the afferent arteriole. This subsequently inhibits renin secretion through increased hydrostatic pressure at the JGA and increased Na^+ and Cl^- delivery to the macula densa.
- Decreased aldosterone
  Via inhibition of aldosterone secretion.
- Vasodilation
  Causes vasodilation of peripheral smooth muscle.

References

1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
2. CICM September/November 2014
3. ANZCA July/August 2000

Last updated 2018-06-25

Valsalva Manoeuvre

> Explain the response of the circulation to situations such as ~~changes in posture haemorrhage, hypovolaemia, anaemia, intermittent positive pressure ventilation, positive end-expiratory pressure, and~~ the Valsalva manoeuvre.

A Valsalva is forced expiration against a closed glottis. This can be achieved by increasing P_{AW} to 40mmHg for 15 seconds. This increase in intrathoracic pressure alters many haemodynamic parameters.

Phases

A Valsalva manoeuvre consists of four phases:

Phase I

- P_{AW} is increased to 40cmH_2O, with a corresponding increase in $P_{Thoracic}$
- SBP and DBP increase due to:
  - Compression of the aorta
  - Increased LV preload due to ejection of blood in the pulmonary vasculature

Phase II

- VR falls due to increased $P_{Thoracic}$
- CO falls due to decreased VR
- SBP and DBP fall due to decreased CO
- Baroreceptors are activated by the fall in BP, and SNS outflow increases, causing:
  - Increased HR
  - Increased SVR
    - BP therefore starts to recover late in Phase II

Phase III

- The Valsalva ceases, and P_{AW} returns to 0cmH_2O
- PVR rapidly drops as alveolar vessels re-expand
- SBP and DBP rapidly fall due to:
  - Decreased PVR causing decreased LV preload
  - Loss of high intrathoracic pressure compressing the aorta

Phase IV

- VR normalises
- CO normalises due to normal VR and PVR
- SBP and DBP transiently increase due to a normal CO entering a baroreceptor-driven high-SVR vascular bed
- Baroreceptors respond to high SBP an DBP by increasing vagal tone:
  - HR falls (reflex bradycardia)
  - BP falls

Abnormal Responses

Abnormal responses occur in cardiac failure and autonomic neuropathy.

CCF

In CCF a square-wave patten is produced:

- Increasing P_{AW} resulting in a sustained **increase** in SBP and DBP
- There is a slight decrease in SBP and DBP for the few seconds in phase III when airway pressure is released

Appears to be due to the increased circulating volume, as this difference resolves in venesected cardiac patients, and is demonstrated in normal individuals who are transfused to a high circulating volume.

Autonomic Neuropathy

Baroreceptor response to the Valsalva is minimal in both phase II and IV:

- In phase II, there is no compensatory increase in sympathetic outflow, so BP continues to fall until P_{AW} returns to 0mmHg
- In phase IV, there is no compensatory increase in vagal tone and so BP returns to normal without overshooting

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References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
2. Judson WE, Hatcher JD, Wilkins RW. Blood Pressure Responses to the Valsalva Maneuver in Cardiac Patients with and without Congestive Failure. Circulation. 1955;11:889-899.

Last updated 2019-07-20

CVS Changes with Obesity

> Describe the cardiovascular changes that occur with morbid obesity

Obesity is a multisystem disorder defined by an elevated body mass index (BMI):

- Normal: BMI < 25
- Overweight: BMI 25 - 30
- Obese: BMI > 30
- Morbidly Obese:
  - Obesity related disease and a BMI > 35
  - BMI > 40

Characteristics of obesity include:

- Complex genetic and environmental causes
- Increased caloric intake
- Increased metabolic rate (normal for BSA)

The effect of obesity on the cardiovascular system is complex, and can be classified into:

- Hormonal changes
  Abdominal visceral fat is responsible for secreting a large number of hormones which affect cardiovascular parameters:
  - Increased leptin
    Contributes to cardiac remodelling and LVH.
  - Angiotensinogen
    Leads to systemic hypertension and LV remodelling.
    - Small amounts are produced in adipocytes, which increases as fat volume increases
  - Plasminogen activator inhibitor-1
    Reduces fibrinolysis and predisposes to VTE.
  - Inflammatory adipokines
    Impair endothelial function, leading to increased SVR.
  - Catecholamines
    Increased contractility, SVR, and worsen endothelial function.
    - Released with:
      - Hypoxia
      - Hypercapnea
      - Negative intrathoracic pressure
      - Fragmented sleep
        Due to OSA.

- Changes in key cardiovascular parameters
  - Increased VO_2
    Due to increased LBM and fat mass.
  - Increased Blood Volume
    Due to increased angiotensin II and aldosterone.
  - Increased Stroke Volume
    Due to:
    - Increased preload (major factor)
    - Increased contractility (minor factor)
      Due to increased circulating adrenal hormones.
  - Increased Cardiac Output

To maintain DO_2.
        - Initially with preserved ejection fraction

- Cardiac changes
    - Diastolic dysfunction
      Due to myocardial fibrosis impairing relaxation.
    - Fatty infiltration of myocardium and conducting system
        - Predisposes to arrhythmias
          Risk is worsened by change in myocardial architecture, hypoxia, and increased circulating catecholamines.
    - Biventricular hypertrophy as a response to increased afterload
        - LV afterload increased due to systemic hypertension
          LVH is much more common than RVH.
            - Eccentric hypertrophy due to volume overload
            - Concentric hypertrophy due to pressure overload or hormonal changes
        - RV hypertrophy due to:
            - LV diastolic failure
            - Increased PVR
                - Hypoxia
                  Due to:
                    - Effects of OSA
                    - Increased shunt through collapsed lung bases
                - Acidosis

References

1. Alvarez A, Brodsky J, Lemmens H, Morton J. Morbid Obesity: Peri-operative Management. Cambridge: Cambridge University Press. 2010.
2. Lotia S, Bellamy MC. Anaesthesia and morbid obesity. Contin Educ Anaesth Crit Care Pain 2008; 8 (5): 151-156.

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Cardiovascular Effects of Ageing

> Describe the cardiovascular changes that occur with ageing.

CVS effects of ageing can be divided into cardiac, vascular, and autonomic changes:

- **Cardiac changes**
  - Decreased receptor density and number
  - Decreased maximum heart rate
    Due to fibrosis of the SA node causing reduced pacemaker cell number and function, and reduction in catecholamine receptor density.
    - $Maximum\ heart\ rate \approx 220 - Age$
  - Decreased inotropy
    Minor.
  - Increased reliance on atrial kick
    Reduced ventricular compliance increases the reliance on atrial kick to achieve adequate preload.
  - Decreased diastolic compliance
    - Due to hypertrophy from increased afterload
- **Vascular changes**
  - Reduced compliance
    Due to loss of elastic tissue in the large arteries.
  - Increased SVR
    Reduced compliance results in increased vascular resistance.
  - Reduced endothelial cell function (decreased NO)
    Impairs the ability of the vascular tree to adapt to changes in pressure/volume leading to:
    - Elevated SBP
    - Reduced DBP
      Reduced elastic recoil causes diastolic run off and a fall in diastolic blood pressure.
  - Reduced catecholamine receptor density
    Reduced responsiveness to (and increased number of) circulating catecholamines.
- **Autonomic**
  - Impaired autonomic function
    Due to decreased catecholamine responsiveness.
  - Impaired baroreceptor response
  - Decreased exercise tolerance
    Reliance on preload to maintain cardiac output.

References

1. ANZCA February/April 2016
2. Cheitlin MD. Cardiovascular physiology-changes with ageing. Am J Geriatr Cardiol. 2003 Jan-Feb;12(1):9-13.

Last updated 2019-07-20

Inotropes

> Understand the detailed pharmacology of inotropes ~~and vasopressors~~

Inotropes are agents which alter myocardial contractility.

- Positive inotropes increase contractility
- Negative inotropes decrease contractility

Classes of Positive Inotrope

Classes	Class I: Increase Intracellular Calcium	Class II: Calcium Sensitisers	Class III: Metabolic/Endocrine
Examples	Adrenaline, milrinone, glucagon, digoxin	Levosimendan	T3, Insulin
General Mechanism of Action	Increase intracellular Ca^{2+} by a variety of different pathways	Increase sensitivity of actomyosin to Ca^{2+}	Variable. T3 potentiates the effect (or increases expression of) cardiac β_1 receptors

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References

1. Leslie RA, Johnson EK, Goodwin APL. Dr Podcast Scripts for the Primary FRCA. Cambridge University Press. 2011.
2. Tielens ET, Forder JR, Chatham JC, Marrelli SP, Ladenson PW. Acute L-triiodothyronine administration potentiates inotropic responses to P-adrenergic stimulation in the isolated perfused rat heart. Cardiovascular Research 32 (1996) 306-310.

Last updated 2017-09-18

Adrenoreceptors

> Understand the pharmacology of adrenoreceptor blocking drugs.

This covers the pharmacology of adrenoreceptors. The production and metabolism of endogenous catecholamines is covered under adrenal hormones. Detailed information on specific sympathomimetic agents, including structure-activity relationships, is in the pharmacopeia.

Adrenoreceptors are classified by their varying sensitivity to different catecholamines. Additionally:

- All adrenoreceptors are G protein-coupled receptors
  - Each receptor contains seven transmembrane α-helical subunits, three extracellular loops, and three intracellular loops
- Alpha receptors have different subunits and mechanisms of action
- **All beta receptors** are:
  - G_s coupled
  - Activate adenylate cyclase increasing cAMP, leading to increased Na/K<sup+ ATPase activity and hyperpolarisation

Adrenoreceptor Subtypes

α_1-receptors:

- Are present in smooth muscle
  Agonism causes vasoconstriction, relaxation of GIT muscle (via presynaptic receptors), and contraction of GU muscle.
- They are:
  - G_q coupled
  - Phospholipase C activated increases IP_3, increase calcium

α_2-receptors:

- Are present in the CNS, arterioles, pancreas
  Agonism causes sedation, analgesia, vasodilatation, and inhibition of insulin release.
- They are:
  - G_i coupled
  - Inhibits adenylate cyclase, decreasing cAMP

β_1-receptors:

- Are present in cardiac muscle and the JGA
  - Cardiac agonism increases inotropy, chronotropy, and dromotropy
  - JGA agonism increases renin release
- Increase in cAMP increases intracellular calcium

β_2-receptors:

- Are present in skeletal vascular and bronchial smooth muscle, the liver, and on cell membranes
- Agonism causes:
  - Vasodilation and bronchodilation
  - Hepatic glycogenolysis
  - Increases activity of the Na^+-K^+ ATPase pump, increasing intracellular potassium
- Increase in cAMP increases Na^+/K^+ ATPase activity and hyperpolarisation

β_3-receptors:

- Are present in fat

Agonism causes lipolysis and thermogenesis.

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
2. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
3. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.

Last updated 2018-05-27

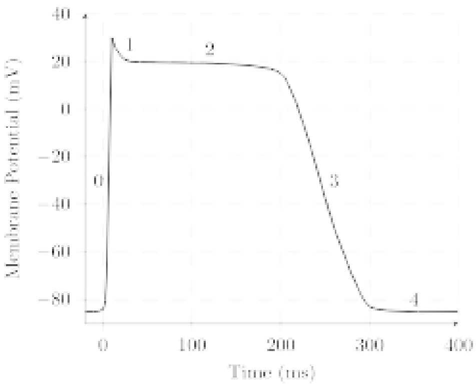
Antiarrhythmics

> Understand the pharmacology of antiarrhythmic drugs

Antiarrhythmic drugs are typically classified using the **Vaughan Williams** classification system, which divides drugs into four classes based on their effect on the cardiac action potential. Many drugs will act via multiple mechanisms.

- **Class I**: Block voltage-gated Na channels
  - Class Ia: Intermediate dissociation
  - Class Ib: Fast dissociation
  - Class Ic: Slow dissociation
- **Class II**: β-Blockers
- **Class III**: Prolong the action potential (Usually via K^+ channel blockade)
- **Class IV**: Ca^{2+} antagonists

This classification is notably incomplete, as some drugs (such as amiodarone) fit into multiple categories, and others (such as digoxin, adenosine, and magnesium) fit into none.



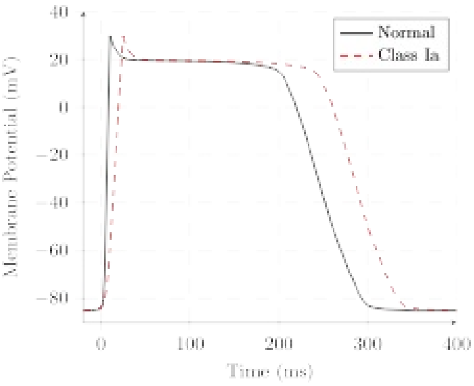
Class I

- Na^+-channel blockade inhibits action potential prolongation by blocking **active and refractory** sodium channels in a **use-dependent fashion**
- This inhibits tachyarrhythmias whilst allowing normal conduction
- Extent of block depends on the heart rate, membrane potential, and the subclass of drug
- Sodium channel blockade **increases pacing threshold** and **defibrillation energy requirement**

Class Ia

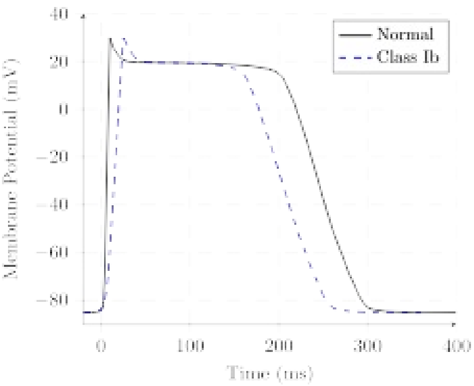
- Class Ia drugs have mixed properties of Ib and Ic, and also have Class III effects
- As they **prolong the AV conduction** and **prolong the action potential** they **increase both QRS duration and the QT interval**
- Examples include **procainamide**

Pro-arrhythmic effects may result because AV nodal conduction may be increased, so despite decreased atrial activity increased ventricular conductance results in a potentially fatal shortening of diastolic time



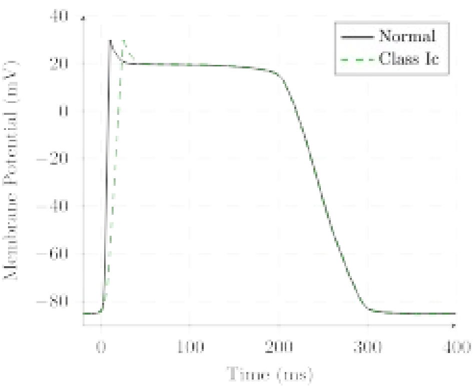
Class Ib

- Class Ib drugs bind to open sodium channel, and will **associate and dissociate** from a sodium channel **in the course of a normal beat**
- Tachyarrhythmias are prevented because dissociation occurs too slowly for a further action potential to be generated
- Class Ib drugs will bind selectively to refractory channels, such as occurs in ischaemia
- As they have **little effect on normal cardiac tissue** they have **little effect on the ECG**
- Examples of class Ib agents include include **phenytoin** and **lignocaine**



Class Ic

- Class Ic drugs **associate and dissociate slowly creating a steady-state level of block**
- This causes indiscriminate blockade and general reduction in excitability
- Class Ic agents are used to suppress unidirectional or intermittent conduction pathways
- As they markedly slow conduction velocity they **increase QRS duration**
- Examples of Class Ic agents include **flecainide**

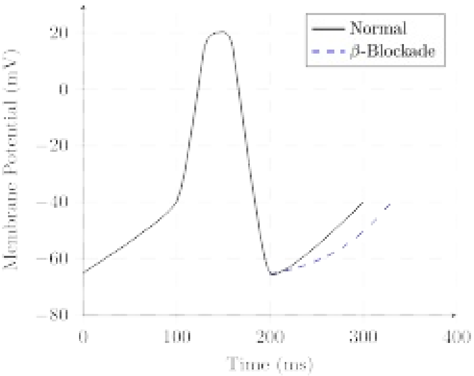


Class II

Normal β-adrenergic stimulation has a number of pro-arrhythmic effects:

- Increased pacemaker potential current
- Increased slow-inward Ca^{2+} current
- Increased repolarising K^+ and Cl^- currents
- Increased Ca^{2+} stored in the sarcoplasmic reticulum, which may be spontaneously released causing a delayed-after-depolarisations
- Reduced serum $[K^+]$*

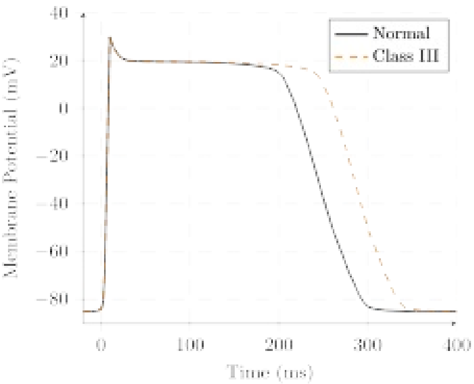
β-blockers have an antiarrhythmic effect by antagonising these mechanisms. They are useful for treatment of arrhythmias occurring with sympathetic over-activation, such as post MI.



Class III

Blocking of outward K^+ channels slows cardiac repolarisation, which increases the cardiac refractory period. This has a number of beneficial effects:

- Decreased automaticity
- Decreased ectopy
- Reduced defibrillation energy requirement
- Increased inotropy



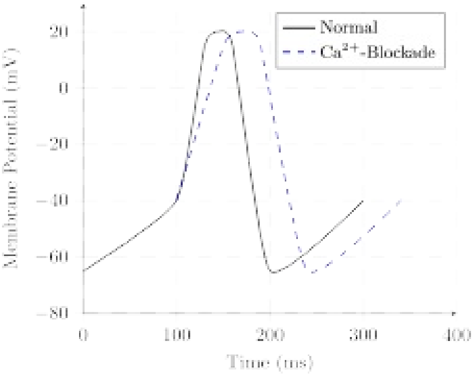
Due to the prolonged repolarisation, they will also cause a **long QT** (though in the case of amiodarone this is not associated with an increased risk of TPD).

Class IV

2+

Class IV drugs **inhibit L-type Ca^{2+} channels**, inhibiting the slow inward calcium current, which:

- Slows SA and AV nodal conduction
  AV blockade slows transmission of supra-ventricular arrhythmias.
- Reduces inotropy
- Prevents after-depolarisations
  This suppresses ectopy by reducing calcium leak from sarcoplasmic reticulum.



Alternatives to Vaughan Williams

As the Vaughan Williams classification system does not neatly divide agents, and some agents do not fit into any category, they may also be classified by their uses:

Indication	Examples
SVT	Digoxin, adenosine, verapamil, β-blockers
VT	Lignocaine, mexiletine
SVT/VT	Amiodarone, flecainide procainamide, sotalol
Digoxin toxicity	Phenytoin

References

1. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.
2. Brunton L, Chabner BA, Knollman B. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th Ed. McGraw-Hill Education - Europe. 2011.
3. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

Last updated 2019-07-18

Functional Anatomy and Control of Renal Blood Flow

> Describe the functional anatomy of the kidneys and renal blood flow.

Functional Anatomy

The functional unit of the kidney is the **nephron**. Nephrons:

- Are composed of the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct
- Are divided by their location into:
  - **Superficial cortical** nephrons
    Have **short loops** of Henle.
  - **Juxtamedullary** nephrons
    Have **long loops** of Henle, and the efferent arteriole forms the vasa recta for the kidney.
  - **Mid-cortical nephrons**
    May have either long or short loops.

Control of Renal Blood flow

The kidneys:

- Receive **22% of cardiac output** at rest
- Extract only **10% of delivered O_2**
- Have a **high renal blood flow** exceeds that required for metabolism
  High flow is instead needed **to produce** the large volume of **glomerular filtrate** (125ml.min^{-1}) required for excretion of waste.

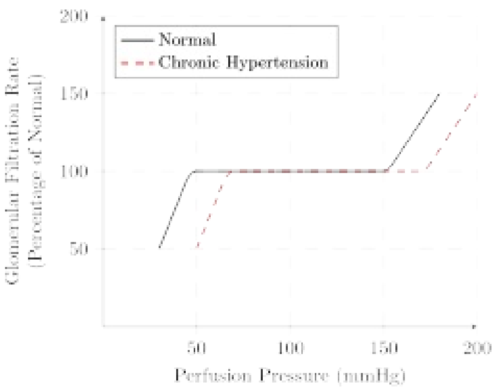
Autoregulation

Renal blood flow is **autoregulated** over a wide range of mean arterial pressures (60-160mmHg) via:

- **Myogenic** autoregulation
- **Tubuloglomerular** feedback

Myogenic autoregulation:

- Describes the intrinsic constriction of the afferent arteriole in response to an increased transmural pressure
- This increases vascular resistance in proportion to the increase in pressure, keeping flow constant



Tubuloglomerular feedback is more complicated, and describes the constriction or dilation of the afferent arteriole in response to adenosine or NO (respectively) release from the macula densa:

- The macula densa lies in the wall of the ascending limb of the loop of Henle
- It detects change in tubular flow rate (probably via changing Na^+ flux across its membrane)
    - Increased flow in the loop indicates an increased perfusion pressure, prompting release of adenosine and constriction of the afferent arteriole
    - Decreased flow indicates a decreased perfusion pressure, reducing adenosine release and prompting the release of NO and renin, which causes the afferent arteriole to dilate

Notably, flow to **juxtamedullary** nephrons is **not autoregulated**. High blood pressure increases juxtamedullary flow, increasing GFR and impairing renal concentration, resulting in a **pressure diuresis**.

Neuronal Control

The kidneys are innervated by noradrenergic sympathetic nerves, which causes:

- Afferent and efferent arteriolar constriction
  This increases capillary hydrostatic pressure (increasing filtration) and also increases capillary oncotic pressure (decreasing filtration).
    - This leads to an overall slight reduction in GFR

Hormonal Control

Renin:

- Is released from the juxtaglomerular apparatus by β_1 stimulation
- Catalyses the production of angiotensin I from circulating angiotensinogen
  Angiotensin I is then converted into Angiotensin II by circulating ACE.
    - *The actions of the RAAS are described in more detail in the endocrine functions of the kidney.*

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1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
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Last updated 2018-06-25

Glomerular Filtration and Tubular Function

> Describe glomerular filtration and tubular function.

Glomerulus

- The **glomerulus** is a set of capillaries which invaginate **Bowman's capsule**
- Fluid filters out of the capillary bed into Bowman's space based on **Starling forces**:
    - Membrane permeability
    - Hydrostatic pressure gradients
    - Oncotic pressure gradient
        - Reflection coefficient

Glomerular Filtration Rate

Glomerular Filtration Rate is:

- The volume of *plasma* filtered by the glomerulus each minute
  Normal renal *blood* flow is 1.1 $L.min^{-1}$, however renal *plasma* flow is less (600 $ml.min^{-1}$ for a normal haematocrit).
  Therefore, the normal filtration fraction (proportion of renal blood flow which is filtered) is ~20%.
- Typically **125ml.min^{-1}**
    - Decreases with age (partially due to loss of nephron number)

GFR can be expressed as the **product** of **Net Filtration Pressure** and the combination of membrane permeability and membrane surface area, designated **K_f** (the filtration coefficient):

$$GFR = NFP \times K_f$$

- **Net Filtration Pressure** is given by opposing **Starling Forces** across the glomerular membrane:
  $$NFP = P_{Glomerular\ Hydrostatic} - P_{Bowman's\ Hydrostatic} - P_{Glomerular\ Oncotic}$$
  As protein is not filtered in normal states, the oncotic pressure in Bowman's Space is usually assumed to be 0mmHg.
    - The average capillary NFP is ~17mmHg
    - **Hydrostatic pressure**
      Determined by renal blood flow and the relative constriction of the **afferent** and **efferent** arterioles. Hydrostatic pressure **decreases along the capillary**. Affected by:
        - MAP
            - Catecholamines
            - Local autoregulation
                - Myogenic
                - Tubuloglomerular Feedback
                - Hormones
                    - Angiotensin II constricts the efferent arteriole more than the afferent arteriole, causing an increase in renal resistance with only a small decrease in GFR.
                    - Prostaglandin E2 dilates the afferent arteriole, increasing GFR
    - **Osmotic pressure**
      Increases along the capillary, as protein free-fluid is filtered leaving a higher concentration of protein within the capillary. This change in capillary oncotic pressure is proportional to the filtration fraction - a greater filtration fraction will cause a higher oncotic pressure of fluid in the capillary.

- **Membrane permeability**
  Overall permeability is:
  - A function of:
    - Membrane permeability, in turn affected by:
      - **Capillary endothelium**
      - **Basement membrane**
        Negatively charged molecules have **reduced filtration** as the basement membrane is also negatively charged which opposes movement out of the capillary.
      - **Foot processes** of podocytes
        Molecules **less** than **7000 Dalton** are **freely filtered**, whilst larger molecules are filtered less.
    - Membrane Surface Area
      Typically very high for water and solutes.
    - Affected by:
      - Glomerulonephritis
        - Change in basement membrane or podocyte foot processes
      - Angiotensin II causing contraction of mesangial cells

Tubular Function

Proximal Tubule

The proximal tubule reabsorbs 60% of glomerular filtrate. It **reabsorbs basically everything**, including protein, and secretes H^+, organic ions (such as uric acid and salicylates), ammonium, and up to 60% of filtered urea load.

Loop of Henle

The loop of Henle consists of a **thin descending limb** and a **thick ascending limb**;

- The descending limb reabsorbs water only
- The thick ascending limb:
  - Reabsorbs common ions (Na^+, K^+, Cl^-) and HCO_3^-
  - Excretes H^+
- The function of the loop is to concentrate urine in states of water deprivation
  This is done via the countercurrent mechanism.

Countercurrent Multiplier

The countercurrent concentrating system is:

- Formed from the loop of Henle and collecting ducts
- Driven entirely by the removal of NaCl from the ascending limb
- Most easily understood in stages:
  - NaCl is actively transported out of the thick ascending limb, increasing interstitial osmolality *at that level*
  - Increased interstitial osmolality results in water reabsorption from the descending limb, increasing tubular osmolality *at that level*
  - This more concentrated tubular fluid then flows to a deeper, more concentrated level, and more water is reabsorbed
  - The effect is progressive concentration of tubular and interstitial fluid, but with a low and stable energy cost as the relative gradients that each transport pump works against is small
  - The end result is a dilute urine leaving the ascending limb, but a highly concentrated medullary interstitium

Countercurrent Exchange

The **vasa recta** are peritubular capillaries that:

- Surround the loop of Henle of juxtamedullary nephrons
- Follow the loop into the medulla
- Have typically low blood flow
  This prevents "washout" of the countercurrent multiplier, as the slow blood flow allows solute concentrations to equalise at each level of the loop.
    - In hypovolaemic situations, renal blood flow falls and vasa recta flow decreases, further reducing washout
    - When renal blood flow is high, vasa recta flow increases
      This washes out part of the medullary concentration gradient and reduces the concentrating ability of the kidney.

Distal tubules

Fluid entering the distal tubule has about **one-third** the **osmolarity** of plasma. The distal tubule:

- Reabsorbs: Na^+, Cl^-, HCO_3^-, Ca^{2+}
- Secretes: K^+, H^+

Collecting Ducts

- The collecting ducts lie in the interstitium (concentrated by the loop of Henle)
- In the absence of aquaporins, the collecting ducts are **impermeable to water**
    - Osmolality can fall as low as **50 mmol.L^{-1}** due to continued reabsorption of solute
    - In the presence of aquaporins, water flows down the osmotic gradient into the concentrated interstitium, resulting in a highly concentrated urine
    - ADH also **increases** collecting duct permeability of **urea**
        - Urea moves via solvent drag with water

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Handling of Organic Substances

> Describe the role of the kidney in the handling of glucose, nitrogenous products and drugs

Broadly speaking, the kidney:

- Reabsorbs important substances
- Filters and secretes waste products

Methods of Reabsorption

Reabsorption from tubule to blood can occur via two mechanisms:

- **Transcellular reabsorption**
  Substance is absorbed into tubular epithelium and then secreted into blood. This is typically achieved by symporters, which rely on the low intracellular sodium concentration to move substances out of the tubule against their concentration gradient.
- **Paracellular reabsorption**
  Substance passes through the matrix of tight junctions between epithelial cells.

Rate Limitation

There are functional upper limits on the rate of reabsorption of substances from the tubule. There are two limits:

- **Tubular Maximum (T_{max}) Limited**
  Saturation of transporters occur, so a further increase in solute concentration does not increase the rate of substance reabsorption.

  The maximum solute concentration for a T_{max} system is a function of the transporter.
- **Gradient Limited**
  Leaks in the tight junctions will result in solute moving from the interstitium back into the tubule if the tubular concentration falls too low.

  The maximum solute concentration for a gradient limited system is related to the permeability of the tight junctions.

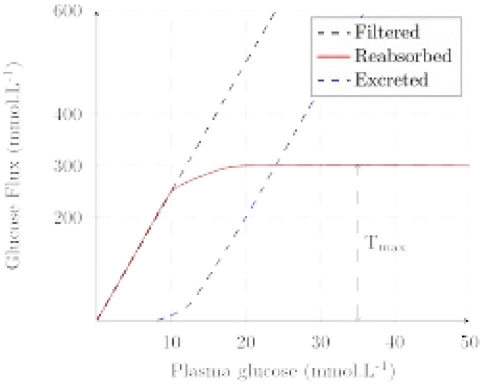
Glucose

Glucose is:

- Freely filtered at the glomerulus
- Completely reabsorbed via the **transcellular route** in the proximal convoluted tubule under normal circumstances
- Actively transported via the SGLUT (Sodium-dependent Glucose symporter) transmembrane protein
  - Secondary active transport (down the established Sodium gradient)
  - There are two subtypes of the SGLUT protein:
    - Low-affinity, high-capacity
      Rapidly reabsorbs glucose, but is ineffective when glucose concentration is low. It is located early in the PCT, and reabsorbs ~90% of filtered glucose.
    - High-affinity, low-capacity
      Slowly reabsorbs glucose, but remains effective even when glucose concentration is low. It is located late in the PCT, where glucose concentration is lower (having already been reabsorbed by the high-capacity transporter), and reabsorbs ~10% of filtered glucose.

- As GFR increases, glucose filtration and therefore glucose absorption increase
- As glucose is co-transported with Na^+, absorption of Na^+ and H_2O also increase
- This phenomenon is known as **glomerulo-tubular balance**

- Glucose reabsorption is a T_{max} system, and is overwhelmed when filtered glucose exceeds 300mg.min^{-1} or 16mmol.min^{-1}
  - This typically occurs when plasma (and therefore filtered) glucose concentrations exceed **12mmol.L^{-1}**



Consequences of Glycosuria

Glycosuria occurs when filtered glucose exceeds the capacity of the PCT to reabsorb it, and causes:

- Increased urine volume
  - Glucose acts as an osmotic diuretic by:
    - Reducing Na^+ reabsorption in the PCT
      As some glucose is not absorbed, the sodium that would normally be reabsorbed with (tubuloglomerular balance) is remaining in the tubule.
    - Reducing water and salt reabsorption in the Loop of Henle
      Due to high tubular flow rates.
      - Impairs the formation of the medullary concentration gradient, limiting concentrating capacity
  - Stimulates ADH release
- Electrolyte derangements
  - Hypokalaemia due to:
    - Reduced K^+ reabsorption due to high tubular flow rates
    - Aldosterone release due to hypovolaemia, increasing Na^+ reabsorption and K^+ secretion
  - ADH release in response to hypovolaemia
- Loss of substrate for ATP generation
- Increase risk of urinary infections

Nitrogenous Products

- Amino acids are reabsorbed by amino-acid transporters
  These are not (entirely) selective, and reabsorb several structurally similar amino acids.
  - These shared pathways create competition for binding sites between amino acids
  - Excess of one substance will lead to both excretion of this substance in urine, as well as inappropriate excretion of related substances

- Larger proteins (such as albumin) are in fact filtered at the glomerulus (though in very small amounts)
  Reuptake occurs in several stages:
  - Endocytosis at the luminal membrane
    This is an energy-dependent process, requiring protein to bind to membrane receptors.
  - Degradation of protein into individual amino acids

    - Reuptake across the basolateral membrane

- Smaller proteins and peptides (e.g. insulin, angiotensin II) are completely filtered
    - Catabolism occurs in the tubular lumen by membrane-surface peptidases
    - Amino acids are reabsorbed by standard amino-acid transporters

Urea

Urea is a small, water soluble molecule produced in the liver from ammonia as a method for eliminating nitrogenous waste.

Urea excretion is complex, as it has an important role in the counter current multiplier. This means that in the short term (hours to days) elimination may not match production, although over weeks they will be equal. Urea is:

- Freely filtered
- ~50% of filtered load is reabsorbed in the PCT by solvent drag (with water reabsorption)
  Urea concentration is slightly increased as more water is reabsorbed than urea.
- The urea reabsorbed in the PCT is then secreted into the Loop of Henle via UT uniporters
    - Luminal concentration of urea is much higher in the ascending limb due to the absorption of water
- ~50% is reabsorbed (again) in the medullary collecting ducts
  Here, urine becomes so concentrated that luminal concentration of urea exceeds medullary concentration.
    - Overall, 50% of filtered load is excreted

pH Dependent Drug Reabsorption

- Many substances, such as drugs, are weak acids or bases
- Reabsorption of these substances is pH dependent
    - **Weak acids** are proportionally **more ionised at a pH above their pKa**
    - **Weak bases** are proportionally **more ionised at a pH below their pKa**
    - Unionised substances are lipid soluble, and able to diffuse into tubular cells down concentration gradients
    - Ionised substances are trapped within the lumen

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Measurement of GFR

> Describe the principles of measurement of glomerular filtration rate ~~and renal blood flow~~

Renal clearance of a substance quantifies the effectiveness of kidneys in excreting substances. The definition of clearance is the *volume* (typically of plasma) cleared of a drug per unit time. Renal clearance can therefore be expressed as:

$Cl = \frac{U_C . U_Q}{P_C}$, where:

- Cl = Clearance
- U_C = Urine concentration
- U_Q = Urine flow rate
- P_C = Plasma concentration

Clearance and GFR

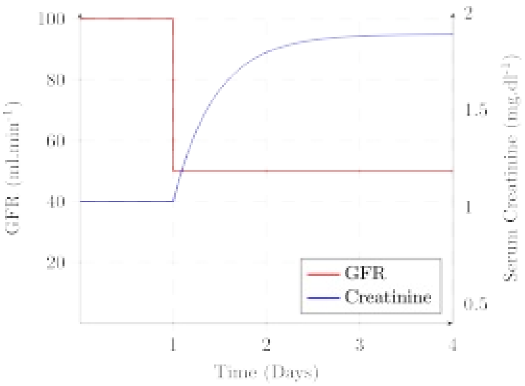
As the elimination of most substances is dependent on glomerular filtration, clearance of a substance can be used to estimate GFR. Methods include:

- **Inulin**
  Inulin is a naturally occurring polysaccharide.
  - Inulin clearance accurately measures GFR as it is:
    - Freely filtered by the glomerulus
    - Not secreted at the tubules
    - Not reabsorbed
  - However, inulin is not produced by the body and so must be given by IV infusion
    This limits its clinical utility.
- **Creatinine**
  Creatinine is a byproduct of muscle catabolism.
  - Creatinine is used clinically to measure renal function because it is:
    - Produced at a relatively constant rate
      Factors affecting creatinine production include:
      - Race
      - Muscle mass
        - Age
        - Sex
      - Diet
    - Not metabolised
    - Freely filtered by the glomerulus
    - Minimally secreted
      As GFR falls the *proportion* of creatinine secreted by renal tubules increases, so plasma creatinine will overestimate GFR when GFR is low.
    - Not reabsorbed
  - GFR can be approximated by creatinine clearance
    This is given by the equation: $$GFR \approx Cl_{Cr} = \frac{U_{[Cr]} . U_Q}{P_{[Cr]}}$$

Serum Creatinine

This formula demonstrates that **GFR is inversely proportional to serum creatinine** concentration.

- **This is only true when both creatinine production and glomerular filtration are at steady-state**
  A sudden drop in glomerular filtration (e.g. aortic cross-clamp) will not result in an immediate rise in creatinine.
  - During acute changes in GFR, serum creatinine will underestimate GFR until a new steady state is reached
    Creatinine must be produced and not eliminated for it to rise.



Estimating Creatinine Clearance

Using the above formula requires measurement of urine volume. This is:

- Typically performed by taking a 24 hour urine collection
- Tedious, and so creatinine clearance is often estimated
  A common method is the **Cockcroft-Gault formula**, which has a correlation of ~0.83 with creatinine clearance:
  $Cl = \frac{(140-A)\times W\times S}{72\times Cr}$, where:
  - = Clearance
  - = Age
  - = Sex coefficient (Male = 1, Female = 0.85)
  - = Creatinine in μmol.L^{-1}

Alternative formulas are **MDRD** and **CKD-EPI**. These equations have two advantages of Cockcroft-Gault:

- They are better predictors of GFR
- They do not require weight, and so can be calculated by the laboratory automatically Other required data (e.g. age) can be taken from hospital records.

These estimates have similar weaknesses to the above:

- Dependent on serum creatinine, which can be highly variable. Formulas are derived from average values of dependent variables, and so will be unreliable at extremes of:
  - Age
  - Muscle mass
  - Critically ill
  - Malignancy
  - Diet

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Last updated 2019-07-18

Endocrine Functions of the Kidney

> Outline the endocrine functions of the kidney

The kidney is involved in a number of endocrine processes and produces or metabolises a number of hormones:

- RAAS
- Vitamin D
- EPO
- Prostaglandins

Renin-Angiotensin-Aldosterone System

The RAAS is a signaling pathway involved in blood pressure control. It involves a number of hormones:

- **Angiotensinogen** is produced by the liver in response to:
  - Glucocorticoids
  - Thyroid hormones
  - Oestrogens
  - Angiotensin II
  - Various inflammatory proteins
- **Renin** is a protease produced by the kidneys in response to β_1 stimulation or hypotension, and exists to **cleave angiotensinogen** to **angiotensin I**
- **ACE** cleaves angiotensin I to angiotensin II, and also cleaves bradykinin into inactive metabolites
- **Angiotensin II** increases blood pressure via a number of mechanisms:
  - Simulates **aldosterone release** from the adrenal cortex, increasing sodium and water retention
  - **Vasoconstriction of efferent greater than the afferent arterioles**
    Results in slight decrease in GFR at a lower perfusion pressure, but increases filtration fraction.
    - NB: Different sources quote different changes (increase or decrease) in GFR
      The final effect may vary depending on the contribution of other autoregulatory processes.
  - **Reduces K_f** through constriction of glomerular mesangial cells
  - Increased SNS activity and **central and peripheral vasoconstriction**
  - **Increases thirst** via hypothalamic stimulation
  - Stimulates **ADH release**, reducing renal water excretion
  - Stimulates release of angiotensinogen
- **Aldosterone** acts on the distal convoluted tubule to:
  - Increase reabsorption of Na^+ and water
  - Increase elimination of K^+ and H^+

Vitamin D

Vitamin D has a complex metabolic pathway which meanders through a number of organ systems:

- Vitamin D_3 may be absorbed in diet or produced in skin by the action of UV light on 7-dehydrocholesterol
- Vitamin D_3 is then hydrolysed in the liver by CYP450 enzymes to form 25-hydroxycholecalciferol (25-OHD_3)
- 25-OHD_3 is then converted in the proximal tubule to calcitriol - the active form

Erythropoietin

Erythropoiesis is stimulated by EPO release:

- In adults, EPO is released from the:
    - Peritubular capillary fibroblasts (85%)
    - Liver (15%)
- EPO is released in response to:
    - Hypoxia
    - Hypotension
    - Low Hct
- Erythropoiesis is inhibited by:
    - High red cell volume
    - Renal failure

      Production of EPO is decreased in renal failure, which is why patients with end-stage renal disease require exogenous EPO.

References

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Acid-Base Balance

> Describe the role of the kidneys in the maintenance of acid/base balance

Acids produced by the body can be:

- **Volatile** (CO_2)
  - Body produces and eliminates **~13-20mol.day^{-1}**
  - Removed by the lungs
- **Fixed** (everything else)
  - Include lactate, sulphate, phosphate, and ketones
  - Body produces and eliminates **10mmol.kg^{-1}.day^{-1}**
  - Eliminated by the kidney
    Mechanisms for elimination of acid include:
    - Reabsorption of HCO_3^-
      This is equivalent to the removal of the same amount of H^+.
      - As there is usually a net production of acid, under normal circumstances **all filtered HCO_3^- is reabsorbed**
      - Note that removal of an acid load is associated with greater HCO_3^- generation and reabsorption, not increased H^+ secretion
    - Bound to filtered buffers
    - As ammonium
  - The rate and extent of these reactions is dependent on ECF pH and ion concentrations, which gives the kidney control over ion concentrations
  - Urinary pH can fall as low as ~4.4, before the active transport of H^+ is inhibited

Bicarbonate and the Kidney

Buffer systems minimise changes in pH until the kidney can eliminate excess hydrogen.

Bicarbonate is the predominant ECF buffer system (see Acid-Base physiology for more on buffers). By adjusting the level of HCO_3^- the kidney is able to adjust pH, as per the Henderson-Hasselbalch equation:

$$\begin{aligned} pH &= pK_a + log\frac{[HCO_3^-]}{[CO_2]} \\ &= 6.1 + log\frac{24}{1.2} \\ &= 7.4 \end{aligned}$$

Where:

- pK_a = 6.1, the pKa of HCO_3^-
- $[HCO_3^-]$ = 24, the normal $[HCO_3^-]$ in mmol.L^{-1}
- $[CO_2]$ = 1.2, the normal $[CO_2]$ in mmol.L^{-1}

Bicarbonate is:

- Freely filtered
  4320 mmol.day^{-1} of HCO_3^- is filtered (24mmol.L^{-1} x 180 L.day^{-1}, normal range is 4-5mol.day^{-1})
- Reabsorbed in the PCT (90%), thick ascending limb, DCT, and CT

Adjusting rate of absorption allows correction of an acidosis or alkalosis. All **HCO_3^- reabsorption is equivalent to a loss of H^+**.

Reabsorption of Bicarbonate

Reabsorption of bicarbonate involves several steps:

- H^+ is secreted into the lumen in one of three ways:
  - Primary H^+ ATPase in the PCT and DCT
  - H^+-Na^+ antiporter in the PCT and ascending limb
  - H^+-K^+ ATPase in the CT
- Secreted H^+ combines with filtered HCO_3^- to form CO_2 and H_2O
- CO_2 and H_2O diffuse into the tubular cell
- CO_2 and H_2O are converted back into HCO_3^- and H^+ in the tubular cell
- HCO_3^- is reabsorbed into the capillary via the HCO_3^--Cl^- antiporter, and the H^+ ion is available to be secreted into the tubule (in exchange for K^+ in the collecting ducts and Na^+ in the proximal tubule)

This complicated process allows HCO_3^- to be moved from the tubule to the tubular cell and then to the capillary. **There is no elimination of H^+** by this method - the purpose of H^+ secretion is to facilitate the **reabsorption of HCO_3^-** into the tubular cell.

Ammonia

Glutamine provides a mechanism for elimination of a large number of H^+ ions:

- This is important in:
  - Elimination of excess metabolic acid
  - Renal compensation for acidosis
- This occurs via:
  - Filtered glutamine is absorbed into **proximal tubular cells** and metabolised to NH_4^+ (ammonium) and HCO_3^-
  - HCO_3^- diffuses into blood, and the NH_4^+ is secreted into the tubule via the NH_4^+-Na^+ antiporter and eliminated in urine
  - The $NH_3 + H^+ \Leftrightarrow NH_4$ reaction has a pKa of 9.2 meaning:
    - Ammonia cannot act as an effective urinary buffer
    - Ammonia is not a **titratable acid**, as it will not release H^+ ions as urinary pH increases
      This means filtered ammonia does not contribute to the lower limit of urinary pH (4.4), which is why it is so important in the renal correction of severe metabolic acidosis.

Bound to Filtered Buffers

Secreted H^+ may also combine with a filtered buffer (e.g. PO_4^{3-}). **These H^+ ions are not reabsorbed**. About **36mmol** of H^+ is eliminated with filtered PO_4^{3-} each day, with each PO_4^{3-} binding **two** H^+ ions.

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Dialysis

Dialysis is the **separation of particles in a liquid based on their ability to pass through a membrane**.

Indications

Failure of normal renal functions, i.e.:

- **A**cid
- **E**lectrolyte derangement
  Particularly hyperkalaemia.
- **I**ntoxications
- **O**verload
- **U**reamia

Physical Mechanisms

Fluid and electrolytes can be removed by four different mechanisms:

- **Diffusion**
  Diffusion is the **spontaneous movement of substances from a higher concentration to a lower concentration**, where rate of movement is proportional to the concentration gradient (as per Fick's Law).

- **Ultrafiltration**
  Movement of water, as determined by Starling's Forces.
    - When a solvent passes through a membrane, the process is called osmosis. The frictional forces between solutes and water molecules will pull dissolved substances along, a process known as bulk flow or **solvent drag**.

Implementation

- **Haemodialysis**
  Uses diffusion.
    - Blood is pumped through an extracorporeal circuit that contains a dialyser.
    - Dialysate flow is countercurrent, which maximises the gradient for diffusion.
    - Solutes move across a membrane between blood and dialysate, as per Fick's Law:
        - Concentration gradient between blood and dialysate
            - Flow rate of blood and dialysate
        - Solubility of the solute
            - Mass
            - Charge
            - Protein binding
        - Dialysis membrane permeability
            - Thickness
            - Porosity
            - Surface area

- **Haemofiltration**
  Uses ultrafiltration.
    - Both a positive hydrostatic pressure in blood and a negative hydrostatic pressure in dialysate is generated, causing

    ultrafiltration and removal of solutes via solvent drag.
  - Elimination via bulk flow is **independent of solute concentration gradients across the membrane**.
  - Transport is dependent on Starling Forces:
    - The transmembrane pressure generated
      This is a function of:
      - Blood flow to the membrane
        Determines hydrostatic pressure.
      - Oncotic pressure gradient
    - Porosity of the membrane
  - Additionally, a high filtration fraction will cause excessive haemoconcentration, and clotting of the filter
  - The filtered fluid (ultrafiltrate) is discarded, and replaced with another fluid depending on the desired fluid balance.

Differences

- Renal Replacement Therapy (RTT) can be via:
  - Peritoneal dialysis (PD)
  - Intermittent haemodialysis (IHD)
    IHD causes greater cardiovascular instability compared to CRRT as the fluid and electrolyte shifts occur more rapidly.
  - Continuous Renal Replacement Therapy (CRRT)
    - Continuous Veno-Venous Haemofiltration (CVVH)
    - Continuous Veno-Venous Haemodiafiltration (CVVHDF)

Method chosen depends desired effect:

- Small molecules (<500 Da) and electrolytes can be removed by filtration or dialysis
- Medium-sized molecules (500-5000 Da) are best removed by filtration
- Low molecular weight proteins (5000-50000 Da) are removed by filtration
  This includes removal of inflammatory proteins, which may be beneficial in sepsis.
- Water is best removed by filtration

Pharmacokinetics of RRT

Pharmacokinetics are unpredictable, but are broadly affected by:

- **Drug factors**
  - **Free drug in plasma**
    Drugs with a small proportion of free drug in plasma are (unsurprisingly) poorly removed by RRT (but **may be removed via plasmapheresis**). These include:
    - Highly (> 80%) protein bound substances
      Examples included phenytoin, warfarin, and many antibiotics.
      - Not that this **may not apply in overdose**
        Once protein binding sites are saturated, both free drug fraction and efficacy of dialysis is increased.
    - Drugs with a V_D greater than $1L.kg^{-1}$
  - **Size/Molecular Weight**
    - Small molecules (< 500 Da) are more easily cleared by diffusive methods of RTT
    - Molecules > 15kDa are poorly dialysed
      This includes proteins, heparins, and monoclonal antibodies.
  - **Volume of distribution**
    Drugs with high volumes of distribution are poorly dialysed, as removal of drug from plasma only removes a small proportion of total-body drug content.

- **Dialysis factors**

- **Dose/Flow rates**
  Reduced flow rates will reduce clearance.
    - Conventional high-flux haemodialysis has more rapid clearance compared to lower-flux haemoperfusion or CRRT
- **Membrane permeability**
- **Timing**
  Drugs given between IHD or SLED sessions will not be cleared until the next session.s

- **Patient factors**
    - **Residual renal function**
      Patients residual GFR will also affect pharmacokinetics.

An Incomplete List of Drugs

Drugs Removed on RRT	Drugs not removed on RRT
Barbiturates	Digoxin
Lithium	TCAs
Aspirin	Phenytoin
Sotalol/Atenolol	Other beta-blockers
Theophylline	Gliclazide
Ethylene Glycol	Benzodiazepines
Methanol	Warfarin
Aminoglycosides, metronidazole, carbapenems, cephalosporins, penicillins	Macrolides, quinolones

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Sodium and Water

> Describe the function, distribution, regulation and physiological importance of sodium~~, chloride, potassium, magnesium, calcium and phosphate~~ ions

Normal total body Na^+ is 60mmol.kg^{-1}, 70% of which is exchangeable. Total body Na^+ is distributed as:

- 50% in ECF
  Sodium is the dominant extracellular cation.
  - Typical ECF [Na^+] of 140mmol.L^{-1}.
- 45% in bone
- 5% in ICF
  A minor intracellular cation.
  - ICF [Na^+] varies with cell type, but is typically 12-20mmol.L^{-1}.
  - Concentration is kept low by the action of the $2Na^+$-$3K^+$ ATPase exchange pump and the low permeability of the cellular membrane to Na^+

Function of Sodium

- **Regulation of ECF volume**
  Principal ECF cation. Changes in sodium levels cause compensatory fluid shifts. Loss of sodium *content* will result in hypotension/hypovolaemia, with consequent baroreceptor stimulation and activation of the RAAS. Baroreceptors will activate with a **7-10% change in volume**.

- **Osmolarity**
  Changes in sodium *concentration* affect osmoreceptors and will affect ADH and thirst mechanisms. Osmoreceptors will activate with a **1-2% change in osmolality**.

- **Acid-Base balance**
  Na^+-H^+ exchange pumps in the kidney are stimulated in acidosis.

- **Resting Membrane Potential**
  Alterations in sodium concentration will affect intracellular potassium to a similar degree, which will alter the RMP.

Regulation of Sodium and Water

Regulation of any system is typically a balance between **input** and **output**:

- Sodium intake is **essentially unregulated**
- Therefore, sodium concentration is a function of:
  - Sodium elimination
  - Sodium reabsorption
  - **Water homeostasis**
    Control of total body water is a major mechanism to regulate sodium concentration.

Sodium Elimination

Sodium is eliminated in:

- Sweat and GIT
  Obligatory and not amenable to regulation.

- GIT
    - Acclimatisation to hot environments improves the efficiency of sweating by reducing its tonicity, reducing sodium loss
- GIT
- Urine
    - Adjust renal elimination is the main mechanism to regulate sodium concentration
      Can be performed in two ways:
        - **Changes in GFR**
          Changes in GFR due to hyper or hypovolaemia will (indirectly) adjust sodium elimination. Increased plasma volume increases GFR, and vice versa.
        - **Changes in sodium reabsorption**
          This is the main mechanism for controlling sodium in euvolaemia, and is mediated primarily by **aldosterone**.

Sodium Reabsorption

Given that:

- Normal glomerular filtrate is ~180L.day^{-1}
- The dominant osmole in glomerular filtrate is sodium
- Normal urine output is ~1.5L^{-1}

The majority of filtered sodium must be reabsorbed. This is called **bulk reabsorption** and occurs in the PCT and LOH:

- 60% of total reabsorption is by the Na^+-K^+ ATPase pump in the PCT
- 30% of total reabsorption is by the Na^+-K^+-$2Cl^-$ co-transporter in the LOH

The remaining 10% of sodium reabsorption occurs in the DCT and CT. As it is under the influence of aldosterone, it is the component which is important in regulation. Aldosterone increases Na^+ reabsorption by increasing the number or activity of these pumps:

- Na^+-Cl^- pumps in the DCT
- Na^+-K^+ ATPase pumps in **principal cells** of the DCT
- Na^+-H^+ pumps in **intercalated cells** of the CT

Water Homeostasis

Body water homeostasis involves:

- Sensors
  Osmoreceptors present in the:
    - Macula densa
    - Circumventricular organs
      Subfornical organ and the vascular organ of the lamina terminalis.
        - Change in cellular volume secondary to changes in osmolality alter hormone secretion.
- Effectors
  Predominantly hormonal:
    - ADH
    - RAAS
    - Natriuretic peptides

References

1. Brandis K. The Physiology Viva: Questions & Answers. 2003.
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3. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
4. National Research Council. Recommended Dietary Allowances. 10th Ed. 1989. National Academies Press.

Last updated 2019-07-18

Potassium

> Describe the function, distribution, regulation and physiological importance of ~~sodium, chloride,~~ potassium, ~~magnesium, calcium and phosphate~~ ions.

Potassium is the major intracellular cation, with 90% of total body potassium present in the ICF. A further 8% is sequestered in bone, with 2% present in the ECF.

- Normal ECF concentration is 3.5-5mmol.L^{-1}
- Normal ICF concentration is ~150mmol.L^{-1}

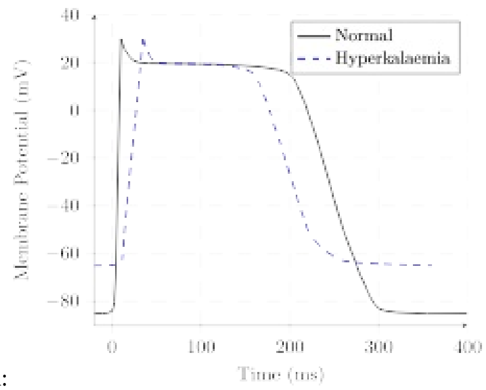
Function and Dysfunction

Potassium is important for:

- Regulation of intracellular pH
- Control of intracellular volume
- DNA and protein synthesis
- Enzymatic function
- Resting membrane potential

The **resting membrane potential** is determined by the ratio of intracellular:extracellular potassium, as per the Nernst equation:

- Small changes in extracellular ion concentration produce large changes in voltage
  This has significant effect on excitable tissues.
- Rapid changes in potassium concentration cause symptoms at lower levels than chronic changes
  Symptoms are related to the change in action potential generation.



Ventricular Action Potential in Hyperkalaemia:

Hyperkalaemia

Hyperkalaemia causes:

- The resting membrane potential to become less negative
  As per the Nernst equation.
  - This results in the resting membrane potential being closer to the threshold potential, increasing irritability
  - Several symptoms, including:
  - Weakness
  - Paralysis
  - Parasthesias
  - ECG findings are those of **prolonged depolarisation** and **rapid repolarisation**:

Serum [K^+] (mmol/L)	ECG Findings
5.5-6.5	Tall tented T waves
6.5-7.5	Loss of P wave, lengthening PR interval
7.5-8.5	Widening QRS
>8.5	Sine-wave QRS

Hypokalaemia

Hypokalaemia:

- Causes the resting membrane potential to become more-negative
  This makes it more difficult for a stimulus to reach the threshold potential, and therefore it is harder to generate and propagate action potential.
- ECG findings are those of **rapid depolarisation** and **prolonged repolarisation**, and include:
  - Prolonged PR
  - Long QT
  - Flat T waves or TWI
  - U waves
  - ST depression
  - Severe hypokalaemia may result in:
  - Frequent supraventricular and ventricular ectopics
  - Supraventricular arrhythmias
  - Ventricular arrhythmias

Regulation

Serum potassium is dependent on intake, sequestration, and elimination.

Intake

Dietary intake may be highly variable. Potassium is completely absorbed from the upper GI tract.

Sequestration

Several factors affect potassium sequestration:

- **Insulin** and **β_2-agonism** results in increase activity of the Na^+-K^+ ATPase pump, shifting potassium into cells following a meal and during exercise
- **Acidosis** causes an **extracellular** shift of potassium, as hydrogen ions are exchanged for potassium ions
  The reverse occurs in alkalosis.
- **Cell lysis** may release a large amount of potassium into circulation and cause significant hyperkalaemia if a large number of cells are destroyed
- **Aldosterone** increases uptake of potassium into cells

Elimination

Elimination of potassium occurs via the kidneys, and is dependent on production of large volumes of glomerular filtrate and secretion by the **distal convoluted tubule** and **collecting duct**.

In normal conditions:

- The PCT and ascending limb reabsorb the majority of absorbed potassium
  This is essentially fixed.
  - PCT absorbs ~55%
  - Ascending limb absorbs ~30%
- The principal cells of the DCT and collecting duct secrete potassium
  Altering potassium secretion is the main method by which the kidney regulates serum potassium.
  - The collecting duct has a much greater role than the DCT
  - With normal dietary intake, more potassium is secreted than reabsorbed
    This changes in conditions of potassium depletion.

Control of Tubular Secretion

Tubular potassium secretion is mainly a function of:

- **Plasma [K^+]**
  Increased plasma [K^+] stimulates the Na^+-K^+ ATPase pump in the principal cells, and also stimulates aldosterone release from the adrenal cortex.
- **Tubular flow rate**
  Movement of potassium out of principal cells occurs down a passive concentration gradient. Increasing tubular flow rate increases the concentration gradient for potassium
- **Aldosterone**
  Aldosterone increases production of the Na^+-K^+ ATPase pump, which increases potassium secretion and uptake into cells.

Minor contributors include:

- Sodium and water content
  - High sodium content inhibits aldosterone release, reducing potassium elimination
  - High water content inhibits ADH excretion and reduces secretion of potassium, however high water content also increases flow through the renal tubule, which indirectly increases tubular secretion of potassium.
- Alkalosis
  Alkalosis increases elimination of potassium as the Na^+-K^+ ATPase pump is stimulated by low H^+ ion concentration.

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1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
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3. Nickson,C. Hyperkalaemia. Life in the Fast Lane.
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Last updated 2017-10-04

Principles of Acid-Base Physiology

> Explain the principles underlying acid-base chemistry

There have been several different theories of acid-base chemistry. The one most relevant for the primary exam is the **Brønsted–Lowry definition**, which defines:

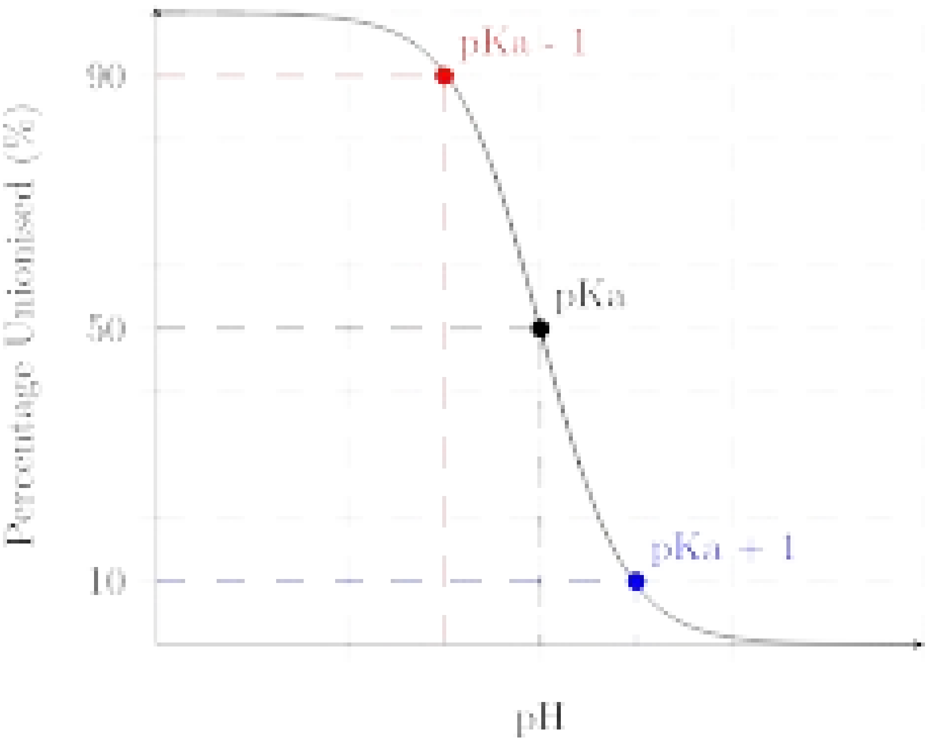
- An **acid** as a **proton donor**
- A **base** as a **proton acceptor**

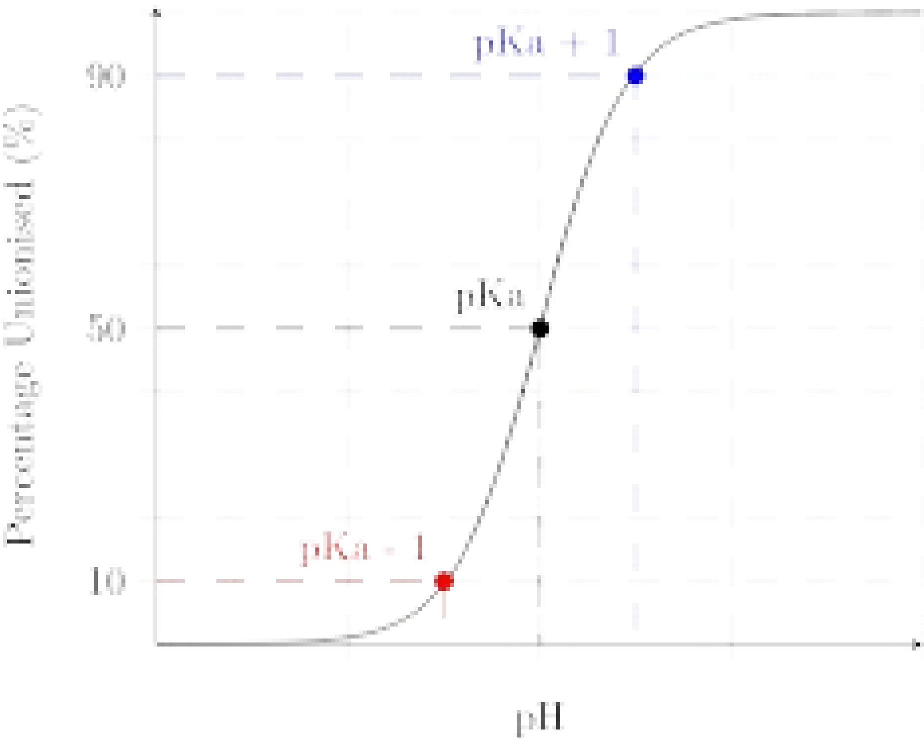
pH

- Stands for the **power of hydrogen**
- Is a measure of **hydrogen ion activity** in a solution
  - Activity can be approximated by concentration
  - Therefore, pH can be expressed as a function of hydrogen ion concentration: $pH = -log_{10}[H^+]$
    Using pH rather than concentration makes it easier to compare different solutions.

pKa

- Strong acids (and bases) dissociate completely in solution
- Weak acids (and bases) only partially dissociate
  They have a dissociated state (A-) and an undissociated state (HA)
- The ratio of concentrations on each side can be used to calculate the **acid dissociation constant**, **Ka**
  $$Ka = \frac{[A^-] \times [H^+]}{[HA]}$$
  This equation describes the strength of an acid by indicating how readily the acid gives up its hydrogen.
- Similar to pH, this value is often log transformed to **pKa** produce an index, which allows easy comparison of different substances:
  $$pKa = -log_{10}Ka$$
- pKa has several useful properties:
  - An acid of base will be 50% ionised when the pH of its solution equals its pKa
  - **A**cids are more **i**onised **a**bove their pKa
  - **B**ases are more **i**onised **b**elow their pKa
  - An increase in pH of 1 above the pKa will result in that substance being either 90% (for an acid) or 10 % (for a base) ionised





Systemic Effects of Acid-Base Disorders

pH disturbance affects many organ systems:

- **Respiratory**
  - Increased $\dot{V}_A$
    Peripheral and central chemoreceptors increase ventilation in response to a fall in pH.
  - Oxyhaemoglobin-Dissociation Curve

Right-shifted by a fall in pH.
  - Bronchoconstriction
    Hypercapnea causes parasympathetically-mediated bronchoconstriction.
- **Cardiovascular**
  - Inotropy
    Inotropy falls in acidosis due to a direct myocardial depressant effect. May be offset by increased SNS tone in low-grade acidosis. Alkalosis may increase inotropy by increasing responsiveness to circulating catecholamines.
  - Decreased response to catecholamines
    When pH < 7.2.
  - Arrhythmias
    Secondary to altered SNS tone and electrolytes.
  - Vasodilation
    Directly due to hypercapnea.
- **CNS**
  H^+ ions cannot cross the BBB, however CO_2 can.
- **Fluid and Electrolyte**
  - Plasma **K^+ increases** by **0.6mmol.L^{-1} for every 0.1 unit fall** in **pH**
    This is due to impairment of the Na^+/K^+-ATPase
  - **H^+ ions bind** to the **same site on albumin as calcium**, so ionised calcium will **increase**
- **MSK**
  - Bones
    Chronic metabolic acidosis consumes bone phosphate to buffer H^+ ions, causing osteoporosis.
- **Cellular**
  - Enzyme function
    Denaturation and functional impairment.
  - Molecular ionisation
    Change in ionisation may change a molecules ability to cross cell membranes (e.g. reducing dose of thiopentone in acidosis), or affect their function
  - Resting membrane potential
    Change in ion permeability will alter RMP, and therefore how easy it is to generate an action potential.

Change with Temperature

pH is temperature dependent:

- **pH increases** by **0.015** for every **1°C fall** in **temperature**
  Due to decreased ionic dissociation of water.
- **Gas solubility** almost always **increases** when **temperature falls**
  Dissolving is typically (not always) an **exothermic** reaction. As the kinetic energy content of a molecule falls, its ability to dissociate from solution decreases.
  - As CO_2 dissolves, $PaCO_2$ falls
- As blood gas machines operate at 37°C, a measurement error will occur if a patient is not close to 37°C
  - A **hypothermic** patient will have a **higher pH** and **CO_2** than measured

There are two common methods for **managing** pH of significantly hypothermic patients (e.g., those on CPB): **pH-stat** and **alpha-stat**.

pH-stat

- CO_2 is added to the circuit so that pH and $PaCO_2$ are normal when corrected for temperature
- This theoretically improves oxygen delivery by preventing the left-shift in the oxyhaemoglobin dissociation curve
- The increased CO_2 also causes cerebral vasodilation, which:

- Increases speed and uniformity of cerebral cooling
- Increases risk of cerebral embolic events

alpha-stat

- pH and CO_2 values are maintained at 'normal for 37°C'
  - Measured values will be different, as:
    - pH will be increased
    - CO_2 will be decreased
- Cellular autoregulation is preserved
- Unlike pH-stat, this does not cause cerebral vasodilation

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
2. ANZCA July/August 1999
3. Chemlab. Solubility. Florida State University.

Last updated 2019-07-18

Compensation

> Explain the principles underlying acid-base chemistry

Metabolic Acidosis

Compensation to metabolic acidosis includes:

- Buffering
  Occurs over minutes to hours. Includes:
  - ECF buffers
    - Bicarbonate
    - Plasma proteins
      - Albumin
  - ICF buffers
    - Include phosphate, proteins
    - Leads to hyperkalaemia due to H^+/K^+ exchange
      K^+ increases by $0.6 mmol.L^{-1}$ per 0.1 unit fall in pH.
  - Bone
    Exchange of Na^+ and Ca^{2+} in bone.
    - Leads to demineralisation and release of alkaline compounds
- Respiratory compensation
  Occurs in minutes.
  - Rapid response
  - Cannot compensate completely
- Renal compensation
  Occurs over days to weeks. Includes:
  - Elimination of H^+ bound to filtered buffers
    - Include ammonium, phosphate
  - Reabsorption of bicarbonate
  - Active secretion of H^+ in the DCT/CT
    Under control of aldosterone.

References

1. Diaz, A. Describe how the body handles metabolic acidosis. Primary SAQs.

Last updated 2017-09-20

Buffers

> Describe the chemistry of buffer mechanisms and explain their relevant roles in the body

A **buffer** is a solution which consists of a **weak acid and its conjugate base**, that can **resist a change in pH** when a stronger acid or base is added.

$$Buffer + H^+ \Leftrightarrow H.Buffer$$

Buffering:

- Is a key part of acid-base homeostasis
- Allows compensation for large changes in acid or alkali load with minimal change in hydrogen ion concentration
  - In one experiment, dogs were infused with 14,000,000 $nmol.L^{-1}$ of H^+, with a corresponding rise in H^+ of only 36 $nmol.L^{-1}$

Efficacy of a buffer system is determined by:

- **pKa** of the buffer
  80% of buffering occurs within 1 pH unit of the pKa of the system.
- pH of the solution
- **Amount of buffer**
- Whether it is an **open or closed system**
  An open buffer system can have the amount of chemical at one (or both) ends adjusted by physiological means.
  - This alters the concentration of reactants at either end of the equation, thus altering the speed of the reaction via the Law of Mass Action

Buffer Systems

Important buffer systems include:

- Bicarbonate buffer system
- Protein buffer system
  - Haemoglobin buffer system
- Phosphate buffer system

All buffer systems are in equilibrium with the same amount of H^+. This is known as the **isohydric principle**.

Bicarbonate Buffer System

The bicarbonate buffer system is:

- The most important ECF buffer system
  - Bicarbonate is formed in the erythrocyte and then secreted into plasma
  - Bicarbonate diffuses into the interstitium and is also the dominant fluid buffer in interstitial space
- Formed in the erythrocyte
- A **buffer pair** consisting of bicarbonate and carbonic acid
  Carbonic acid is exceedingly short lived in any environment even remotely compatible with life and it rapidly dissociates to HCO_3^- and H^+.

Hydrogen ions are consumed or released by the following reaction:

- $H_2CO_3 \Leftrightarrow HCO_3^- + H^+ \Leftrightarrow CO_3^{2-} + 2H^+$

- Carbonic anhydrase (present in erythrocytes) is an enzyme which allows rapid conversion of H_2O and CO_2 to H_2CO_3 (and back again)
- Each stage of the reaction has an individual pKa:
  - As the pKa of the $H_2CO_3 \Leftrightarrow HCO_3^- + H^+$ system is 6.1, these substances predominate at physiological pH
  - The pKa for the second stage of the reaction is 9.3 and so essentially no CO_3^{2-} exists in blood
    Clincically this reaction can be ignored.
- In clinical conditions, the reaction becomes:
  $H_2O + CO_2 \Leftrightarrow H_2CO_3 \Leftrightarrow HCO_3^- + H^+$
  - Addition of a strong acid drives the above reaction to the left, forming (briefly) H_2CO_3 before it dissociates to CO_2 and H_2O
    - CO_2 is then able to be exhaled, which prevents equilibration and allows the system to buffer more acid

Bicarbonate is an effective buffer because it is:

- Present in large amounts
- **Open at both ends**
  - CO_2 can be adjusted by changing ventilation
  - Bicarbonate can be adjusted by changing renal elimination
  - This prevents the bicarbonate buffer system from equilibrating and allows it to resist large changes in pH despite its low pKa
    However, because it relies heavily on changes in pulmonary ventilation it is **unable to effectively buffer respiratory acid-base disturbances**.

Protein Buffer System

- All proteins contain potential buffer groups
  However, the useful one at physiological pH is the **imidazole groups** of the **histidine residues**.
- Extracellularly, proteins have a small contribution which is entirely due to their low pKa
- Intracellularly proteins have a much greater contribution because:
  - Intracellular protein concentration is much greater than extracellular concentration
  - Intracellular pH is much lower (~6.8) and closer to their pKa

Haemoglobin Buffer System

Haemoglobin is:

- A protein buffer system
- Quantitatively the most important non-bicarbonate buffer system of blood
  This is because haemoglobin:
  - Exists in greater amounts than plasma proteins ($150g.L^{-1}$ compared to $70g.L^{-1}$)
  - Each molecule contains 38 histidine residues
    This results in 1g of Hb ~3x the buffering capacity of 1g of plasma protein.

In the cell:

- Haemoglobin exists as a weak acid (HHb) as well as its potassium salt (KHb)
- In acidosis:
  - Additional H^+ ions are bound to Hb molecules
  - HCO_3^- diffuses down its concentration gradient into plasma
    Electroneutrality is maintained through the inwards movement of Cl^-.
  - Dissolved CO_2 will also form carbamino compounds by binding to the terminal amino groups

- The **pKa** of Hb is **variable** depending on whether it has bound oxygen:
  - **Deoxyhaemoglobin** has a **pKa of 8.2**
    Because of its higher pKa, deoxyhaemoglobin will more readily accept H^+ ions which makes it a better buffer of acidic solutions.
  - **Oxyhaemoglobin** has a **pKa of 6.6**
  - Both are essentially equidistant from normal pH, and are equally effective buffers
  - Quantitatively, **per mmol of oxyhaemoglobin reduced, ~0.7mmol of H^+ can be buffered**
    Therefore 0.7mmol of CO_2 can enter blood **without a change in pH**.
    - This is the mechanism behind the **Haldane effect**, and why venous blood is only slightly more acidic than arterial blood

Phosphate Buffer System

Phosphoric acid is:

- Tribasic and can therefore potentially donate three hydrogen ions
- However, only one of these reactions is relevant at physiological pH, with a pKa of 6.8:
  $$H_2PO_4^- \Leftrightarrow H^+ + HPO_4^-$$
- The quantitative effect is low despite the optimal pKa due to the low plasma concentration of phosphate
- At higher concentrations, such as intracellularly and in urine, it is a significant contributor
- In prolonged acidosis, $CaPO_4$ can be mobilised from bones and can be considered as an alkali reserve

Footnotes

1. Alex Yartsev offers an excellent discussion on buffering in his excellent trademark prose at Deranged Physiology
2. Brandis's anaesthesia MCQ is required reading

References

1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
2. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.

Last updated 2019-07-18

Cerebrospinal Fluid

> Describe the physiology of cerebrospinal fluid

CSF is a **transcellular** fluid in the ventricles and subarachnoid space. ~150ml (2ml/kg) of CSF exist in a normal individual, divided evenly between the head and spinal column.

Functions

- **Mechanical Protection**
  Due to its low specific gravity, CSF reduces the effective weight of the brain (by a factor of 30) and therefore reduces trauma caused by the acceleration and deceleration of the brain.
- **Buffering of ICP**
  CSF can be displaced to the spinal subarachnoid and have its rate of reabsorption increased in order to offset an increase in ICP by another space-occupying lesion.
- **Stable Extracellular Environment**
  Neurons are sensitive to ionic changes in the extracellular environment. Ionic concentrations in CSF are tightly controlled, which ensures stable neuronal activity. Additionally, toxins are actively removed from CSF.
- **pH Regulation**
  pH of extracellular fluid is important in the control of respiration, and is also tightly regulated.
- **Nutrition**
  Supply of O_2 and simple sugars and amino acids, and removal of CO_2 occurs occurs in CSF.

Formation

CSF is produced in the **choroid plexus** (70%) and brain **capillary endothelial cells** (30%) at a rate of 0.4 $ml.min^{-1}$ (**500**$\mathbf{ml.day^{-1}}$). It is produced by a combination of **ultrafiltration** and **secretion** from plasma:

- Na^+ is actively transported
  Drives flow of Cl^- ions and water.
- Glucose is transported via facilitated diffusion down its concentration gradient

Factors Affecting Formation

Formation is relatively constant within normal parameters (altering the rate of absorption is the predominant means to control pressure), though it is reduced by:

- **Decreased Choroidal Blood Flow**
  CPP <70mmhg reduces="" CSF formation.

Contents

Content	Relative Change	[CSF]
Na^+	-	140 $mmol.L^{-1}$
Cl^-	↑	124 $mmol.L^{-1}$
K^+	↓	2.9 $mmol.L^{-1}$
Gluc	↓	3.7 $mmol.L^{-1}$

pH	↓	7.33
PCO_2	↑	50mmHg
Protein	↓	Variable*
Ca^{2+}	↓	1.12 $mmol.L^{-1}$
Mg^{2+}	↑	1.2 $mmol.L^{-1}$

* CSF [protein] is variable:

- Highest in the lumbar sac
- Lowest in the ventricles
- Always lower than plasma [protein]
  This means CSF is a **poor buffer solution**, which increases its sensitivity to derangements in respiratory acid-base status.

In summary:

- [Na^+] is unchanged
- [Mg^{2+}] and [Cl^-] are increased
- Concentrations of everything else is less

Circulation

CSF flow is driven by respiratory oscillations, arterial pulsations, and ongoing production in the choroidal plexus.

- **Production** in the **choroidal plexus** in the **lateral ventricles**
- To the **third ventricle** via the **Foramen of Munro**
- To the **fourth ventricle** via the **Aqueduct of Sylvius**
- To the **cisterna magna** via the two lateral **Foramina of Luschka** and the midline **Foramen of Magendie**
- It may now pass either:
  - **Cranially**, to the **basilar cisterns** and via the **Sylvian fissure** to the **cortical regions**
  - **Caudally**, to the **spinal subarachnoid space** via the **central canal**

Reabsorption

Reabsorption of CSF:

- Occurs in the **arachnoid villi**, which are located in the **dural walls** of the **sagittal** and **sigmoid sinuses**
  - 85% of reabsorption occurs in intracranial arachnoid villi
  - Remainder by spinal arachnoid villi
- Is predominantly via pinocytosis and opening of extracellular fluid spaces
- Is **pressure-dependent**
  - Reabsorption occurs when the CSF pressure is **1.5mmHg greater** than venous pressure
    Typically an ICP < 7mmHg results in minimal CSF reabsorption. Above this, CSF absorption increases in a linear fashion up to 22.5mmHg.

References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
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Last updated 2019-07-18

Blood-Brain Barrier

The blood-brain barrier is a **physiological barrier** which prevents substances in the ECF of the body moving freely into the ECF of the brain. The functions of the BBB are:

- Maintain a stable extracellular milieu
  Optimises neuronal function by preventing fluctuations in plasma K^+, Na^+, and H^+ affecting cerebral cells.
- Protection of the brain
  Isolates the brain from toxins.
- Protection of the body
  Isolates the rest of the body from CNS neurotransmitters.

Anatomy

The BBB occurs in three layers:

- Capillary endothelial cells
  Joined with **tight junctions**, preventing free movement of solvent and solute.
  - Substances must move through capillary endothelium to reach the brain
    Capillary endothelial cells contain high numbers of mitochondria, due to the higher energy cost of the active transport mechanisms.
- Basement membrane
- Astrocytes
  Glial cell which extends foot processes around the basement membrane, and reduce permeability of endothelial cells.

Due to their function, several important CNS structures must exist outside of the BBB. These are known as the **circumventricular organs**, and include:

- Sensing structures
  - Chemoreceptor trigger zone (Area Postrema)
    Identifies toxins in the systemic circulation, triggering vomiting.
  - Hypothalamus
    Osmoreceptors detect systemic osmolarity.
  - Subfornical organ
    Role in CVS and fluid balance.
  - Organum vasculosum

- Secreting structures
  - Pituitary
    Secretes hormones.
  - Pineal gland
    Secretes melatonin.
  - Choroid plexus
    Produces CSF via secretion and ultrafiltration of plasma.

Movement of Substances

Substances can move via:

- **Diffusion**
  For lipid soluble molecules only; e.g:

    - CO_2
    - O_2
- **Facilitated diffusion**
  For movement of larger/less soluble molecules down their concentration gradient, e.g:
    - Glucose
    - Water
- **Active transport**
  Responsible for movement of most small ions; e.g:
    - Na^+
    - Cl^-
    - K^+
    - Mg^{2+}
    - Ca^{2+}

Other substances are specifically excluded:

- **Catecholamines**
  Metabolised by MAO in capillary endothelium, preventing their action as CNS neurotransmitters.
- **Amino acids**
  Prevent action as neurotransmitters.
- **Ammonia**
  Metabolised in astrocytes to glutamine, limiting its neurotoxic effects.

References

1. Lawther BK, Kumar S, Krovvidi H. Blood–brain barrier. Continuing Education in Anaesthesia Critical Care & Pain, Volume 11, Issue 4, 1 August 2011, Pages 128–132.
2. Brandis K. The Physiology Viva: Questions & Answers. 2003.

Last updated 2019-07-18

Spinal Cord Anatomy

> Describe the major sensory and motor pathways (including anatomy)

Spinal Cord Anatomy

The spinal cord in transverse section consists of a central section of grey matter containing neuronal cell bodies and synapses, and a peripheral section of white matter containing myelinated ascending and descending pathways. Important pathways are:

- **Corticospinal tract**
  Motor function. Crosses at the brain stem.
- **Dorsal column**
  Light touch and proprioception. Crosses at the brain stem.
- **Spinothalamic tract**
  Pain and temperature. Crosses within two vertebral segments.
- **Spinocerebellar tract**
  Unconscious proprioception. Does not cross.

Spinal Cord Syndromes

Lesions to certain anatomical regions of the spinal cord produce a particular constellations of findings.

Complete Transection

A complete transection results in loss of movement and sensation below the level of the lesion. Initially, paralysis is flaccid (and other signs, such as priapism, may be absent in this 'spinal shock' phase) becomes spastic after a few weeks. Bowel and bladder function is lost.

Lesions above T10 will result in impaired cough in the initial stage as the abdominal wall is unable to contract (intercostal muscle function may be impaired as well, but this is of less importance clinically).

Central Cord Syndrome

Central cord syndrome results in a flacid paralysis and loss of sensation of the **upper limbs greater than the lower limbs**.

Anterior Cord Syndrome

Anterior cord syndrome spares the dorsal columns only, therefore motor function and pain and temperature sensation are affected below the level of the lesion.

Brown-Sequard Syndrome

Hemisection of the cord results in:

- **Ipsilateral** loss of **motor function** below the level of the lesion
- **Ipsilateral** loss of **light touch and proprioception** below the level of the lesion
- **Contralateral** loss of **pain and temperature** sensation below the level of the lesion
- **Ipsilateral** loss of **pain and temperature** sensation **at the level** of the lesion

Cauda Equina

Cauda Equina syndrome results from compression of lumbosacral nerve roots below the level of the conus medullaris. It may produce a combination of UMN and LMN signs:

- Radiculopathy
- Sacral sensory loss
- Asymmetric LMN weakness and atrophy
- Erectile dysfunction and inability to ejaculate
- Urinary retention and overflow incontinence
- Constipation and overflow incontinence

References

1. Goldber S. Clinical Neuroanatomy Made Ridiculously Simple. 3rd Ed. Medmaster. 2005.
2. McMinn, RMH. Last's Anatomy: Regional and Applied. 9th Ed. Elsevier. 2003.

Last updated 2017-09-22

Intracranial Pressure

> Explain the control of intra-cranial pressure

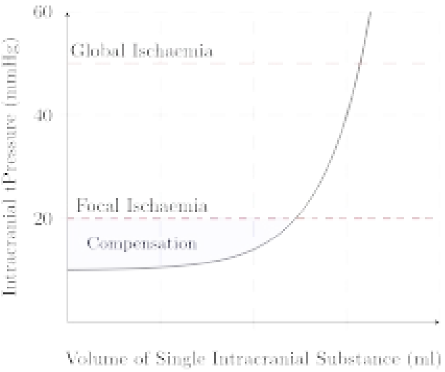
Normal ICP is

- **P1** is the first peak, and represents arterial pulsation
- **P2** is the second peak, and represents intracranial compliance
  If P2>P1, this is suggestive of poor intracranial compliance
- **P3** is the third peak, and is a dicrotic wave representing valve closure

In addition, a second set of Lundberg waves are described:

- **A waves** are **pathological**, and consist of square-wave plateaus up to 50mmHg lasting **5-20 minutes**. They are suggestive of **herniation**, and are always pathological.
- **B waves** are variable spikes in ICP at 30-120 second intervals, suggestive of cerebral **vasospasm**
- **C waves** are oscillations that occur 4-8 times per minute, and are a benign phenomena occurring with respiratory and blood pressure variations

Raised intracranial pressure may cause focal ischaemia when ICP >20mmHg, and global ischaemia when the ICP >50mmHg:



Monroe Kellie Doctrine

This states that:

- The skull is a rigid container of a fixed volume, containing approximately 8 parts brain, 1 part blood, and 1 part CSF
- As it has negligible elastance, any **increase in volume** of one substance must **be met with** a **decrease in volume** of another **or** a **rise in ICP**
  - Elastance is *technically* correct as we are discussing a change in *pressure* for a given change in volume
    Compliance is a change in *volume* for a given change in pressure.

Physiological Responses to an Increase in ICP

- Displacement of CSF into the spinal subarachnoid space
- Compression of vascular bed
- Increased CSF reabsorption

- The Cushing reflex may occur in brainstem herniation
  This is a triad of hypertension, bradycardia, and irregular respiration secondary to SNS activation, and is a reflexive response to medullary ischaemia.
  - Hypertension

To improve CPP.
- Bradycardia
  Due to a baroreceptor response.
- Irregular respiration
  Due to respiratory centre dysfunction.

Physiological Basis of Treatment

Treatment can be classified as per the Monroe Kellie doctrine:

Brain

- **Osmotic agents** such as mannitol and hypertonic saline
  Increase plasma osmolality and expand blood volume, creating an osmotic gradient between brain parenchyma and blood with a resulting reduction in brain oedema and ICP.
- Timely **evacuation** of mass lesions and intracranial haemorrhage

CSF

- **External Ventricular Drain**
  Facilitates removal of CSF.

Blood

- Reducing cerebral metabolic rate
  Results in reduced blood flow due to **flow-metabolism coupling**. May be achieved with:
  - **CNS depressants** such as propofol, benzodiazepines, or barbiturates
    Have several beneficial effects:
  - Depress cerebral metabolism which reduces oxygen requirements
  - Reduce **seizure** risk, which is detrimental because it greatly increases cerebral O_2 demand and impairs venous return
  - Improves ventilator dyssynchrony, limiting coughing and bearing down, and subsequent rises in ICP
  - **Hypothermia**
    Causes a reduction in cerebral metabolism and risk of seizures.
  - **Prevention of hypoxia or hypercapnea**
    Hypoxia and hypercapnea both cause vasodilatation, with a subsequent increase in cerebral blood volume, blood flow, and ICP.
    - Induced **hypocarbia**
      Causes vasoconstriction and a subsequent reduction in cerebral blood flow and blood volume. This leads to:
      - Reduction in ICP
      - Reduction in cerebral oxygen delivery
        Consequently, a low-normal $ETCO_2$ target is used to avoid tissue hypoxia.

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Intraocular Pressure

Normal intraocular pressure is ~**15mmHg**, with a range of 12-20mmHg. Regulation of intraocular pressure is important for:

- Vision
  Sustained high (>25mmHg) can lead to blindness due to compression of axons of the optic nerve and the optic artery at the optic disc.

Determinants of Intraocular Pressure

As the globe has typically poor compliance, a small increase in volume can cause a large increase in intraocular pressure. Factors affecting volume include:

- Volume of **aqueous humor**
  Aqueous humor is a clear fluid that fills the anterior and posterior chambers of the eye, and provides avascular tissues with nutrients and oxygen whilst still allowing light to pass freely between the lens and retina. Volume of aqueous humor is a function of:
  - Production
    Aqueous humor is produced by secretion and filtration from capillaries in the ciliary body in the posterior chamber, and circulates through into the anterior chamber.
    - Production is accelerated by $\beta 2_2$ agonism
    - Production is inhibited by α_2 agonism
    - Carbonic anhydrase inhibitors decrease aqueous humor production probably by decreasing sodium secretion into the eye
  - Reabsorption
    Aqueous humor is reabsorbed into venous blood in the **canal of Schlemm**.
    - The **trabeculae meshwork** is the main source of resistance to reabsorption
      If this is blocked, a significant reduction in reabsorption can occur and IOP will increase.
    - Reabsorption is affected by:
      - Haemorrhage
        Blocks trabecular meshwork.
      - Muscarinic antagonism
        Dilates pupil, which brings the iris closer to canal and decreases absorption.
      - α_1 agonism
        Dilates the pupil, decreasing absorption.
      - $PGF_{2\alpha}$
        Relaxes ciliary muscle, increasing absorption.

- Volume of **blood** within the globe
  Affected by:
  - MAP
  - Venous obstruction

- **External factors**
  Other factors affecting volume or compliance of the globe:
  - Extraocular muscle tension
  - Extraocular compression

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Sleep

> Describe the physiology of sleep

Sleep is a naturally occurring state of unconsciousness from which one can be aroused by an external stimuli.

Sleep is important in:

- Homeostasis of many organ systems
- Memory formation
- Preservation of cognitive function

Stages of Sleep

Stages of sleep are classified based on EEG changes:

- **REM sleep**
  Characterised by EEG activity resembling that of awake individuals. REM sleep:
  - Lasts for 5-30 minutes
    Event frequency decreases with age.
  - In REM sleep:
    - Irregular eye movements
    - Dreaming occurs
    - Irregular HR and RR
    - Muscle contraction occurs (but muscle tone is decreased)

- **Non-REM sleep**
  Deep sleep, characterised by depression of HR, SVR, BP, RR, and metabolic rate (~0.9 METs) It is divided into four stages on EEG:
  - Stage 1: 4-6Hz θ waves replace α-waves
    Dosing, easily roused.
  - Stage 2: Similar to stage 1 with occasional high frequency 50μV bursts (sleep spindles)
  - Stage 3: 1-2Hz high-voltage δ waves appear
  - Stage 4: Large δ waves become synchronised
    Deep sleep.

Periods of REM sleep alternate with non-REM sleep during the night, with an average of 4-5 cycles of REM sleep per night.

Respiratory Effects

GABAergic neurons depress the respiratory centre, leading to respiratory depression:

- Decreased MV
  - Decreased V_T
    Greatest decrease occurs during REM sleep, where it falls by ~25%.
  - Unchanged RR
- Increased $PaCO_2$
- Decreased PO_2
  More pronounced in elderly.

- Collapse of airway soft tissue

Due to reduced tonic activity of pharyngeal muscles.

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Pain

> Describe the physiology of pain, including the pathways and mediators

Key definitions:

- **Pain**
  Pain is an "unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in such terms." Pain can be broadly classified by:
  - Aetiology
    - **Nociceptive pain**
      Stimulation of nociceptors by noxious stimuli.
    - **Visceral pain**
    - **Neuropathic pain**
      Nervous system dysfunction.
  - Duration
    - Acute pain
      Pain due to symptoms of current pathology.
    - **Chronic pain**
      Pain occurring after the pathological process has resolved.

- **Hyperalgesia**
  Increased response to a normally painful stimulus.
  - Primary hyperalgesia
    Local reduction in pain threshold.
  - Secondary hyperalgesia
    Hyperalgesia away from the site of injury due to alteration in spinal cord signaling.

- **Allodynia**
  Painful response to a normally painless stimuli. Occurs due to pathological synapse between second-order neurones in the spinal cord.

- **Anaesthesia dolorosa**
  Pain in an area which is anaesthetised.

Peripheral Nociception

Nociceptors are receptors which respond to a noxious stimulus. Nociceptors:

- Can be **stimulated** or **sensitised** by:
  - Chemical signals
    See table.
  - Mechanical signals
    - Shear stress
  - Thermal signals
    - Hot nociceptors activate above 43°C
    - Cold nociceptors activate below 26°C
- Stimulation initiates a nervous impulse
- Sensitisation increases a receptors sensitivity to a stimulating mediator

Key chemical stimulating and sensitising mediators include:

Stimulating Mediators	Sensitising Mediators
H^+	Prostaglandins
K^+	Leukotrienes
ACh	Substance P
Histamine	Neurokinin A
5-HT	Calcitonin GRP
Bradykinin	

Nociceptors

Impulses are conducted by two types of **primary afferent fibres**:

- Aδ fibres:
  - Small (~**2-5μm** diameter)
  - **Myelinated**
  - Conduct sharp pain at up to $40m.s^{-1}$
  - Mediate initial reflex responses to acute pain
  - Synapse in laminae I in the dorsal horn
    Substance P is the neurotransmitter at the NK1 receptor.
- C fibres:
  - **<2μm** diameter
  - **Unmyelinated**
  - Conduct dull pain at $2m.s^{-1}$
  - Synapse in laminae II in the dorsal horn
    Substance P is the neurotransmitter at the NK1 receptor.

Pain Pathway and Site of Action of Analgesics

The response to a painful stimulus requires a cascade of processes:

- **Activation of nociceptors**
  Membrane depolarisation in response to stimulus. If the stimulus is great enough to reach the threshold potential, an action potential is generated.
  - **NSAIDS** reduce nociceptor mediated inflammation
  - **Opiates** act on peripheral MOP receptors
  - **Local anaesthetics** prevent signal propagation
- **Synapse in the dorsal horn**
  Input from both Aδ and C fibres, and descending interneurons.
  - Descending inhibitory input reduces nociceptive transmission
    Basis of "gate control" theory. Descending input increased with:
    - Touch
      Aβ 'touch' fibres stimulate inhibitory interneurons in the dorsal horn, 'closing the gate' by increasing **descending inhibition** and prevent signals from peripheral C fibres from rising to the thalamus.
    - Arousal
    - Opioid receptors
      Particularly MOP (pre- and post-synaptically).
      - **Opioids** act pre-synaptically to reduce Substance P and glutamine release.
    - α_2 receptors

        Clonidine, **tricyclic antidepressants**, **noradrenaline-reuptake inhibitors**, and endogenous catecholamines.
    - **Gabapentin and pregabalin** inhibit presynaptic neurotransmitter release
  - **Wide dynamic range** neurones
    Receive afferent input from chemical, thermal, and mechanoreceptors.
    - Typically more difficult to stimulate
    - Important in **wind-up**
      Mediated by NMDA agonism.
      - **Ketamine** reduces windup and central sensitisation
    - Lead to secondary hyperalgesia
    - Lead to allodynia
      Via additional synapses to sensory neurones in lamina III and IV.
    - Interneuron synapses with a **second-order neurones** fibre
      These secondary afferents:
  - Cross within 1-2 vertebral segments and ascends in the spinothalamic tract
  - Receives input from descending fibres
  - **Opioids** act post-synaptically to hyperpolarise second-order neurones

- **Reflex arc**

- **Higher centres**
  Pain perception occurs in the somatosensory cortex.

Neuropathic Pain

Pain due to a lesion of the somatosensory system, rather than a stimulus itself. Neuropathic pain is divided into:

- Central neuropathic pain
  From CNS injury, e.g. spinal cord injury, CVA, multiple sclerosis.
- Peripheral neuropathic pain
  Damage from:
  - Diabetes
    Ischaemia of Schwann cells causes demyelination, causing the exposed axon to generate action potentials inappropriately.
  - Trauma
    Transected axons may regrow with endings that spontaneously fire or that have altered threshold potentials.

Mechanisms of Neuropathic Pain

- Neuroma
  Healing of damaged nerves leads to neuroma formation. Neuromas:
  - Are more sensitive to painful stimuli
  - Cause spontaneous pain
  - May sprout and innervate local tissues
    Movement of these tissues may lead to pain.
- Windup
- Phantom limb pain
  Neurons damaged in removal of a limb develop additional synapses, leading to phantom sensations.

Features of Neuropathic Pain

Neuropathic pain is associated with:

- Injury or disease that causes nerve injury
- Burning or electrical quality
- Reduced or absent sensation
- Poor response to typical analgesia

Chronic Regional Pain Syndrome

Damage to the SNS can lead to abnormalities in autonomic function:

- Change in temperature due to vasomotor dysfunction
- Altered sweating
- Reduced hair growth
- Osteoporosis
- Hyperalgesia and allodynia

Pain in the Elderly

Nervous System Changes:

- **Peripheral Nervous System**
  - Nerve deterioration
  - Decreased myelination
  - Decreased conduction velocity
  - Reduced range and speed of ANS responses
  - Increased resting sympathetic tone
- **Central Nervous System**
  - Decreased pain perception
  - Increased sensitivity to anaesthetic and analgesics
    Reach ceiling effects more rapidly.
  - Degeneration of myelin
    Subsequent cognitive dysfunction due to neuronal circuit dysfunction.
  - Generalised atrophy
  - Decreased neurotransmitter production

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Autonomic Nervous System

> Describe the autonomic nervous system, including anatomy, receptors, subtypes and transmitters (including their synthesis, release and fate)

The ANS is the section of the nervous system which regulates involuntary and visceral functions. These include:

- Haemodynamics
- Digestion
- Urination and defecation
- Thermoregulation
- Sexual function

The autonomic nervous system can be divided into

- **Central ANS**
  Control occurs in the **hypothalamus**, **brainstem**, and **spinal cord**.
- **Peripheral ANS**
  Divided anatomically and functionally into the:
  - **Sympathetic** nervous system
  - **Parasympathetic** nervous system

GRAPH FROM PAGE 258 of GANONG

Central Control

The hypothalamus controls autonomic functions by neural and endocrine mechanisms. It is subdivided anatomically into four regions:

- **Anterior hypothalamus**
  Controls the PNS and thermoregulation. It also **releases** **ADH** in response to increased plasma osmolality, and **oxytocin**.
- **Medial hypothalamus**
  Inhibits appetite in response to increase in blood glucose.
- **Lateral hypothalamus**
  Contains the thirst centre and drive to seek food.
- **Posterior hypothalamus**
  Controls vasomotor centres, modulating sympathetic vasoconstriction, as well as positive and negative inotropy and chronotropy. Also modulates wakefulness in response to sympathetic stimuli.

Signals from the hypothalamus have a tonic output to:

- All smooth muscle
- Heart
- Exocrine organs
- Endocrine organs
- GIT
- GU

Central Anatomy

In the grey matter of the spinal cord, efferent nerves synapse with two other nerves connected in series. This maintains tonic autonomic outflow.

FIGURE FROM PAGE 67 - POWER AND KAM

Efferent nerves exit the spinal root anteriorly, and form the **ventral root**.

Conversely, **afferent** nerves exit posteriorly, forming the **dorsal root** and then **dorsal root ganglion**, before synapsing in the spinal cord.

Sympathetic Nervous System

The sympathetic nervous system optimises the body for short-term survival.

Sympathetic innervation is from the **sympathetic trunks**. These:

- Are a paired bundle of sympathetic neurons which run lateral to the vertebral bodies from **T1 to L2**
  The trunk is subdivided into four parts:
  - The **cervical part** innervates the head, neck, and part of the thorax
  - The **thoracic part** is further subdivided into:
    - Upper thoracic from T1-T5, which innervates the aorta, heart, and lungs
    - Lower thoracic from T6-T12, which innervates the foregut and midgut
  - The **lumbar part** forms the coeliac plexus
  - The **pelvic part** innervate the pelvic visceral and lower limb vasculature
- Contain the sympathetic ganglion, which is a synapse between the:
  - **Short pre-ganglionic fibre**
    Cell body is located in the lateral horn of the spinal cord, and connects to the sympathetic ganglion.
    - Releases ACh to stimulate the post-ganglionic fibre.
  - **Long post-ganglionic fibre**
    Cell body is located in the sympathetic ganglion, and stimulates the effect site.
    - Has a **nicotinic** ACh receptor
    - Releases NA at the effect site
    - Sensitivity (for ACh) and activity (for NA release) is modulated by a number of other substances:
      - Enkephalin
      - Neuropeptide Y
      - Dopamine
      - Adrenaline
      - Prostaglandin
      - GABA
      - Neurotensin

There are three exceptions to the above structure:

- The **adrenal gland** is a **modified sympathetic ganglion**. It is:
  - Directly innervated by preganglionic neurons releasing ACh
- Sweat glands have muscarinic receptors, and are stimulated by ACh rather than noradrenaline
- Skeletal muscle arterioles also have muscarinic ACh receptors, and are stimulated by ACh

Effect

Sympathetic stimulation has a number of effects by either direct neural innervation or adrenaline release. They are consistent with a 'fight or flight' response, and optimise the body for short-term stress conditions.

Effector	Sympathetic	Response

Organ	Innervation	Response
Eye	Cervical	Pupillary dilatation
Lungs	Thoracic	Bronchodilation
Heart	Thoracic	↑↑↑ Chronotropy, ↑↑↑ inotropy, ↑↑↑ lusitropy, ↑↑ dromotropy
Vasculature	Sacral	Constriction
MSK	Sacral	Sweating, contraction, lipolysis
Endocrine	Lower thoracic	Adrenaline and noradrenaline release
GIT	Thoracic, lumbar	Decreased salivation and GIT motility, increased sphincter tone, gluconeogenesis
GU	Pelvic	Detrusor relaxation, sphincter contraction, ↑ uterine tone

Parasympathetic Nervous System

Parasympathetic innervation arises from the:

- **Cranial nerves**
  From CN III, VII, IX, and (mostly) X.
  - The vagus is the major cranial parasympathetic, innervating the:
    - Heart via the cardiac plexus
      - The SA node is innervated by the right vagus
      - The AV node is innervated by the left vagus
        The ventricles are also sparsely innervated from the left vagus.
    - Lungs via the pulmonary plexus
    - Stomach, liver, spleen, and pancreas, and gut proximal to the splenic flexure via the gastric plexus.
- **Hypogastric plexus**
  Arises from S2-S4, and innervates the bladder, uterus, and gut distal to the splenic flexure.

The parasympathetic nervous system ganglia site close to the target organ. This means that the:

- Pre-ganglionic fibre is long
  - Preganglionic cell body sits within the brainstem (cranial nerves) or sacral grey matter (hypogastric plexus)
  - Releases ACh to stimulate the post-ganglionic neurone at a **nicotinic ACh** receptor
- Post-ganglionic fibre is short
  - Releases ACh to stimulate the target organ at a **muscarinic ACh** receptor

Effect

Effector Organ	Parasympathetic Innervation	Response
CNS	CN III via the Edinger-Westphal nucleus, CN VII	Pupillary constriction (CN III), lacrimation (CN VII)
Lungs	CN X	Bronchoconstriction, increased mucous production
Heart	CN X	↓↓↓ Chronotropy, ↓↓↓ dromotropy, ↓ inotropy, ↓ lusitropy (↓ in inotropy and lusitropy is greater in the atria than the ventricles)
	CN VII (submaxillary and mandibular salivary glands), CNIX	

GIT	(parotid gland), CNX (stomach to proximal two-thirds of the transverse colon), hypogastric plexus (distal one-third of the transverse colon to rectum)	Salivation, decreased sphincter tone, increased motility
GU	Hypogastric plexus	Detrusor contraction, erection

Ganglion Blockade

Blockade of the ganglion (at the nicotinic ACh receptor) blocks transmission and reduces sympathetic and parasympathetic impulse transmission. Clinical effect of ganglion blockade depends on which part of the ANS is dominant in that organ system:

- SNS dominant organ systems
  Effective sympatholysis:
  - Vasculature
    Vasodilation, hypotension.
  - Sweat glands
    Anhydrosis.
- PNS dominant organ systems
  Effective parasympatholysis:
  - Heart
    Tachycardia.
  - Iris
    Mydriasis.
  - GIT
    Decreased ton.
  - Bladder
    Urinary retention.
  - Salivary
    Reduced secretions.

Enteric Plexus

The **enteric plexus** is a system of autonomic nerves in the GIT which is free of CNS control. It consists of sensory and integrative neurons as well as excitatory and inhibitory motor neurons which generate coordinated muscular activity.

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Anticonvulsants

> An understanding of the pharmacology of ~~anti-depressant, anti-psychotic,~~ anti-convulsant~~, and anti-Parkinsonian~~ medication

Anticonvulsants work via a number of different mechanisms:

Sodium Channel Blockers

Sodium channel blockers:

- Stabilise the inactive state of the channel, preventing return to the active state and prevent generation of further action potentials
  This halts post-tetanic potentiation and limits the development of seizure activity.
- May also have Class I antiarrhythmic properties
  Due to Na^+ blocking effects.
- Include:
  - Phenytoin
  - Carbamazepine
  - Lamotrigine

GABA Mediators

GABA is the key inhibitory neurotransmitter in the CNS. GABA mediators:

- Enhance the effect of GABA
  Multiple potential mechanisms:
  - Direct GABA-receptor agonists
    e.g. Benzodiazepines and phenobarbital.
  - Positive allosteric modulation
    e.g. Propofol and thiopentone.
  - GABA reuptake inhibition
    e.g. Tiagabine.
  - GABA transaminase inhibition
    e.g. Vigabatrin.
  - Increase GABA synthesis
    e.g. Sodium Valproate.

Glutamate Blockers

Glutamate is an important CNS excitatory neurotransmitter. Glutamate antagonists:

- Are generally avoided due to their side effect profile, which includes psychosis and hallucinations
- Include topiramate

Other Agents

Gabapentin and pregabalin:

- Do not appear to mediate GABA
- Inhibit of excitatory $\alpha_2\delta$ voltage-gated calcium channels in the CNS
  This gives them anticonvulsant properties.

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Neurotransmitters

> Describe the major neurotransmitters and their physiological role, with particular reference to GABA, excitatory and inhibitory amino acids, acetylcholine, noradrenaline, dopamine and serotonin and NMDA receptor

GABA

Gamma aminobutyric acid is the major inhibitory CNS neurotransmitter. GABA receptors have three subtypes:

- $GABA_A$
  Inotropic receptor important for the action of many drugs.
  - Pentameric structure
    - 2 α
      Bind GABA.
    - 2 β
    - 1 γ
  - Affected by many different drugs:
    - Benzodiazepines
      Positive allosteric modulation at at the α/γ interface.
    - General anaesthetic agents
      Including propofol, barbiturates, halogenated volatiles, and etomidate.
      - Act at the β subunit
        Cause a conformational change which increases Cl^- opening time, hyperpolarising the cell.
- $GABA_B$
  Metabotropic receptor.
- $GABA_C$
  Inotropic receptor located only in the retina.

NMDA

N-methyl D-aspartate receptor is an inotropic receptor that is:

- Agonised by glutamate
  - Glycine is co-agonist
- Voltage dependent
  - Central pore usually blocked by an Mg^{2+} ion
  - Becomes unblocked when partially depolarised
- Important in the action of drugs which do not act at the $GABA_A$ receptor
  Antagonised by:
  - Ketamine
  - Xenon
  - N_2O

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Local Anaesthetics

> Understanding of the pharmacology of local anaesthetic drugs, including their toxicity

Local anaesthetic drugs create a use-dependent temporary blockade of neuronal transmission by blocking the voltage-gated sodium channel in the cell membrane, preventing depolarisation.

Mechanism of Action

Action is dependent on blockade of the sodium channel. Two theories exist:

- **Unionised** drug **passes through the cell membrane**, and then becomes **ionised intracellularly**
- The ionised drug is then able to bind to the **open** sodium channel, and prevent conduction of sodium and therefore generation of an action potential
  - Local anaesthetics also display reduced affinity for K^+ and L-type Ca^{2+} channels
  - This theory explains use-dependent blockade, as sodium channels can only be blocked in their open state
- An alternative suggested mechanism of action is the drug enters the cell membrane and mechanically distorts the channel, rendering it ineffective
- Onset is inversely proportional to the size of the fibre
  From fastest to slowest:
  - Pain
  - Temperature
  - Touch
  - Deep pressure
  - Motor

Chemical Structure of Local Anaesthetics

All local anaesthetics are weak bases consisting of:

- A hydrophilic component
- A lipophilic aromatic ring
- An amide or ester link connecting the two

Chemical structure influences pharmacological behaviour:

- Hydrophilic portion
  Typically the tertiary amine.
  - Determines ionisation
    - 3 bonds: Lipid soluble
    - 4 bonds: Water soluble
- Lipophilic portion
  Typically aromatic ring.
  - Determines lipid solubility, and therefore potency, toxicity, and duration of action
- Ester vs. amide
  - Amides
    - Hepatically metabolised (hydroxylation and N-de-alkylation)
      This is slower, therefore there is a **greater risk** of systemic toxicity.
    - Stable in solution

  - Esters
    - Heat-sensitive
      Cannot be autoclaved.
    - Rapidly hydrolysed in plasma
      Organ independent elimination.
    - Have a greater incidence of allergy
      Due to the inactive metabolite PABA.
- Amine group length
  - Potency and toxicity increase as carbon-chain increases
  - Toxicity (but not potency) continues to increase beyond 10 carbons
- Isomerism
  Alters behaviour:
  - Levobupivacaine is less toxic
  - R-ropivacaine is less potent and more toxic

Key Characteristics of Local Anaesthetics

Characteristics are related to chemical structure. These include:

- **Potency**
  - Potency is expressed with the minimum effective concentration of local anaesthetic (C_m)
    This is the concentration of LA that results in complete block of a nerve fibre in 50% of subjects in standard conditions. More potent agents have a lower C_m.
  - Potency is a function of:
    - Lipid solubility
      Potency (and also toxicity) increases with greater lipid solubility.
    - Vasodilator properties
      In general, local anaesthetics cause vasodilation in low concentrations, and vasoconstriction at high concentrations (except cocaine, which causes vasoconstriction at all concentrations).
- **Duration of action**
  Duration of action is a function of:
  - Drug factors
    - Vasodilator properties
      Vasoconstriction increases the duration of block.
    - Use of additives
      Addition of adrenaline to lignocaine increases duration of block.
    - Lipid solubility
      Increased lipid solubility increases duration of action, as agent remains in the nerve for longer.
      - Potency therefore has a positive correlation with duration of action
      - Duration of action is increased when pH increases, as the ionised portion falls
    - Protein binding
      Highly protein bound agents have an increased duration of action due to increased tissue binding.
      - Protein binding decreases with decreasing pH, increasing the fraction of unbound drug
        This is why agents such as bupivacaine are more cardiotoxic in acidotic patients.
      - Local anaesthetics are predominantly bound to α-1-acid glycoprotein (AAG)
        AAG is reduced in pregnancy, increasing the free drug fraction and therefore reducing the toxic dose of LA in pregnant patients.
  - Patient factors
    - Tissue pH
      Decreased duration of block when tissue pH is low.

            - Metabolic impairment
                - Hepatic failure increases duration of action of aminosteroids
                - Butylcholinesterase deficiency increases duration of ester local anaesthetics
            - Site of administration Well vascularised tissue (e.g. intercostal area) will have greater systemic uptake of drug than vessel poor tissue.
- **Onset**
  Speed of onset is related to:
    - Drug factors
        - Dose
          Increasing the dose increases the speed of onset, as per Fick's Law.
            - Increased concentration will increase speed of onset and block density
            - Increased volume (without increasing dose, resulting in decreased concentration) will decrease speed of onset
        - Lipid solubility
          An increased lipid solubility increases the speed at which the local anaesthetic enters the nerve. **However**:
            - Lipid solubility also correlates with potency
            - Therefore, **in practice**, more lipid soluble agents are administered in lower doses, and so have a **reduced speed of onset**
              This is known as Bowman's Principle.
        - Ionised portion
          Only unionised drug can cross cell membranes. Ionisation is a function of:
            - pKa
            - Tissue pH
                - This is also why anaesthetics are ineffective in anaesthetising infected tissue, as the low pH makes the majority of the LA ionised and unable to cross the cell membrane.
    - Patient factors
        - Nerve activity
          Local anaesthetics produce a **frequency dependent blockade**, meaning nerves firing frequently will be blocked more rapidly than quiescent nerves
        - Nerve fibre size
          Larger nerves require an increased concentration of local anaesthetic to achieve blockade than smaller nerves.
        - Nerve type
          Different nerve fibres are affected at different speeds, which is mostly (though not entirely) a function of critical length.
            - Aγ (proprioceptive) are affected first
            - Small myelinated Aδ (sharp pain, cold) fibres are affected second
            - Large myelinated nerves are affected third These include Aα (motor) and Aβ (touch) fibres.
            - Unmyelinated nerves are affected last
              These include C (dull pain, heat) fibres.
        - Hyperkalaemia
          Reduces onset of action.

Toxicity

Local anaesthetics are:

- Toxic to both the CNS and **CVS**
- Toxicity occurs when there is an excess plasma concentration
  This occurs when the rate of drug entering the systemic circulation is greater than the drug leaving the systemic circulation due to redistribution and metabolism.

Toxicity is related to the:

- **Drug factors**
  - **Drug used**
    Agents are compared using the **CC/CNS ratio**, which is the ratio of the dose of drug required to cause cardiovascular collapse (CC) compared to the dose required to cause seizure. It is a crude alternative to the therapeutic index.
  - **Dose used**
    Continuous infusions are more likely to cause a delayed onset of local anaesthetic toxicity.

- **Block factors**
  - **Site** of administration
    This affects the rate of uptake into the systemic circulation, and the likelihood of inadvertent intravascular injection. Ranked (from highest to lowest):
    - Intravascular (obviously)
      This is the most common cause of LA toxicity.
      - Site is also relevant here: an injection into the carotid artery will cause toxicity at a lower dose than if injected into a peripheral vein.
    - Intercostal
    - Caudal
    - Epidural
    - Brachial plexus
    - Subcutaneous
  - Use of **adjuncts**
    - Adrenaline
      Vasoconstrictor properties reduce systemic absorption of LA.
  - **Technique**
    - Frequent aspiration
    - Test dose
    - Use of ultrasound

- **Patient factors**
  Anything that increases peak [plasma] can lead to an increased risk of LA toxicity.
  - Blood flow to affected area
  - α1-acid glycoprotein
    Low levels of this protein increase free drug fraction.
    - Neonates and infants have half the level of AAG than adults.
  - Hepatic disease
    Reduces clearance of amides, which may cause toxicity with repeated doses or use of infusions.
  - Age
    Organ blood flow (and therefore clearance), as well as pharmacokinetic interactions may affect clearance of LA. Both **children and the elderly** have **reduced clearance** of LA.
  - Acidosis
    Increases unionised portion.
  - Hypercarbia
    Increases cerebral blood flow.

Cardiac Toxicity

Cardiac toxicity occurs due to:

- Blocking of the cardiac Na^+ channel (K^+ and Ca^{2+} channels may also be involved)
  Severity of toxicity will vary depending on how long the agent binds to the channel, with **less toxicity** caused by agents spending **less time bound**:
  - Lignocaine

    Spends the shortest time bound to the channel, so causes the least amount of toxicity. This is also why lignocaine can be used as an antiarrhythmic, but other agents can not.
  - Bupivacaine
    Takes **10x as long** to dissociate as lignocaine. This can lead to re-entrant arrhythmias, and then VF. The **risk** of this is **increased in tachycardia** due to use-dependent blockade.
  - Ropivacaine
    Dissociates more rapidly from cardiac channels than bupivacaine.
- Direct myocardial depressant effects
  Reduces cAMP levels by disrupting metabotropic receptors.

Cardiac toxicity is **triphasic**:

- Initial phase
  - Hypertension
  - Tachycardia
- Intermediate phase:
  - Hypotension
  - Myocardial depression
- Terminal phase:
  - Severe hypotension
  - Vasodilation
  - Various arrhythmias
    - Sinus bradycardia
    - Variable degree heart block
    - VT
    - VF
    - Asystole

CNS Toxicity

Local anaesthetics in their unionised state can cross the BBB and interfere with CNS conduction. **CNS toxicity is biphasic**:

- Initially, inhibitory interneurons are blocked
  This causes excitatory effects:
  - Perioral tingling
  - Slurred speech
  - Visual disturbances
  - Tremulousness
  - Dizziness
  - Confusion
  - Convulsions
    Typically signifies the end of the excitatory phase.
- Secondly, there is a general depression of all CNS neurons
  This causes inhibitory effects:
  - Coma
  - Apnoea

Treatment

Toxicity is managed with an **ABC approach**, though definitive management uses **Intralipid emulsion**:

- Intralipid is an emulsion of soya oil, glycerol, and egg phospholipids.
  Mechanism of action in uncertain, but theories include:

- Lipid sink
  ILE binds unionised LA, causing it to distribute off receptor sites.
- Fatty acid metabolism
  Cardiac fatty acid metabolism is interrupted by LA. ILE provides a source of fatty acids to allow metabolism to continue.
- Competitive antagonism
  ILE may directly inhibit LA binding.

- Dosing of Intralipid 20%:
  - Bolus of 1.5ml.kg^{-1} over 1 minute
  - Infusion at 15ml.kg^{-1}.hr^{-1}
- Complications include **pancreatitis**
  Note that ILE interferes with amylase and lipase assays, and so these will be unreliable.
- Note that whilst propofol can be used to treat seizures, the amount of lipid contained in propofol is inadequate to bind LA

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Neuraxial Blockade

> Describe the physiological consequences of a central neuraxial block

Central neuraxial blockade refers to blockade of fibres in the spinal cord by administration of intrathecal or epidural local anaesthetic.

Respiratory Responses

An increasing level of block will lead to greater effects:

- Thoracic
  - Impediment to active expiration and expectoration due to blockade of intercostals and abdominal wall musculature
  - Loss of vital capacity
  - Loss of some accessory muscle use
- Cervical
  Impediment due to diaphragmatic blockade.

Cardiovascular Responses

Occur due to blockade of sympathetic chain fibres in the thoracolumbar region.

An increasing level of block will lead to greater effects:

- Sacral
  Parasympathetic blockade only. Minimal CVS effects.
- Lower thoracic/lumbar
  Arteriolar and venous vasodilation in lower abdomen and lower limbs, causing a fall in SVR, BP, and GFR.
- Upper thoracic
  Loss of cardioaccelerator fibres above T5, causing a reduction in heart rate and contractility, compounding hypotension due to fall in SVR.
- Cranial Nerves
  Vagal blockade will reduce PNS tone and attenuate some of the loss of SNS tone.
- Brainstem
  Inhibition of vasomotor centre with profound fall in CVS parameters.

CNS Responses

An increasing level of block will lead to greater effects:

- Cervical
  Horner's syndrome (miosis, anhydrosis, ptosis) due to loss of sympathetic trunks.
- Cranial nerve Pupillary dilation due to CN III blockade.
- Brainstem and Cerebral Cortex Anaesthesia due to blockade of the reticular activating system and thalamus.

References

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Acetylcholine Receptors

> Understanding of the pharmacology of anticholinesterase drugs.

> Describe the adverse effects of anticholinesterase agents.

This covers the pharmacology of acetylcholine receptors and the production and metabolism of ACh. Detailed information on specific agents is in the pharmacopeia.

Acetylcholine is a neurotransmitter vital for normal function of:

- CNS
- ANS
- Muscle contraction

Synthesis, Release, and Metabolism

ACh is produced is the nerve cytoplasm by **acetyltransferase** from:

- Choline
  From diet and recycled ACh.
- Acetyl-coenzyme A
  Produced in the inner mitochondrial matrix.

Once synthesised, ACh is then packaged into vesicles (each containing ~10,000 ACh molecules), which are **released in response to calcium** influx occurring at the culmination of an action potential.

Acetylcholine is metabolised by acetylcholinesterase on the post-junctional membrane. AChE:

- Has two binding sites:
  - Anionic binding site
    Binds the positively charged quaternary ammonium moiety.
  - Esteratic binding site
    Binds the ester group of ACh.
- Once bound, ACh is acetylated
- Acetylated-ACh is then hydrolysed to produce **acetic acid**

ACh Receptor Subtypes

There are two types of ACh receptor:

- **Nicotinic ACh receptors**
  - Inotropic
    Linked to an ion channel.
    - Non-specific - may allow Na^+, K^+, or Ca^{2+} to cross
  - Consists of five subunits:
    - Two α
      Bind ACh.
    - One β
    - One δ
    - One γ
  - Located in:

        - Post-synaptic NMJ
        - Preganglionic autonomic nervous system
          Antagonism causes **ganglion blockade**.
        - Brain
    - Known as nicotinic because nicotine agonises this receptor
    - Activation:
        - 2 ACh molecules must bind to activate the receptor
        - Once bound, receptor undergoes a conformational change which opens the central ion pore
          Permeability to Na^+ (and to a lesser extent, K^+ and Ca^{2+}) increases, leading to depolarisation

- **Muscarinic ACh receptors**
    - Metabotropic
      G-protein coupled.
    - Known as muscarinic because muscarine also agonises this receptor
    - Subdivided into:
        - M_1 (Gq)
          Secretory glands and CNS.
        - M_2 (Gi)
          Heart.
        - M_3 Gq
          Bronchial and arteriolar smooth muscle.
        - M_4 (Gi) and M_5 (Gq)
          CNS.

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Opioids

Key definitions:

- **Opiates** are all naturally-occurring substances with morphine-like properties
- **Opioids** is a general term for substances with an affinity for opioid receptors
- **Opium** is a mixture of alkaloids from the poppy plant

Classification of Opioids

- **Naturally occurring**
    - Endogenous opioids
        - Endorphins
        - Enkephalins
        - Dynorphins
    - Opium derivatives
    - Phenanthrenes
        - Morphine
        - Codeine
- **Semisynthetic**
  Simple modifications to morphine.
    - Diacetylmorphine
    - Buprenorphine
    - Oxycodone
- **Synthetic**
    - Phenylpiperidines
        - Fentanyl
        - Alfentanil
        - Remifentanil
        - Pethidine
    - Diphenylpropylamines
        - Methadone

Opioid Receptor Classification

All opioid receptors are Gi receptors. Activation:

- Inhibits adenylyl cyclase, reducing cAMP
    - Pre-synaptically inhibits voltage-gated Ca^{2+} channels
        - Decreases Ca^{2+} influx
        - Reduces neurotransmitter release
    - Post-synaptically stimulates activates K^+ channels
        - Causes K^+ efflux
        - Leads to membrane hyperpolarisation

Receptor	Actions	Notable Properties
MOP	Analgesia (spinal and brain), euphoria, meiosis (via stimulation of the Edinger-Westphal nucleus), nausea and vomiting (via CTZ), sedation, bradycardia, inhibition	Only opioid receptor to cause

	of gut motility, urinary retention, physical dependence	nausea/vomiting
KOP	Analgesia (predominantly spinal), sedation, meiosis, dysphoria	Less respiratory depression
DOP	Analgesia, respiratory depression, urinary retention, physical dependence	Minimal constipation
NOP	Anxiety, depression, change in appetite	Hyperalgesia at low doses, analgesic at high doses

Mechanism of effects:

- **Respiratory depression**
  Decreases central chemoreceptor sensitivity to CO_2.
- **Constipation**
  Stimulation of opioid receptors in the gut.
  - Normally activated by local endogenous opioids (used as neurotransmitters)
  - Agonism of these receptors (μ, k, and to a smaller extent, δ) reduces GIT secretions and peristalsis

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Inhalational Anaesthetics

> Structure-activity relationships of inhalational agents

> Describe the uptake, distribution and elimination of inhalational anaesthetic agents and the factors which influence induction and recovery from inhalational anaesthesia including the:
> - Concepts of partition coefficients, concentration effect and second gas effect
> - Relationships between inhaled and alveolar concentration
> - Significance of the distribution of cardiac output and tissue partition coefficients on uptake and distribution of volatile agents

> Describe the concept and clinical application of MAC in relation to inhaled anaesthetic agents

> Describe how the pharmacokinetics of drugs commonly used in anaesthesia in neonates and children differ from adults and the implications for anaesthesia

> Properties of an ideal inhalational anaesthetic agent

Inhaled anaesthetics are chemicals with general anaesthetic properties that can be delivered by inhalation. They can be divided into:

- **Volatile** anaesthetic agents
  Volatility refers to the tendency of a liquid to vapourise. Volatile agents include:
  - Sevoflurane
  - Isoflurane
  - Desflurane
  - Methoxyflurane
  - Enflurane
  - Halothane
  - Ether
- Anaesthetic gases
  - Nitrous oxide
  - Xenon

Key Principles of Inhalational Agents

Key principles:

- The **clinical effect** of an inhalational agent **is dependent on** its **partial pressure** within the CNS
- **At equilibrium**, the partial pressure in the CNS (**P_B**) **equals** the partial pressure in blood (**P_a**), and in the alveoli (**P_A**)
  Reaching equilibrium is rarely achieved in practice as it takes many hours.
- Rate of onset and offset of an inhalational agent are dependent on both physiological and pharmacological factors affecting the transfer of agent:
  - Into the alveoli
  - From the alveoli into blood
  - From blood into the CNS

Minimum Alveolar Concentration (MAC)

MAC is **defined** as the minimum alveolar concentration at **steady state** which prevents a movement response to a standard surgical stimulus (1cm forearm incision) in 50% of a population.

Note that this definition:

- Does not reflect lack of awareness
- Does reflect the action of an agent on spinal cord reflexes
  This is why 1 MAC is adequate for the majority of patients, as awareness and recall are suppressed at lower MAC values than are required for immobility.
- Consciousness is better estimated by MAC-awake
  End-tidal concentration of agent that prevents appropriate responses to a verbal command in 50% of a population.
  - Note that this technically measures *awareness* rather than memory.
  - **MAC-awake** is typically **one-third** of **MAC** for commonly-used agents
- Is only valid at **sea-level**
  The **clinical effect** of an agent is **dependent** on its **partial pressure *not* concentration**.
  - At 1atm, these are almost the same
    1atm $\simeq$ 100kPa; therefore 2% sevoflurane is $\simeq$ 2kPa
  - As altitude increases, the actual partial pressure will fall for any given concentration i.e. 2% sevoflurane at 0.5atm is $\simeq$ 1kPa of sevoflurane.

MAC is:

- A measure of potency (i.e. the EC_{50} of the agent, where the outcome is movement)
  The MAC of an agent is inversely proportional to potency; i.e. more potent agents require smaller alveolar concentrations to produce anaesthesia.
  - This gives rise to the **Meyer-Overton hypothesis**, which suggests that anaesthesia requires a sufficient number of molecules to dissolve into the neuronal cell membrane.
    - If this was true, the product of the oil:gas partition coefficient and MAC would be constant, which is not the case.
- Additive
  The MACs of different agents used simultaneously are additive.
- Normally-distributed
  Not all patients will be unresponsive at 1 MAC.
  - The standard deviation is **0.1**, so 95% of patients will not move in response to a stimulus at 1.2 MAC
- Estimated clinically using **end-tidal** gas measurement
  MAC is not based on arterial partial pressure (F_a) of agent.
  - This is an important difference, because **even at steady-state, $\mathbf{F_a \neq F_A}$**
  - This occurs due to:
    - V/Q mismatch
      Shunted alveoli will not absorb anaesthetic agent, and unperfused alveoli will contain agent that is not being absorbed.
      - This is worsened by the effects of anaesthesia
    - Volatile agents are heavy and have finite diffusibility
  - However, the difference between F_a and F_A for any agent is the same at steady state (and in absence of nitrous oxide)
    This means that, **at steady-state**, MAC will be proportional to, and an accurate measure of, P_a.
- One of several related terms:
  - MAC awake
    Concentration required to prevent response to a verbal stimuli in **absence of noxious stimuli**.
    - Typically ~1/3rd of MAC for most agents (sevoflurane, isoflurane, desflurane)
    - Notably higher for nitrous oxide (MAC-awake ~2/3^{rds} of MAC)
    - MAC-awake is typically less than MAC-asleep as:
      - Hysteresis between alveolar and effect site concentrations
        During induction, alveolar concentration is higher than effect site concentration, and so overestimates effect.
        During wash out, alveolar concentration is less than effect site concentration, and the reverse effect occurs.
      - "Neural inertia"
        Intrinsic resistance of nerve cells to a change in their state.

- MAC-BAR
  Minimum alveolar concentration required to **b**lock **a**drenergic **response**, i.e. to prevent a rise in HR or BP following skin incision.
- MAC_{95}
  The MAC required to prevent a movement response to a standard surgical stimulus in 95% of the population.
- $MAC.hr^{-1}$
  The amount of time a patient is exposed to 1 MAC of an agent. Used to compare different agents.

Factors Affecting MAC

Decreases MAC	Increases MAC
Age (~6%/10 years ↑) and neonates	Youth
Hypothermia	Hyperthermia
Hypocapnea	Hypercapnea
Hyponatraemia	Hypernatraemia
Hypothyroidism	Hyperthyroidism
Acute alcohol and other CNS depressant intoxication	Chronic ETOH and CNS depressant abuse
Chronic amphetamine intake	Acute amphetamine intake
Hypovolaemia/Hypotension	
Lithium	
Hypoxia	
Anaemia	
Pregnancy	
	SNS activation and anxiety
	Increased P_{atm}

Note that addition of other agents (e.g. opioids) will affect different MAC subtypes (e.g. MAC_{50} vs MAC_{BAR}) differently.

Partition Coefficients

A **partition coefficient** describes the **relative affinity** of an agent for two phases, and is **defined** as the **ratio of the concentration** of agent in each phase, when both **phases are of equal volume** and the partial pressures are in **equilibrium at STP**.

- The **blood:gas partition coefficient** describes the solubility of the agent in blood relative to air, when the two phases are of equal volume and in equilibrium at STP
  A **low** blood:gas partition coefficient indicates a **rapid** onset and offset. This is because:
  - Poorly soluble agents generate a high P_a, which creates a steep gradient between P_a and P_B, giving a rapid onset of action
  - Conversely, soluble agents dissolve easily into pulmonary blood without substantially increasing P_a
    This causes leads to a slow onset due to:
    - A large fall in P_A as the agent leaves the alveolus, decreasing the gradient for further diffusion
    - A small gradient between P_a and P_B

- The **oil:gas partition coefficient** describes the solubility of the agent in fat relative to air, when both phases are of equal volume and in equilibrium at STP
  A **high** oil:gas partition coefficient indicates a greater potency, and therefore a low MAC.

Pharmacokinetics of Inhalational Agents

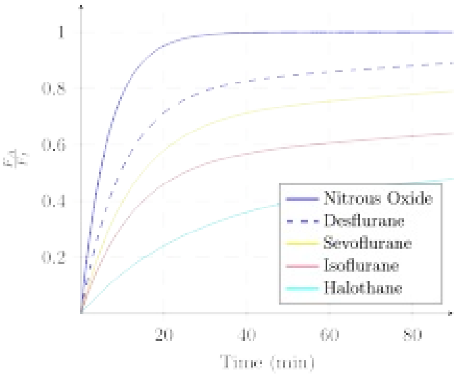
Achieving the required P_B requires maintaining P_A at a high enough level. By increasing P_A, the pressure gradient for diffusion into blood, and therefore CNS, is increased.

As discussed above, rate of onset of an inhalational agent is dependent on rate of uptake:

- Into the alveoli
- From the alveoli into blood
- From blood into the CNS

Factors affecting **alveolar concentration of agent:**

- **Inspired concentration**
  A high inspired concentration (F_i) will increase the rate of increase of alveolar concentration (F_A). Inspired concentration is dependent on:
  - Delivered concentration in fresh gas
  - Fresh gas flow
    Increasing FGF (and the concentration of agent in the added gas) increases F_i.
  - Volume of the breathing system
    A **lower circuit volume** will increase the rate at which the patient reaches equilibrium with the circuit, and therefore **increase F_i**.
  - Circuit absorption
    Absorption of agent by the circuit will **decrease F_i**.
- **V_A**
  Increased alveolar ventilation increases F_i, as it replenishes agent that has been taken up into the vasculature.
  - Similarly, increased **dead space** will prolong induction, as anaesthetic gas will be delivered to non-perfused alveoli
- **FRC**
  A **large FRC** will dilute the amount of agent inspired with each breath, and so **reduce F_i**.
  - This is measured with the V_A/FRC ratio
    Increased ratio increases speed of onset.
    - Normal in adults: 1.5:1
    - Normal in neonates: 5:1
- **Second gas effect**
  Use of N_2O with another agent will increase the P_A of that agent. This is because:
  - N_2O is **20x** as soluble in blood as either blood or nitrogen, and is administered in high concentrations, so it is rapidly absorbed from alveoli
  - If nitrous oxide is delivered at high concentrations, it's rapid absorption means that alveoli will **shrink**, causing:
    - An increase in the fractional concentration of all other gases
      This is known as the **concentration effect**, and increases the pressure gradient driving diffusion into blood, increasing speed of onset.
      - The concentration effect is the cause of the second gas effect
      - The concentration effect is **more pronounced as FiN_2O increases**
      - The concentration effect is more profound in lung units with moderately **low V/Q ratios**, causing in a large increase in F_a
        This results in a larger value of F_a for any given F_A, *even at steady state*.
    - Augmented ventilation as more inhalational agent is drawn in the alveoli from dead space gas
  - The second gas effect also causes **diffusion hypoxia**
    When inspired N_2O is reduced, N_2O will leave blood and enter the alveolus, displacing other gases in the alveolus.
    - This can cause a reduction in PAO_2, and therefore hypoxaemia
    - Diffusion hypoxia is avoided by delivering 100% oxygen, which maintains an adequate PAO_2 as N_2O is removed



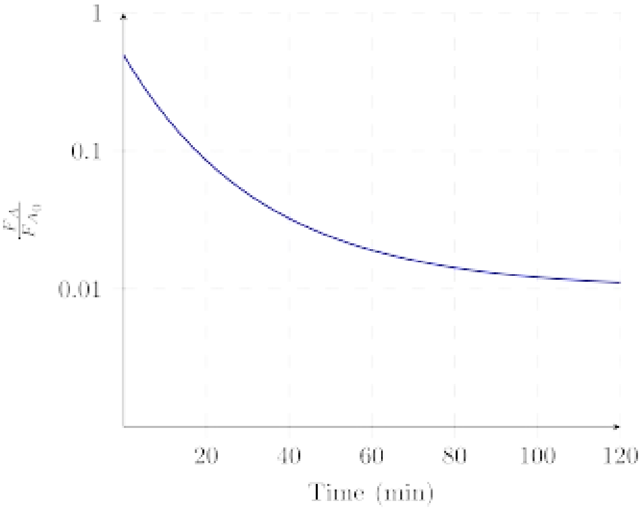
- Note that N_2O reaches a higher ratio faster than desflurane, despite its lower blood:gas partition coefficient, due to the concentration effect

Factors affecting **drug uptake from the lungs:**

- **Blood:gas partition coefficient**
  Agents with a low blood:gas partition coefficient reach $\frac{F_A}{F_I}$ equilibrium more rapidly. The blood:gas coefficient is affected by:
  - Temperature
    Blood:gas partition coefficients decrease as temperature increases.
  - Haematocrit
    Variable effect, which depends on the particular agents affinity for red cells or plasma (and serum constituents, e.g. albumin).
    - An agent that is less soluble in red cells (e.g. isoflurane) will have a decreased blood-gas partition coefficient in anaemia.
  - Fat
    Blood:gas partition coefficient increases following fat ingestion.
- **Alveolar blood flow**
  Increased alveolar blood flow increases uptake and delivery to tissues, including the CNS.
  - However, the increased uptake causes a reduction in P_A
    Therefore, **rate of onset** is **reduced** when **alveolar blood flow** is **high**.
    - This effect is more pronounced with agents with a high blood:gas partition coefficient
    - Alveolar blood flow is a function of:
      - Cardiac output
      - Shunt
- **Alveolar-Venous partial pressure gradient**
  The difference in partial pressure of agent in the alveolus and venous blood is due to the uptake of drug in tissues. Tissue uptake is dependent on:
  - Tissue blood flow
    As the CNS has a high blood flow, it will equilibrate more quickly.
  - Blood:tissue solubility coefficients
    - Muscle has similar affinity to blood, but equilibrates more slowly than the CNS due to lower blood flow
    - Fat has a much higher affinity for anaesthetic than muscle, but equilibrates very slowly due to the very low blood flow
      This is of greater importance in the obese, especially during prolonged anaesthesia, as they have a longer equilibration time and therefore prolonged emergence.

Wash-out of Inhalational Agents

Recovery is dependent on how quickly an inhalational agent can be eliminated from the effect site, and can be graphed by the F_A/F_{A0} ratio over time:



Washout can be divided into:

- Rapid washout
  Of agent in circuit and FRC.
  - The time constant for removal of agent from the circuit is a function of circuit volume and fresh gas flow, i.e.
    $$\tau = \frac{CV}{FGF}$$
- Slow washout
  Of agent in patient.
  - The time constant for removal of agent from the patient is a function of FRC and minute ventilation, i.e.
    $$\tau = \frac{FRC}{MV}$$

Factors affecting volatile washout:

- Brain-Blood and Tissue-Blood
  - Tissue:Blood coefficient of agent
  - Duration and depth of anaesthesia
    Important for highly soluble agents used in long cases.
- Blood-Alveolus
  - Blood:gas coefficient of agent
    Highly soluble agents will have an increased amount of drug dissolved in tissue, so a large reservoir of drug exists that will have to be removed.
  - Alveolar Cardiac output
    Decreased cardiac output **increases** elimination.
    - Shunt
      Decreases elimination.
- Alveolus-Air
  - MV_A/FRC
    Increased alveolar ventilation increases elimination.
- Other factors
  - Metabolism of agent
    Agents undergoing metabolism are eliminated more rapidly.
  - Absorption of agent into circuit
  - Percutaneous loss

Loss of agent by diffusion from tissues into external environment.

Alteration to Pharmacokinetics

Increased rate of induction in **children** due to:

- Increased V_A/FRC ratio
  Increases P_A.
- Lower albumin and cholesterol
  Reduced blood-gas solubility coefficients for some agents.

Increased rate of induction in **elderly** due to:

- Lower MAC requirement
- Lower albumin
  Reduces blood-gas solubility coefficients for some agents.
- Lower cardiac output
  P_a and therefore P_B is established more rapidly.

Altered rate of induction in **pregnancy** due to:

- Increased V_A/FRC ratio
  - Increased minute ventilation
    This is of greater importance in spontaneous ventilation, as this is controlled by the anaesthetist during controlled ventilation.
  - Decreased FRC
    Increases P_A, increasing P_B and speed of onset.
- Lower albumin
  Reduces blood-gas solubility coefficients for some agents.
- Increased CO
  Reduces rate of rise of P_A, reducing P_B and therefore speed of onset.
- Reduced MAC requirement
  Progesterone has some sedative properties.

Alteration to Pharmacokinetics with Special Methods of Administration

In **target-controlled anaesthesia**, FGF and agent F_I are controlled by the machine to reach the target F_A rapidly at low concentrations. This causes:

- An initial over-pressure of F_I, in order to fill the FRC and reach the desired F_A
- A more rapid induction, as the target F_a is reached more rapidly

In **liquid injection**, anaesthetic agent is injected into the breathing system. This causes:

- A very large degree of overpressure
  In this circumstance, the rate of rise of end-expired agent concentration is identical for different agents.
  - i.e. Onset is independent of the blood:gas coefficient

Mechanism of Action of Inhaled Anaesthetic Agents

Mechanisms of action can be divided into:

- **Macroscopic**
  At the level of the brain and spinal cord.
  - In the spine by:

        - Decreasing transmission of noxious afferent signals at the thalamus
        - Inhibition of spinal efferents, decreasing motor responses
    - In the brain by:
        - Global depression of CBF and glucose metabolism
- **Microscopic**
  Synapses and axons by:
    - Inhibiting pre-synaptic excitatory activity:
        - ACh
        - 5-HT
        - Glutamine
    - Augmenting post-synaptic inhibitory activity:
        - $GABA_A$
- **Molecular**
  Anaesthetic agents may alter the function of molecules within the CNS. These include:
    - Alteration of α-subunits of the $GABA_A$ receptor
      This prolongs the time it spends open once activated, prolonging the inhibitory Cl^- current and increasing the degree of hyperpolarisation.
    - Enhance the activity of two-pore K^+ channels
      Increases the resting membrane potential of both pre-synaptic and post-synaptic CNS neurons.

Incomplete Theories of the Mechanism of Action of General Anaesthetic Agents

Meyer-Overton Hypothesis:

- Potency of anaesthetics relates to their lipid solubility
- Anaesthetic molecules dissolve into CNS membranes, disrupting their effect
- Flaws:
    - Not all lipid soluble drugs have general anaesthetic affects
    - Other factors disrupt cell membranes without causing anaesthesia

Volume Expansion, **Pressure Reversal** (Mullin's Critical Volume Hypothesis):

- CNS cell membranes expand with general anaesthetic agents
  This distorts channels responsible for maintaining membrane potential and generating action potentials.
- Increased ambient pressure reverses general anaesthesia
- Flaws:
    - Does not account for stero-selectivity of drug-receptor interactions
      I.e. receptors select for one stereoisomer over others.

Structure-Activity Relationships of Inhaled Anaesthetics

- Chemical structures of different volatile anaesthetics are covered in the pharmacopeia.

Different chemical and physical properties alter the effect of inhalational agents:

- Physical
    - Molecular weight
      A decrease in molecular weight decreases boiling point and therefore increases SVP.
- Chemical
    - H^+ content
      Greater hydrogen content:
        - Increases flammability
        - Increases potency

-

   - F^- content
     Greater fluoride content:
     - Decreases flammability
     - Decreases oxidative metabolism
       This decreases toxicity.
     - Decreases potency
   - Cl^- content
     Increased chloride increases potency.
   - $-CHF_2$ (Di-fluor-methyl group)
     - Produces CO in the presence of dry soda lime

The Ideal Inhaled Anaesthetic Agent

From the properties discussed above, we can construct the following ideal agent:

- Physicochemical
  - Liquid at room temperature
  - High SVP
  - Low specific heat capacity
  - Long shelf-life
  - Light stable
  - Heat stable
  - Does not react with the components in the breathing circuit
    - Rubber
    - Metal
    - Plastic
    - Soda lime
  - Not flammable/explosive
  - Smells nice
  - Preservative free
  - Environmentally friendly
  - Cheap
- Pharmacokinetic
  - High oil:gas partition coefficient
    Low MAC.
  - Low blood:gas partition coefficient
    Rapid onset and offset.
  - Not metabolised
  - Non-toxic
- Pharmacodynamic
  - Does not cause laryngospasm or airway hyperreactivity
  - No effect on HDx parameters
  - Analgesic
  - Hypnotic
  - Amnestic
  - Anti-epileptic
  - No increase in ICP
  - Skeletal muscle relaxation
  - Anti-emetic
  - No tocolytic effects

  - Not teratogenic or otherwise toxic
- No drug interactions

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Hormones

A **hormone** is a chemical messenger produced by a **ductless gland** which has its action at a distant target cell via a specific receptor.

- **Lipid hormones**, divided into:
    - **Steroids**
      Steroids are synthesised from cholesterol, and are released as they are produced (they are not stored). They are highly lipid soluble and act on cytoplasmic and intra-nucleic receptors.
        - Aldosterone
        - Testosterone
        - Oestrogen
        - Cortisol
    - **Eicosanoids**
      Eicosanoids are formed from cell membrane phospholipid.
        - Prostaglandins
        - Thromboxanes
        - Leukotrienes
- **Peptide hormones**
  Peptide hormones are store in granules and released by exocytosis. They are divided into:
    - **Short-chain**
        - Insulin
        - ADH
        - Oxytocin
        - ACTH
    - **Long-chain**
        - GH
        - Prolactin
    - **Glycopeptides**
      Proteins with carbohydrate groups.
        - LH
        - FSH
        - TSH
- **Monoamine derivatives**
  Derived from a single amino acid.
    - Catecholamines
      Stored in granules and act at membrane receptors.
        - Adrenaline
        - Noradrenaline
    - Serotonin
    - Thyroxine

References

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Insulin, Glucagon, and Somatostatin

> Describe the physiology of insulin, glucagon and somatostatin.

Insulin

Insulin is a **polypeptide** hormone, and is:

- Synthesised from **proinsulin** in the rough endoplasmic reticulum of **B cells** in the **Islets of Langerhans**
- Excreted via exocytosis in response to an increase in intracellular Ca^{2+}
- **Minimally protein bound** with a **tiny volume of distribution**
  V_D 0.075 $L.kg^{-1}$, increased to 0.146 $L.kg^{-1}$ in diabetics.
- **Metabolised** in liver, muscle, and kidney **by glutathione insulin transhydrogenase**, with renal elimination of inactive metabolites
  Circulatory **half-life** of **~5min**.

Actions of Insulin

Insulin binds to a specific insulin receptor (a membrane-spanning protein composed of α and β subunits) on the cell membrane. The complex is internalised, and its effects are mediated by tyrosine kinase.

	Seconds	Minutes	Hours
Muscle	Increased glucose, amino acid, ketone, and K^+ uptake	Increased anabolism, decreased catabolism	
Fat	Increased glucose (via GLUT4), amino acid, and K^+ uptake	Increased glycerol phosphate synthesis	Increased fatty acid synthesis
Liver		**Decreased**: gluconeogenesis, ketogenesis. **Increased**: glycogen synthesis, glycolysis, protein synthesis, lipid synthesis	
General			Increased cell growth

Glucose Tolerance

Hyperglycaemia occurs in diabetes due to **decreased peripheral utilisation** as glucose uptake is reduced due to absence of or resistance to insulin. In addition, the suppressive effect of insulin on hepatic gluconeogenesis is absent or reduced.

Glucagon

Glucagon is a **polypeptide** hormone, and is:

- Synthesised in the **A cells** of the pancreas
- Has a circulating **half-life** of **~5min**
- Metabolised predominantly in the liver
  Secreted directly into the portal vein, and **undergoes first-pass metabolism** resulting in low circulating levels.

System	Effect

Liver	Glycogenolysis, gluconeogenesis, glucose release, ketone formation
CVS	Inotropy
Fat	Lipolysis
Metabolic	Increased metabolic rate, GH release, somatostatin release, insulin release

Secretion of glucagon is influenced by a number of factors:

Stimulate Release	Inhibit Release
Hypoglycaemia and starvation	Somatostatin
Amino acids	Secretin
Physiological stress: Exercise, infection	Free Fatty Acids
β-agonists	α-agonists
Cortisol	Insulin
ACh	Ketones
Theophylline	GABA

Somatostatin

Somatostatin is a **polypeptide** hormone that:

- Inhibits secretion of other hormones including:
    - Glucagon
    - Insulin
    - Other pancreatic peptides
- May function as a neurotransmitter in the CNS

References

1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
2. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Control of Blood Glucose

> Explain the control of blood glucose

Normal blood glucose in the non-diabetic is 4-6 mmol.L^{-1}, though will rise after consumption of carbohydrate. Glucose regulation can be divided into:

- Short-term
  Regulation via secretion or inhibition of insulin and glucagon from the pancreatic islets.
- Long-term
  Regulation via both neuronal (SNS activation) and hormonal (cortisol, GH) mechanisms.

Hormonal Mechanisms

Short Term

Glucose levels are sensed directly in the pancreas and will result in insulin release when the **BGL is >5.6** mmol.L^{-1}. **Pancreatic B cells** respond directly to glucose by secreting insulin in a biphasic fashion:

- An initial, rapid increase in release
  - **Glucose enters** via the GLUT-2 transporter, and is converted to pyruvate which enters **the citric acid cycle** and produces ATP
  - ATP **inhibits** ATP-sensitive **K^+ channels**, reducing K^+ efflux and **causing depolarisation**
  - Depolarisation causes **Ca^{2+} release**, resulting in **exocytosis** of insulin granules
- A prolonged, slow increase in release
  - Glutamate is produced as a by-product of the citric acid cycle
  - Glutamate stimulates maturation of other insulin granules
  - Release of these granules causes the second phase of insulin release

Conversely, a low glucose level stimulates secretion of glucagon. This is typically less important than the effect of insulin unless in situations of starvation or severe physiological stress.

Long Term

Sustained hypoglycaemia increases fat utilisation and decreases glucose utilisation (limiting further drops in blood glucose), via stimulating release of:

- GH
- Cortisol

Neuronal Mechanisms

Hypoglycaemia directly stimulates the hypothalamus, causing:

- Increased SNS tone
  Adrenaline release in turn stimulates hepatic glucose release.

Organ Effects

Glucose levels are influenced by the:

- Liver
  Insulin and glucagon act on the liver to continually adjust the relative rates of glycogenolysis and glycogenesis, allowing it to function as an effective **buffer** of **blood glucose**.
  - Hepatic disease significantly limits the efficacy of this system, and results in a widely-fluctuating blood glucose level
- Kidney
  - A transient glycosuria may be seen as hyperglycaemia decreases renal absorption of glucose

Physiological Responses to Hypoglycaemia

BSL ($mmol.L^{-1}$)	Symptoms	Endocrine Response
4.6		Insulin secretion inhibited
3.8	Autonomic dysfunction	Glucagon, adrenaline, and GH secretion
2.8	CNS dysfunction	
2.2	Lethargy, Coma	
1.7	Convulsions	
0.6	Permanent brain damage, Death	

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1. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th Ed. McGraw Hill. 2012.
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Hypothalamus and Pituitary

> Describe the control, secretions and functions of the pituitary and the hypothalamus

Hypothalamus

The hypothalamus is a circumventricular organ that regulates a large number of autonomic processes:

- **Thermoregulatory**
  Integrates thermoreceptor input and controls activity of heat loss and heat gain mechanisms.
- **Satiety**
  Feelings of hunger are modulated by glucose, CCK, glucagon, and leptin.
- **Water balance**
  - Contains osmoreceptors which control ADH release from the posterior pituitary
  - Angiotensin II stimulates thirst and ADH release via the subfornical organ and organum vasculosum
- **Circadian rhythms**
  Balance between anterior and posterior hypothalamic stimulation controls sleep-wake cycle.
- **Pituitary control**
  - Anterior pituitary by hormone secretion into the long portal vein. Secreted hormones include:
    - GnRH, stimulates FSH and LH release
    - CRH, stimulates ACTH release
    - GHRH, stimulates GH release
    - TRH, stimulates TSH release
    - Somatostatin, inhibits GH and TSH release
    - Dopamine, inhibits prolactin release
  - Posterior pituitary by neuronal innervation
- **Behaviour**
  Punishment and reward centres.
- **Sexual function**

Pituitary

The **hypothalamic-pituitary axis** describes the complex feedback loops between these endocrine organs:

- **Short-loop feedback** describes negative feedback from the pituitary on the hypothalamus, e.g. GH inhibiting GHRH release
- **Long-loop feedback** describes negative feedback from a pituitary target gland (i.e. thyroid, adrenal, gonads) on the hypothalamus, e.g. cortisol inhibiting CRH (as well as ACTH) release.
  - These axes are also named with target gland, e.g. hypothalamic-pituitary-adrenal axis

Pituitary Hormones

The pituitary gland secretes **eight hormones** from **two lobes**:

- **Anterior Pituitary**
  Secretes **six** hormones in response to hypothalamic endocrine stimulus. These are classified as:
  - **Stimulating** hormones, which act at another gland:
    - **ACTH**
      Short-chain peptide that stimulates cortisol release from the zona fasciculata. Release is stimulated by CRH, and inhibited by cortisol.

        - **TSH**
          Glycoprotein that stimulates synthesis and release of T_3 and T_4. Release is stimulated by TRH, and inhibited by T_3.
        - **FSH**
          Glycoprotein gonadotropin. Release is stimulated by GnRH, and inhibited by circulating sex steroids. Has different effects depending on sex:
            - Females: Stimulates oestrogen synthesis and ovarian follicle development.
            - Males: Stimulates sperm maturation.
        - **LH**
          Glycoprotein gonadotropin with different effects depending on sex:
            - Females: Rapid increase stimulates ovulation and corpus luteum development.
            - Males: Stimulates testosterone synthesis.
    - **Direct acting** hormones:
        - **GH**
          Long-chain peptide released in a pulsatile fashion. Release is stimulated by GHRH and is typically high with exercise, hypoglycaemia, and stress. Release is inhibited by somatostatin and IGF-1. GH has generally anabolic effects:
            - Directly stimulates lipolysis, increasing circulating FFA
            - Indirectly stimulates IGF-1 release, promoting cell growth and development
        - **Prolactin**
          Long-chain peptide which promotes breast development during gestation, and lactation after delivery.

- **Posterior pituitary**
  Secretes **two** hormones:
    - **ADH**
      Short-chain peptide which is:
        - Released in response to osmoreceptors in the circumventricular organs detecting a change in osmolality
          ADH release is:
            - Reduced when osmolality is <275 mosm.l-1</sup>
            - Increased when osmolality is >290 mOsm.L^{-1}
        - Effective at:
            - V_1 receptors in vascular smooth muscle, causing vasoconstriction
            - V_2 receptors in kidney collecting ducts to increase water reabsorption, and on endothelium to increase vWF and factor VIII release
            - V_3 receptors in the pituitary to stimulate ACTH release
    - **Oxytocin**
      Short-chain peptide, structurally similar to ADH, which causes:
        - Uterine contraction
        - Let-down reflex
          Stimulates milk release on suckling.
        - Psychological
          Pair bonding.

References

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Thyroid

> Describe the control, secretions and functions of the thyroid.

The thyroid gland:

- Produces and secretes two hormones in response to TSH:
    - T_4 (thyroxine, 93%)
    - T_3 (tri-iodothyronine, 7%)
- Secretions are controlled via a negative-feedback loop on the hypothalamic-pituitary-thyroid axis
  Increased TSH results in:
    - Increased iodine uptake
    - Increased iodination to form T_4 and T_3
    - Increased proteolysis of thyroglobulin, which releases T_4 and T_3
- Secretions are decreased with decreased iodine uptake
    - Perchlorate
      Blocks Na^+/I^- symporter.
    - Wolff-Chaikoff effect
      A reduction in thyroid hormone production due to a high circulating [iodide].

Synthesis

Thyroid hormones are:

- **Synthesised** in **follicles**
  A follicle is formed of a single layer of cuboidal epithelium around a central lumen (follicular cavity) containing thyroglobulin.
    - **Iodide** is transported into follicular cells via a **secondary active transport** mechanism
      Na^+/I^- co-transporter.
    - Iodide is then **oxidised to iodine**
    - Thyroglobulin is synthesised in the endoplasmic reticulum of the follicular cell and excreted into the follicular cavity
    - Iodine is excreted into the follicular cavity using a chloride exchange pump
    - In the follicular cavity:
        - **Thyroid peroxidase** catalyses the iodination of thyroglobulin, forming mono-iodotyrosine and di-iodotyrosine
        - These are subsequently **oxidised**, forming T_3 and T_4 respectively

In summary:

- Iodide is taken into the thyroid follicles by secondary active transport, and oxidised to iodine
- Thyroglobulin is synthesised in the follicle, and excreted into the follicular cavity
- Iodine is secreted into the follicular cavity, where it combines with thyroglobulin to produce T_4 and T_3

Secretion and Metabolism

Thyroid hormones are:

- Secreted in vesicles via endocytosis into the surrounding capillaries
    - Colloid enters thyroid cell via pinocytosis at the apical membrane
    - Vesicles then fuse with lysosomes

  - Thyroid hormone cleaved from thyroglobulin by proteases
  - Free T_3 and T_4 diffuse through the base of the thyroid cell into surrounding capillaries
- Highly protein bound to albumin and thyroxine-binding globulin
  - T_4 has a $t_{1/2}$ of 7 days
  - T_3 has a $t_{1/2}$ of 24 hours
  - Both are deiodinated in the liver, kidney, and muscle
    - 55% of T_4 will be first deiodinated to T_3

Physiological Effects

Thyroid hormones:

- Act on thyroid receptors in the **cell nucleus**
  Increasing gene transcription, protein synthesis, and mitochondria size and number.
- **T_3 is 3-5x more active than T_4**

Effects of thyroid hormone are predominantly metabolic:

System	Effect
Resp	↑ MV due to ↑ CO_2 production
CVS	↑ HR, ↑ inotropy, ↑ CO, ↓ SVR, ↓ DBP
CNS	↑ Excitability: Seizures, tremor
MSK	↑ Osteoblastic activity
GU	Impotence (men), oligomenorrhoea (women)
GIT	↑ GIT motility
Metabolic	↑ BMR up to 100%, ↑ carbohydrate metabolism (↑ glucose uptake, ↑ glycolysis, ↑ gluconeogenesis), ↑ fat metabolism (↑ lipolysis, ↑ non-shivering thermogenesis, ↓ plasma cholesterol, ↓ plasma phospholipids, ↓ triglycerides), ↑ protein metabolism (↑ anabolism at physiological levels, ↑ catabolism at high levels)

References

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Adrenal Hormones

> Describe the control, secretions and functions of ~~renal and~~ adrenal hormones

This covers the production of adrenal hormones. Information specific to catecholamines receptor function can be found under adrenoreceptors, whilst detailed information on specific agents, including structure-activity relationships, is in the pharmacopeia.

The adrenal glands are paired triangular glands at the superior pole of the kidney. The gland can be divided into:

- Adrenal cortex
  Consists of three layers which produce **steroid hormones** (A good mnemonic is GFR for the layers, and ACT(H) for hormones)
  - Zona Glomerulosa
    Predominantly produces mineralocorticoids (aldosterone).
  - Zona Fasciculata
    Predominantly produces glucocorticoids (cortisol).
  - Zona Reticularis
    Predominantly produces sex steroids (testosterone).
- Adrenal medulla
  Produces catecholamines.

Steroid Hormones

Mineralocorticoids

Aldosterone is the key mineralocorticoid hormone, accounting for 95% of mineralocorticoid activity:

- Release is stimulated by:
  - Increased serum K^+
  - Increased Angiotensin II
    - Hypovolaemia
    - Decreased osmolarity
  - Increased ACTH
  - Decreased serum pH
- Acts to increase sodium and water retention (and removal of potassium), via:
  - Increased expression and activation of Na^+/K^+ pumps on the basolateral membrane of DCT and CT cells, causing increased Na^+ (and water) reabsorption and K^+ elimination
  - Stimulation of the Na^+/H^+ pump in intercalated cells on the DCT

Glucocorticoids

Cortisol (hydrocortisone) is the primary glucocorticoid in the body, accounting for 95% of endogenous glucocorticoid effect. Cortisol is:

- Produced at ~15-30mg.day^{-1}
- Released in response to ACTH
  ACTH is released in response to CRH, which is:
  - Released in response to stress
  - Modulated by circadian rhythms, and demonstrates diurnal variation:
    - CRH peaks just before waking
    - CRH troughs during sleep

Cortisol has effects on many organ systems, and in **physiological** amounts cause:

- CVS
  - Increased sensitivity to catecholamines
  - Increases fluid retention
- Metabolic
  (Essentially anti-insulin effects):
  - Gluconeogenesis
    To provide substrates, it also stimulates:
    - Proteolysis
    - Lipolysis
  - Decreased glucose uptake

Catecholamines

Naturally occurring catecholamines include:

- Adrenaline
- Noradrenaline
- Dopamine

Synthesis of catecholamines occurs in the **adrenal medulla**, which is a **modified sympathetic ganglion** composed of **chromaffin cells**.

- Synthesis and release is dependent on **ACh release** by the presynaptic neuron
  Unlike many other hormones, catecholamine secretion is not a negative-feedback loop.

Process of catecholamine synthesis:

- **Tyrosine** is concentrated in the adrenal medulla
- Tyrosine is hydroxylated to DOPA by **tyrosine hydroxylase**
  This is the **rate-limiting** step, and is probably the best enzyme to remember.
- DOPA is decarboxylated to dopamine
- Dopamine is converted to noradrenaline
- Noradrenaline is converted to adrenaline by **PNMT** (Phenylethanolamine N-methyltransferase)
  This may only occur in the adrenal medulla.

Plasma half-lives of noradrenaline and adrenaline are small as a consequence of their metabolism and elimination.

- Extraneuronal uptake in the lungs, liver, kidney, and GIT
- Neuronal uptakeby sympathetic nerve endings
- Inactivation by MAO in nerve cytoplasm
- Inactivation by COMT in the liver and kidney

References

1. Brandis K. The Physiology Viva: Questions & Answers. 2003.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Calcium Homeostasis

> Describe the function, distribution, regulation and physiological importance of ~~sodium, chloride, potassium, magnesium,~~ calcium ~~and phosphate~~ ions

> Describe the control of plasma calcium.

Calcium is a bivalent cation. Almost all (99%) of calcium is located in bone, with the remainder in plasma and soft tissues. Normal plasma levels are 2.2-2.55 $mmol.L^{-1}$, which (in plasma) may be:

- Ionised (free) calcium (50%)
  Normal range 1.1 to $1.3mmol^{-1}$.
- Bound to albumin (40%)
- As calcium compounds (10%)

Functions of Calcium

- **Cell Signaling**
  Calcium has a number of roles in cell signaling:
  - Affects cell sodium permeability and therefore the RMP of excitable cells
  - Calcium triggers exocytosis of neurotransmitter vesicles
  - Calcium is an important second messenger for some G proteins
- **Bone**
  Calcium has two functions in bone:
  - Physical structure
  - Alkali reserve
    Calcium phosphate can be mobilised to buffer acidosis.
- **Enzymatic cofactor**
  Calcium is an important cofactor in enzymatic pathways, including the coagulation cascade. Clinical hypocalcaemia does not cause coagulopathy however, as calcium levels low enough to prevent coagulation are not compatible with life.

Regulation of Calcium

Calcium is regulated to maintain a stable **ionised** calcium level. Three hormones are involved in the regulation of calcium:

- **Parathyroid Hormone**
  Protein hormone secreted by the four parathyroid glands, located on the posterior surface of the thyroid, in response to a fall in iCa^{2+} levels, and acts to **increase plasma calcium**:
  - Increase calcium reabsorption in the PCT and late DCT
  - Increase osteoclastic activity in bone
  - Increase vitamin D activation in the intestine, which in turn increases intestinal absorption of dietary calcium
- **Vitamin D/Calcitriol**
  Once converted to calcitriol in the kidney (via stimulation from PTH), vitamin D acts to:
  - Increase calcium reabsorption from kidney and gut
  - Increase bone calcification
- **Calcitonin**
  Peptide hormone secreted by the C cells of the thyroid gland, in response to a rise in iCa^{2+} greater than $2.4mmol.L^{-1}$.

Calcitonin acts to:

- Decrease absorption of calcium from gut and kidney
- Decrease osteoclastic activity of bone

References

1. Brandis K. The Physiology Viva: Questions & Answers. 2003.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

Last updated 2017-09-08

Histamine

> Describe the physiology of histamine ~~and serotonin~~

Histamine is an endogenous amine produced by decarboxylation of **histidine**. Histamine is:

- Present in all tissues
  Particularly abundant in those exposed to the outside environment:
  - Lungs
  - Gut
  - Skin (lungs, gut, skin)
- Produced in and released by:
  - Mast cells
    Released by exocytosis during inflammatory and allergic reactions.
  - Basophils
  - Histaminocytes in the stomach
  - Histaminergic neurons in the CNS
- Metabolised by:
  - Histaminase
  - Imidazole N-methyltransferase

Histamine Receptors and Effects

Histamine acts on:

- H_1 receptors
  Gq receptor involved broadly in inflammation and vasodilation.
- H_2 receptors Gs receptor involved in gastric acid secretion.
- H_3 receptors
  Gi presynaptic receptor in the CNS.
- H_4 receptors
  Gi receptor located in bone marrow and other solid haematological organs (spleen, liver, thymus).

System	H_1	H_2	H_3	H_4
Resp	Bronchoconstriction	Bronchodilation		
CVS	↑ Vasodilation (endothelial effect), coronary vasoconstriction, ↓ AV nodal conduction	↑ HR, ↑ inotropy, coronary vasodilation, ↑ capillary permeability		
CNS			Presynaptic inhibition of neurotransmission	
MSK	Weal due to local vasodilation, itch, ↑ nociception			
GIT	↑ Peristalsis	↑ Gastric acid secretion		
Haeme				Alter IL-16 release

References

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Prostanoids

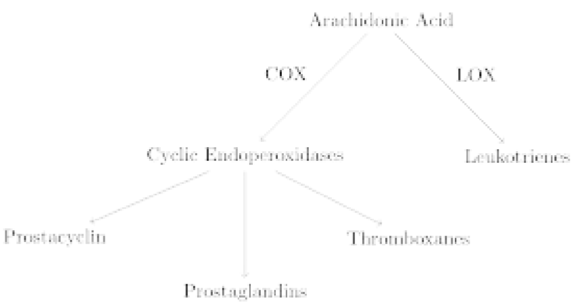
Prostanoids are a diverse family of eicosanoids (20-carbon molecules), produced from arachidonic acid, and include:

- Thromboxane
- Prostacyclin
- Prostaglandins

Synthesis

Arachidonic acid is converted into:

- Leukotrienes by LOX
- Cyclic endoperoxidases by COX enzymes
  These undergo further metabolism to produce:
    - Thromboxanes
        - Thromboxane A_2
    - Prostacyclins
        - PGI_2
    - Prostaglandins
        - PGE_2
            - EP_1
            - EP_2
            - EP_3
        - $PGF_{2\alpha}$
        - PGD_2



Effects

Receptor	Receptor	Respiratory	Vascular	GIT	GU	Othe
Thromboxane A_2	Gq		Vasoconstriction			Platelet aggrega
PGI_2	Gs	Bronchodilation	Vasodilation (renal and pulmonary)			
PGE_2 EP_1	Gq	Bronchoconstriction		Increased contraction	Renal vasodilation	
PGE_2 EP_2	Gs	Bronchodilation	Closure of ductus arteriosus	Decreased contraction	Renal vasodilation	

PGE_2 EP_3	Gi			Gastric mucous production, GIT contraction	Uterine contraction	
$PGF_{2\alpha}$	Gq	Bronchoconstriction	Vasoconstriction		Uterine contraction	
PGD_2	Gs				Renal vasodilation	Promote sleep

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Last updated 2019-07-18

Skeletal Muscle

> Describe the anatomy and physiology of skeletal ~~, smooth, and cardiac~~ muscle

> Describe the mechanism of excitation-contraction coupling

Skeletal muscle has a number of functions:

- Facilitate movement
- Posture
  Via tonic contraction of antagonistic muscle groups.
- Soft tissue support
  Abdominal wall and pelvic floor support viscera.
- Voluntary sphincter control
- Heat production

Structure and Contents

Skeletal muscle consists of long tubular cells, known as muscle fibres, which run the length of the muscle. Skeletal muscle cells:

- Are under voluntary control from the somatic nervous system via α-motor fibres
  α-motor fibres may control multiple myofibres, forming a **motor unit**.
- Are 10-100μm in diameter
- Contain several hundred peripheral nuclei
- Contain multiple mitochondria
  - Slow oxidative fibres (red fibres)
    Contain multiple mitochondria, produce sustained contraction, and are resistant to fatigue.
  - Fast glycolytic fibres (white fibres)
    Contain low numbers of mitochondria and large amounts of glycogen, and produce strong contractions but are more easily fatigued.
- Contain sarcoplasmic reticulum
- Contain large amounts of glycogen
  ~200g total.
- Contain myoglobin
- Appear striated microscopically due to the arrangement of myofibrils
  - Myofibrils are multiple myofilaments arranged in parallel
  - Myofilaments are formed from multiple sarcomeres arranged in series
  - A sarcomere is the functional unit of muscle

Muscle fibres are surrounded by layers of connective tissue:

- Endomysium
  Thin layer which surrounds each muscle fibre.
- Perimysium
  Surrounds bundles of muscle fibres.
- Epimysium
  Thick layer which surrounds an entire muscle.

These layers of connective tissue join at the end of a muscle to form a tendon or aponeurosis.

Sarcomere

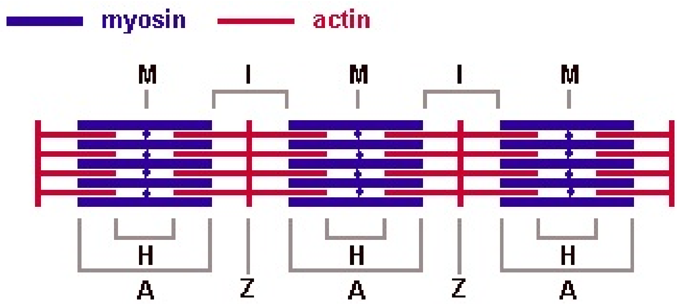
The sarcomere is the functional contractile unit of muscle. Average sarcomere length is 2.5μm.

The sarcomere contains two main proteins:

- Myosin (**thick**) filaments
  Myosin is a large protein with two heads, which bind actin and ATP. The myosin head flexes on its neck during contraction.
- Actin (**thin**) filaments
  Actin is a smaller protein than myosin, and potentiates the ATPase of myosin. Actin filaments have a groove which contains another protein called **tropomyosin**, to which **troponin** attaches to.
  - Troponin has three subunits:
    - Troponin T - binds troponin to tropomyosin
    - Troponin I - prevents myosin binding to actin by physically obstructing the binding site
    - Troponin C - Binds Ca^{2+} which initiates contraction

These proteins are arranged to form three bands and two lines:

- A-band
  The myosin filaments.
- H-band
  The section of myosin filaments not overlapping with actin filaments.
- I-band
  The section of actin filaments not overlapping with myosin filaments.
- Z-line
  Each end of the sarcomere. Actin from adjacent sarcomeres are connected at the Z line.
- M-line
  Band of connections between myosin filaments.



Bands and lines in the contractile apparatus of skeletal muscle

Excitation-Contraction Coupling

Muscle contraction normally requires the coordination of electrical (signaling) events with mechanical events.

- In response to ACh stimulating nicotinic receptors, the Na^+ and K^+ conductance of the end-plate increases and an **end-plate potential** is generated
- Muscle fibres undergo successive depolarisation and an action potential is generated along T tubules
  These deliver the AP deep into the cell, and close to the sarcoplasmic reticulum.
- Ca^{2+} is released from sarcoplasmic reticulum
  This process involves:
  - Dihydropyridine Receptor
    Specialised voltage-gated L-type Ca^{2+} channel, activated by T-tubular depolarisation. Responsible for a small amount of Ca^{2+} transport.
  - Ryanodine Receptor

2+

A second Ca^{2+} channel which is attached to, and activated by, the dihydropyridine receptor, causing a much larger release of Ca^{2+}.

- Ca^{2+} is released from the SR (increasing intracellular Ca^{2+} 2000x) and binds to **troponin C**, weakening the troponin I - actin link and uncovering myosin-binding sites on actin
- Cross-linkages form between actin and myosin, which releases ADP
- The release of ADP triggers a **power stroke**, which is a process of attachment, pulling, and detachment
  Each cycle shortens the sarcomere by **~10nm**:
  - The myosin head rotates on its 'neck', moving to a new actin binding site
  - ATP binds to the (now free) binding site on the myosin
  - ATP is hydrolysed to ADP, in the process "re-cocking" the myosin head
    This process causes the thick and think filaments to slide on each other, with the myosin heads pulling the actin filaments to the centre of the sarcomere. Therefore, over the course of a power stroke:
    - The A-band is unchanged
    - The H-band shortens
    - The I-band shortens
- Power strokes continue as long as there is ATP and Ca^{2+} available
- In relaxation:
  - Ca^{2+} is pumped back into the sarcoplasmic reticulum
    This is an ATP-dependent process, and is why muscle relaxation is active.
  - Troponin releases Ca^{2+}
  - Binding sites are occluded by troponin, and no further contraction occurs

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Skeletal Muscle Innervation

> Explain the concept of motor units

> Describe the relationship between muscle length and tension

> Describe the monosynaptic stretch reflex, single twitch, tetanus and the Treppe effect

Motor Units

- A motor unit consists of an α-motor neuron and the group of muscle cells that it innervates
    - An action potential in this neuron will cause contraction of all the myocytes in the unit
    - Large muscles have many myocytes per unit
    - Small, precise muscles (e.g. extraocular) have few myocytes per unit

Force of Contraction

Muscle tension is dependent on three factors:

- **Initial myocyte fibre length**
  Optimal stretch maximises the number of overlapping actin and myosin filaments.
- **Number of contracting myocytes**
  Recruitment of additional motor units increases the force of contraction.
- **Frequency of Action Potentials**
  High frequency action potentials cause accumulation of calcium in the cytoplasm (the Bowditch or Treppe effect), increasing force of contraction.
    - As the absolute refractory period of skeletal muscle is shorter than cardiac muscle, **tetany**, or sustained muscle contraction, can occur

Proprioception

Proprioception is the ability of the body to determine it's position in space. There are two key proprioceptive sensors:

- Muscle spindles
- Golgi tendon organs

Muscle Spindles

Muscle spindles sense **changes in muscle length**. They:

- Are a specialised muscle fibre, known as **intrafusal fibres**
- Run **parallel** to myocytes (also known as **extrafusal fibres**)
- Consist of two elements:
    - Central, non-contractile portion which senses tension
    - Contractile ends
      This allows the muscle spindle to adjust its length with its muscle, so that a constant tension in the non-contractile portion can be maintained over a range of muscle lengths.

Muscle spindles have both afferent and efferent innervation:

- Afferent type Ia fibres adjust their electrical output to signal both current fibre length and rate of change
- Afferent type II fibres only signal fibre length
- Efferent γ neurons innervate the contractile elements

Voluntary muscle contraction results in contraction of both motor units (α1 neurons) and intrafusal fibres (γ-motor neurons).

Tonic innervation of γ-motor neurons increases muscle tone by stretching the non-contractile portions, increasing Ia firing and subsequent α-motor unit firing.

Golgi Tendon Organs

Golgi tendon organs are stretch receptors located between muscle and tendon. They:

- Run **in series** to myocytes
- Sense stretch
- Cause reflexive muscle **relaxation**, intended to prevent muscle damage

Reflexes

A reflex is an involuntary, predictable movement in response to a stimulus. There are two types:

- **Monosynaptic**: Motor neuron synapses directly with the sensory neuron
  Monosynaptic reflexes are rapid, but only generate simple responses. There are five components to a monosynaptic reflex:
    - Sensory receptor
      Typically muscle spindles.
    - Afferent neuron
      Type Ia afferents relay signal from muscle spindle to ventral horn via the dorsal root.
    - Synapse between afferent and efferent neuron
      In the ventral horn
    - Efferent neuron
      α-motor neuron travels from the ventral horn and innervates the motor unit.
    - Effector muscle Innervated motor unit contracts in response.
- **Polysynaptic**: Motor neuron is separated from the sensory neuron by one or more interneurons in the dorsal horn
  This allows modulation of signal. Responses are slower but more complex, e.g. withdrawal of a limb from a hot object.

Twitch and Tetany

- A **twitch** is the response of a muscle to a **single stimulus** (action potential)
- A **tetanic** contraction describes the sustained contraction produced by **repetitive stimulation** before relaxation can occur
    - This stimulation must be causing above a **critical frequency**, which is dependent on the action potential duration for a cell
    - Repetitive stimulation causes repeated SR depolarisation, leading to sustained high intracellular Ca^{2+} levels as Ca^{2+} entry exceeds Ca^{2+} exit
    - Force from tetanic contraction is up to 4x greater than that of a twitch

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1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
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Neuromuscular Blockers

> Understanding of the pharmacology of neuromuscular blocking drugs

The neuromuscular junction is a chemical communication between the motor neuron and the muscle cell. Vesicles containing ACh are released when activated by Ca^{2+}, and influx of which occurs when the action potential reaches the nerve terminal.

Nicotinic ACh receptors sit on the shoulders of junctional folds of muscle cells, whilst acetylcholinesterase is buried in the clefts.

Factors Affecting Neuromuscular Blockade

Patient Factors

Factor	Effect	Mechanism
Hepatic Disease	Prolonged duration of aminosteroids and suxamethonium	Decreased metabolism, decreased production of pseudocholinesterase in severe disease
Pseudocholinesterase deficiency	Prolonged duration of suxamethonium	Decreased metabolism
Age	Increased sensitivity in neonates, particularly premature infants	Incomplete maturation of NMJ
Hypokalaemia	Potentiates non-depolarising blockade, reduces depolarising blockade	Increases magnitude of stimulus required to depolarise cell
Hyperkalaemia	Potentiate depolarising blockade, reduce non-depolarising blockade	Decreases magnitude of stimulus required to depolarise cell
Hypermagnesaemia	Potentiates blockade	Decreases ACh release, decreases sensitivity of post-synaptic membrane
Hypocalcaemia	Potentiates blockade	Decreases presynaptic ACH release, decreases sensitivity of post-synaptic membrane
Respiratory acidosis	Potentiates blockade	Enhances effect of NMB agents
Hypothermia	Potentiates blockade	Reduces hepatic metabolism, renal elimination, Hoffman degradation
Hypovolaemia	Slows rate of onset and enhances duration	Prolonged circulation time
Myasthenia Gravis	Increased sensitivity to non-depolarising agents	Autoimmune blockade of receptors gives pre-existing level of block
Eaton-Lambert Syndrome	Increased sensitivity to all NMBs	Autoimmune destruction of voltage-gated Ca^{2+} channels prevent ACh vesicle exocytosis

Drug Factors

Drugs	Effect	Mechanism
Frusemide	Potentiates blockade at low dose, reduces blockade at high dose	Inhibits protein kinases (reducing AMP/ATP synthesis) at low dose, inhibits PDE at high doses which increases ACh release
Inhalational anaesthetics	Potentiates blockade	Stabilise post-junctional membrane, blockade of presynaptic ACh receptors

Antibiotics	Potentiate blockade	Variable. Aminoglycosides and tetracyclines prolong blockade
Local anaesthetics	Potentiate blockade	Reduce ACh release and stabilise post-junctional membrane
Anticholinesterases	Reduces blockade	Increase ACH levels at the NMJ by decreasing breakdown
OCP	Potentiates depolarising blockade	Competes for binding sites on plasma cholinesterases
Ca^{2+}-channel blockers	Potentiate blockade	Inhibit Ca^{2+} dependent ACh release
Lithium	Potentiates blockade	Augments action of NMBs

Additional Factors Affecting Onset of Neuromuscular Blockade

Most of these can be related to Fick's Law:

Factor	Effect	Mechanism
Potency	Low potency decreases time to onset	Bowman's principle: Less potent drugs must be administered in higher doses, and so have a greater concentration gradient driving diffusion to the effect site
Dose	Increased dose decreases time to onset	Greater concentration gradient
Cardiac Output	High output decreases time to onset	Increased drug delivery
Muscle group flow	High muscular flow decreases time to onset	Increased drug delivery
Priming Principle	(May) decrease time to onset	A 'priming' dose of non-depolarising blocker is to an awake patient given prior to induction. This occupies less than 70% of receptors, so does not cause significant neuromuscular blockade. After induction, a second dose is given to occupy the remaining receptors and complete blockade.

References

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Last updated 2019-07-18

Basal Metabolic Rate

> Describe basal metabolic rate and its measurement

> Outline the factors that influence metabolic rate

Basal Metabolic Rate is the **energy output required to sustain life at rest**.

- 'Resting' is defined as an individual who is:
  - Fasted for 12 hours
  - In a comfortable external environment
  - At mental and physical rest
- Normal values are:
  - $100W.day^{-1}$
  - $70kcal.hr^{-1}$

Metabolic rate is the actual energy consumption of an individual, and is greater than BMR due to a number of factors.

Factors Affecting Metabolic Rate

Metabolic Rate is affected by:

- **Age**
  BMR decreases as age increases.
  - Neonates have a BMR twice that of an adult
  - Children have an increased BMR relative to that of an adult
  - BMR declines by 2% for each decade of life
- **Body Composition**
  Lean muscle has a greater energy requirement than fat.
  - Higher body fat percentage results in a lower BMR
    - Females have a lower BMR for this reason - when adjusted for lean mass there is no difference
- **Diet**
  - Digestion increases BMR by ~10% due to the energy required to assimilate nutrients
    This is known as the **specific dynamic action** of food.
    - Protein > carbohydrate > fat
      Note that the Specific Dynamic Action for each macromolecule is not related to the respiratory quotient for that food type.
  - Starvation decreases the BMR
- **Exercise**
  - Skeletal muscle is the largest and most variable source of energy consumption
- **Environment**
  - Cooler environments increase BMR
  - Temperate environments decrease BMR up to 10%
- **Physiological states**
  - Pregnancy increases BMR up to 20% in 2nd and 3rd trimester
  - Lactation increases BMR
  - Catecholamines increase BMR
  - Corticosteroids increase BMR
- **Disease states**
  - Malignancy increases BMR

- Sepsis increases BMR
- Hyperthyroidism increases BMR

Measurement of BMR using Indirect Calorimetry

BMR is measured using **indirect calorimetry**, which calculates heat production via measurement of VO_2 and VCO_2. A number of methods exists depending on whether the patient is intubated or not, or whether they are requiring supplementary oxygen.

In general:

- Patients should be relaxed and fasted
- FiO_2 needs to be calculated (or taken from the ventilator settings), and E_TCO_2 and E_TO_2 must be measured
- Steady-state should be achieved across a five minute period
    - The average MVO_2 and $MVCO_2$ changes by <10%
    - The respiratory quotient ($RQ = \frac{VCO_2}{VO_2}$) change by <5%
        - This ratio will vary depending on the substances metabolised:
            - Carbohydrates = 1
            - Protein ≈ 0.8
            - Fat ≈ 0.7

Resting Energy Expenditure is given by the **abbreviated Weir equation**:

$REE = 3.94 \times (FiO_2 - E_TO_2) + (1.1 \times VCO_2)$ in Watts per unit time of measurement.

Errors in Indirect Calorimetry

- Air leaks and measurement errors
- Measures consumption (rather than requirements)
- Point estimate of a dynamic process

Footnotes

The **respiratory quotient** is the value of $\frac{VCO_2}{VO_2}$ at steady-state, whilst the **respiratory exchange ratio** is affected by metabolic rate.

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Last updated 2019-07-18

Fat Metabolism

> Describe the physiology and biochemistry of fat~~, carbohydrate and protein~~ metabolism

Digestion

Triglycerides are the main constituent of body fat in animals and vegetables, and therefore in dietary fat. They consist of **three fatty acid** molecules joined by a **glycerol molecule**.

As fats are not water soluble, they tend to clump together in chyme and are hard to digest due to the low surface area:volume ratio. **Emulsification** speeds up the digestive process, and occurs via the action of:

- Bile salts
  Many bile salts have a hydrophobic and a hydrophilic end, which give a detergent action. Bile salts bound to fatty acids form a **mixed micelle** which can be further digested by enzymes or directly absorbed.
- Partially digested fats
- Mechanical action of the stomach

Once emulsified, triglycerides can be hydrolysed by **lipase** into fatty acids and monoacylglycerol.

Absorption

Absorption occurs in a number of stages:

- Mixed micelles, free fatty acids, monoacylglycerol, and cholesterols are absorbed via facilitated diffusion into the enterocyte
- From the enterocyte:
  - Short-chain fatty acids (those with < 12 carbon atoms) enter the portal vein and travel directly to the liver
  - Long-chain fatty acids are re-esterified and packaged with a layer of **protein** and **cholesterol** to form a **chylomicron**
    Re-esterification maintains the concentration gradient for diffusion of fatty acids, allowing further uptake to occur.
    - Chylomicrons are ejected from the cell into the lymphatics and travel to the systemic circulation
    - Chylomicrons are removed from circulation by **lipoprotein lipase**
      Lipoprotein lipase is found on capillary endothelium and bound to albumin.
    - Lipoprotein lipase breaks down triglyceride in chylomicrons and VLDL to free fatty acids and glycerol
      This reaction uses **heparin** as a **cofactor**.
    - Free fatty acids and glycerol are then free to enter adipose tissue

Storage

Fat is stored as **triglycerides**, and forms the bulk of energy storage of the body.

Triglycerides are synthesised by the liver:

- Occurs when insulin levels are high and glycogen stores are full
- From excess carbohydrate and amino acids
  These are converted to fatty acids and glycerol, and then esterified to form triglyceride. This is known as lipogenesis.

Metabolism

Free fatty acids can be absorbed by adipocytes for storage, or be **β-oxidised to acetyl CoA** in the liver, which can enter the citric acid cycle to produce ATP.

References

1. Chaney S. Overview of Lipid Metabolism. University of North Carolina School of Medicine. 2005.
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Last updated 2019-07-18

Carbohydrate Metabolism

> Describe the physiology and biochemistry of ~~fat,~~ carbohydrate ~~and protein~~ metabolism

Storage

Carbohydrates are stored in liver and muscle as glucose polymers known as **glycogen**.

- The liver contains ~100g of glycogen
  This can maintain plasma glucose for ~24 hours.
- Skeletal muscle contains ~200g of glycogen
  This cannot be released into circulation, and is for use only by the muscle.

Production of glycogen is stimulated by insulin, which is released as plasma glucose levels rise following carbohydrate ingestion. When plasma glucose levels fall, the release of glucagon and adrenaline stimulates glycogenolysis.

Glycolysis

Glycolysis:

- Describes the process of converting glucose into pyruvate
  This is known as the Embden-Meyerhof pathway.
- Occurs in the cytoplasm
- Does not consume oxygen or produce carbon dioxide
- Produces 2 ATP
  Glycolysis allows production of ATP in anaerobic conditions.

Gluconeogenesis

Gluconeogenesis is the production of glucose from other molecules. Gluconeogenesis:

- Requires ATP to perform
  Some organs (heart, brain) rely on glucose for ATP
- Has many potential substrates:
  - Lactate
  - Pyruvate
  - Glycerol
  - Amino acids
  - CAC-intermediates
- Is stimulated by glucagon
- Is inhibited by biguanides (metformin)

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

Last updated 2019-07-18

Protein Metabolism

> Describe the physiology and biochemistry of ~~fat, carbohydrate and~~ protein metabolism

Essential amino acids cannot be produced by transamination - they must be supplied in the diet.

Metabolism

Protein **catabolism** involves the **deamination** of amino acids. Deamination can occur in one of two ways:

- **Oxidative deamination**
  Hepatic deamination, removing the amino group to create a ketoacid and ammonia. Ammonia produced in the liver enters the urea cycle and becomes urea, which requires **3 ATP**.
- **Transamination**
  Amino group is transferred by aminotransferases to another amino acid or a ketoacid to produce:
  - Keto acids, which:
    - Enter the citric acid cycle and produce ATP
    - Get converted to glucose or fatty acids
  - Amino groups
    - Enter the urea cycle and become urea

Footnotes

Ammonia can also be produced in the kidney by the deamination of glutamate in the kidney. In this instance:

- It is eliminated directly in urine as ammonium
- Does not enter the urea cycle

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References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Requirements and Starvation

> Describe the normal nutritional requirements

Fasting

Fasting is the metabolic state achieved after complete digestion and absorption of a meal.

Fasting can be divided into:

- **Early fasting**
  Less than 24 hours.
  - Plasma glucose falls due to consumption
    Leads to hormonal changes:
    - Insulin release decreases, causing:
      - Liver
        - Decreased glycogenesis
        - Increased gluconeogenesis
      - Muscle
        - Decreased glucose utilisation
        - Decreased glycogenesis
        - Decreased protein synthesis
      - Fat
        - Decreased lipogenesis
          Due to:
          - Decreased glucose uptake
          - Decreased TG uptake
        - Increased lipolysis
    - Adrenaline release increases, causing:
      - Decreased insulin release
      - Increased lipolysis
      - Increased muscle FFA use
      - Increased hepatic glycogenolysis and gluconeogenesis
    - Glucagon release increases
  - Cellular metabolism alters:
    - Decreased glucose uptake by non-obligate glucose consumers
      e.g. Muscle.
    - Increased FFA and ketone body use
      β-oxidation of FFAs to meet ATP requirements, leading to formation of ketone body.
- **Sustained fasting**
  Greater than 24 hours. See starvation below.

Starvation

Starvation is the failure to absorb sufficient calories to sustain normal body function, requiring the body to survive on endogenous stores.

- **Days**:

    - Energy is conserved through reduction in movement
    - Hormonal changes
        - Increased gluconeogenesis, using glycerol, lactate, and amino acids
        - Insulin concentrations fall further
        - Cortisol levels increase
        - Glucagon levels peak at 4 days
    - Metabolic changes
        - Glucose use continues to fall, and FFA use increases
        - Further fall in muscle protein synthesis

- **Weeks**:
    - Tissues adapt to metabolise ketones (with plasma levels rising up to 7 $mmol.L^{-1}$, and gluconeogenesis falls
        - The brain still requires 100g of glucose per day
    - BMR falls
    - All but life-saving movement ceases
    - Death typically occurs after 30-60 days, when muscle catabolism weakens the respiratory muscles such that secretions can no longer be cleared, and pneumonia occurs

Refeeding Syndrome

Refeeding syndrome is a deranged metabolic state that occurs with feeding after a period of prolonged fasting, typically >5 days.

There are three pathogenic mechanisms:

- A large spike in insulin causes increased cellular uptake (and low plasma levels) of:
    - Glucose
    - Magnesium
    - Phosphate
    - Potassium
- Sodium and water retention occurs, which may precipitate cardiac failure
- Increased carbon dioxide production increases minute ventilation and work of exhausted respiratory muscles

Management is by slow institution of feeding and aggressive electrolyte management.

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
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Anaerobic Metabolism

> Describe the consequences of anaerobic metabolism and ketone production

Lactate

The **Embden-Meyerhof** pathway:

- Describes the conversion of glucose to pyruvate (and two ATP)
- Does not consume O_2 or produce CO_2
  Therefore it occurs in both anaerobic and aerobic conditions.
- Consumes two NAD^+ and produces two NADH

In anaerobic conditions (in the erythrocyte, and in the setting of cellular hypoxia):

- There is no oxygen available to allow further ATP production via the electron transport chain
  There is also no regeneration of NAD^+ in the ETC.
- In order for glycolysis to continue, NAD^+ is regenerated via production of lactate
  $Pyruvate + NADH \rightarrow Lactate + NAD^+$

About 1400mmol of lactate is produced per day. Lactate is either:

- Oxidised in the cell
  This requires restoration of NAD^+, e.g. resolution of cellular hypoxia.
- Circulated to the liver
  Lactate is then:
  - Oxidised to pyruvate
  - Converted to glucose
    This process is known as the **Cori cycle**.

Ketones

Ketones:

- β-oxidation of fatty acids in the liver produces acetyl-CoA
- Acetyl-CoA usually enters the citric acid cycle to produce ATP
- When large amounts of acetyl CoA are produced, they may instead condense to form **acetoacetate**, which can then be reduced to **β-hydroxybutyrate**
  These substances are known as ketones
- Ketones can only be produced by the liver, and only used as a substrate by the kidney, as well as skeletal and cardiac muscle
- Production of ketones is accelerated by glucagon and adrenaline

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References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
2. ANZCA August/September 2011

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Regulation of Body Temperature

> Outline the mechanisms for heat transfer between the body and its environment.

> Define the thermoneutral zone, and describe the mechanisms by which normal body temperature is maintained.

- Regulation of body temperature is done by **balancing heat loss and heat production**, predominantly through behavioural mechanisms and skin
- The body is able to maintain a relatively constant core temperature under a wide range of environmental conditions
  - The **thermoneutral zone** is the range across which the basal rate heat production (and oxygen consumption) is balanced by the rate of heat loss
    - For an adult it is **typically 27-31°C**
    - In neonates it is higher, **typically 32-34°C**.

Principles

Net flux of heat is determined by the balance of metabolic heat production and the contribution of four mechanisms of heat loss:

- **Radiation**
- **Conduction**
- **Convection**
- **Evaporation**

Radiative

Radiative heat exchange:

- Describes the loss of heat through EMR by all objects above 0°K
  - Radiative heat loss is proportional to temperature
  - Radiative heat loss does not require a transfer medium
- Makes up ~45% of heat loss under thermoneutral conditions.
- Depends on the temperature differential between an individual and their environment
  - A cold environment (e.g. operating theatre) causes a large radiant heat loss
    The heat loss from the patient is greater than the heat gain from the surrounding environment.

Conduction

Conduction is the **transfer of heat (as kinetic energy) by direct contact** from a higher temperature object to the lower temperature one. Conduction:

- Requires physical contact between bodies to conduct heat
  - Solids conduct heat better than gases
  - There is no conduction in a vacuum
- Heat loss via conduction is minimal in air but is a major cause of heat loss in immersion
  - As arteries and veins typically run next to each other, arterial heat tends to be transferred to the (cooler) veins, limiting further heat loss
    This is similar to counter-current exchange in the kidney.
- As fat is a poorer conductor of heat than muscle, increased body fat will slow heat loss by conduction

Convection

Convection is loss of heat by conduction by a moving object. Convection is:

- The predominant mechanism of heat loss in the naked human
  Effects are greater effects at higher wind speeds.

Evaporation

Evaporative losses describe the loss of heat energy due to the latent heat of vapourisation of water. Evaporation of 100ml of water will reduce body temperature by ~1°C.

Temperature Sensation and Regulation

Temperature sensors are **central** and **peripheral**, whilst **regulation** occurs centrally.

Central Sensation

Central temperature sensors exist in the:

- Abdominal viscera
- Spinal cord
- Hypothalamus
  Anterior hypothalamus is the most important central thermoreceptor, and responds to both increased and decreased temperatures by **altering their rate of depolarisation**, eliciting an array of neuronal and hormonal responses.
- Brainstem

The **inter-threshold range** is the range of core temperatures not triggering a response.

- Normal is 0.2 to 0.4°C.
- Widens under anaesthesia to ~4°C

Peripheral Sensation

Peripheral temperature sensors are:

- **Free nerve endings**
- Extremely sensitive
  Alter their rates of firing by orders of magnitude in response to temperature change.
- Divided into:
  - **Cold receptors**
    Lie beneath the epidermis, and are excited by cooling (inhibited by warming), active from 10-40°C, with a static maxima at 25°C.
  - **Warm receptors**
    Lie deep to the dermis, are excited by warming (and inhibited by cooling), active from 30-50°C, with a static maxima at 44°C.

Regulation

Temperature sensation runs from cutaneous receptors via the spinothalamic tracts and medulla to the hypothalamus. Cortical input is received via the thalamocortical relay, whilst primitive responses are effected via the midbrain.

Effector Responses

	Increase heat loss	Reduce heat loss/Increase heat gain
CNS	Remove clothing, sprawl, reduce activity.	Huddle, seek shelter, add clothing
Cardiovascular	Increase peripheral vasodilation and AV shunting, and cardiac output to improve flow to cutaneous tissues	Vasoconstriction, peripheral circulatory shut down
Musculocutaneous	Sweating	Piloerection, Shivering
Metabolic		Increased BMR, non-shivering thermogenesis

- **Vascular changes** are **the least metabolically costly** and can result in dramatic increases (up to 60% of cardiac output) in skin blood flow
- When environmental temperature exceeds body temperature, conduction and convection result in heat gain - **evaporative cooling via sweating** is the only way to reduce body temperature
- Efficacy of sweating is related to **relative humidity**

- Piloerection (hair standing on end) traps a layer of warm air close to the body to act as an insulator
  This is of more importance in other primates than in man, as they have enough body hair to make it effective.

- Increasing basal metabolic rate and 'waste' heat production is essential to maintain temperature in cold environments. This can be through:
  - Shivering
    The simultaneous contraction of agonistic and antagonistic muscles.
  - Non-shivering thermogenesis:
    - Hormonal
      Levels of thyroid hormone and adrenaline increase, raising metabolic rate in all cells
    - Brown fat
      Brown fat produces heat through **uncoupled oxidative phosphorylation**, which uses the electron transport chain to produce heat rather than ATP. Brown fat is:
      - A vital mechanism for heat production in the **neonate** (they have an **immature shivering response**), and forms ~5% of neonatal mass
      - Located in:
        - Neck
        - Supraclavicular
        - Interscapular
        - Suprarenal
      - Sympathetically innervated
        Contains large numbers of β_3 receptors

Effect of Anaesthesia

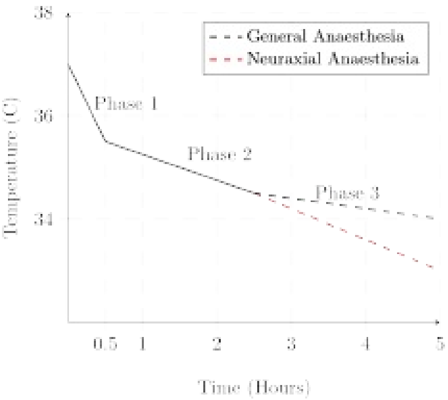
General anaesthesia causes a 1-3°C drop in core body temperature, which occurs in three phases:

- Rapid reduction
  Core temperature falls by 1-1.5°C in the first 30 minutes.
  - Predominantly due to vasodilation, which is due to:
    - Reduction in SVR, with generalised vasodilation and increased skin blood flow
      Heat redistribution is the major initial factor (rather than heat loss), as vasodilation leads to increased heat content of peripheries.
    - Impairs thermoregulatory vasoconstrictive responses
      Inter-threshold range is widened to 4°C (up from 0.4°C)

- Gradual reduction
  Further drop in core temperature of 1°C over following 2-3 hours.
  - Due to heat loss exceeding heat production
    Non-shivering thermogenesis is the only response available to paralysed, anaesthetised patient.
- Plateau
  Once core body temperature falls far enough, thermoregulatory responses are activated and further heat loss is attenuated by increased metabolic heat production.

Neuraxial anaesthesia:

- Hypothermia is less extreme as thermoregulation is only affected in areas covered by the blockade
- Plateau does not occur as vasoconstrictive responses are inhibited by the blockade



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Inflammation

> Describe the factors involved in the process of inflammation and the immune response, including innate and acquired immunity

Inflammation is a non-specific response triggered by a pathogen or tissue injury, which aims to limit further tissue damage.

Inflammation is classically characterised by:

- **Pain**
- **Heat**
- **Redness**
- **Swelling**
- **Loss of function**

This is a consequence of:

- Vasodilation
  Increases blood flow to area, which increases supply of immune cells and resources for cellular repair.
- Increased vascular permeability
  Increases extravasation of protein and immune cells.
- Migration of phagocytes
  Remove pathogens and cellular debris.

Process of Inflammation

- Tissue damage
  - Trauma causes mechanical disruption of vasculature and mast cell degranulation, causing local inflammation and activation of haemostatic mechanisms
  - Infection stimulates degranulation of local macrophages, releasing inflammatory cytokines and triggering mast cell degranulation
- Local inflammatory response
  - Histamine causes arteriolar and post-capillary venule dilatation and subsequent extravasation
  - Release of chemotactic molecules attracts circulating inflammatory cells
- Systemic inflammatory response
  Severe inflammation may lead to cytokines in the systemic circulation, causing:
  - Fever
  - Neutrophil recruitment from bone marrow
  - Release of acute-phase proteins from liver

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Innate Immunity

> Describe the factors involved in the process of inflammation and the immune response, including innate and acquired immunity

The innate immune system consists of protective mechanisms which are present life-long, and typically forms the first line of defence against pathogens.

Key features of innate immunity include:

- Immediacy
- Non-specific response
- Not modified by repeat exposures

The innate immune system consists of **three components**:

- Physicochemical barriers
- Humoral mechanisms
- Cellular Mechanisms

Physicochemical Barriers

These include:

- Skin
- Mucous membranes
    - Mucous
    - Mucociliary elevator
- Gastric acid
- Urination
  Optimised by high flow rates and low residual bladder volumes.

Innate Humoral Mechanisms

Humoral mechanisms describes the role of inflammatory proteins in innate immunity:

- **Complement**
  The complement system is a complex group of about **25 plasma proteins** important in both innate and adaptive immunity.
    - The complement system is activated by:
        - Antigen-antibody complexes
          The 'classical pathway.'
        - Substances in the bacteria cell wall
          The 'alternative pathway.'
    - Complement has a number of inflammatory functions:
        - Destruction of bacteria
          Several complement proteins come together to form a **membrane attack complex**, which creates large pores in cell membranes, causing water to diffuse in and bacteria to burst.
        - Opsonisation of bacteria
          Bound complement acts as a binding site for phagocytes.
        - Activation of monocytes and phagocytes
        - Chemotaxis

    Attracts leucocytes.
    - Mast cell degranulation
      Augments inflammation.

- **Acute-Phase Proteins**
  Inflammatory proteins with a number of effects:
  - Opsonisation
  - Inflammatory mediators
    Increase blood flow and delivery of inflammatory cells via three mechanisms:
    - Dilatation and increased capillary permeability
    - Endothelial activation increasing leukocyte adhesion
    - Attraction of neutrophils and monocytes

- **Proteolytic enzymes**
  Bactericidal enzymes located in saliva, tears, respiratory mucous, and neutrophils.

Innate Cellular Mechanisms

Cellular components of the innate immune system include:

- **Mast cells**
  Exist in loose connective tissue and mucosa, and contain many intracellular granules of heparin and histamine.

- **Leukocytes**
  - Neutrophils (60% of all leukocytes)
    Phagocytose bacteria and fungi (15-20 per neutrophil). This process consists of a number of steps:
    - Exit circulation by **marginating** along capillary border when activated
    - Migrate via **chemotaxis** towards the tissue insult
    - **Phagocytose opsonised** bacteria and fungi
    - Kill organisms with a **respiratory burst**:
      A granule containing hydrogen peroxide, hydroxyl and oxygen radicals fuses with the target cell membrane, destroying both the target and the neutrophil.
  - Monocytes
    Become **macrophages** when they leave circulation and enter tissue. Macrophages have a lifespan of 2-4 months, and can phagocytose up to 100 bacteria before it dies. Functions include:
    - Phagocytosis and destruction of pathogen
      Especially intracellular pathogens (*listeria*, *mycobacteria*), parasites, and fungi.
    - Breakdown of damaged body cells
    - Present antigen to T-helper cells
    - Secretion of inflammatory mediators
  - Eosinophils
    Kill multicellular parasites.
  - Basophils
    Contain heparin and histamine.
  - Lymphocyte
    Subtype of leukocyte important in adaptive immunity. Include:
    - **Natural Killer cells**
      Active against viral and tumour cells.
    - B cells
    - T cells

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1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.

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Adaptive Immunity

> Describe the factors involved in the process of inflammation and the immune response, including innate and acquired immunity

The adaptive immune system responds to an exposure, demonstrating **specificity** and **memory**, with improved efficacy on repeat exposure.

Adaptive immunity may be:

- **Active**
  Primary immune response generated by exposure to antigen.
  - Infection
  - Vaccination
    An inactive (but still foreign and therefore antigenic) protein component of a pathogen is given to the patient, resulting in an immune response. Subsequent exposure to the whole pathogen triggers a secondary immune response.
- **Passive**
  Preformed antibody is given to the patient. This will provide treatment/coverage for the life of the antibody, but immunity will be lost when the antibody breaks down or supplies are exhausted.
  - Transplacental
  - Colostrum
  - Administration of serum

Components of the active immune system include:

- **Cellular**
  Predominantly T lymphocytes
- **Humoral**
  Including complement and antibody.

Adaptive Cellular Immunity

Lymphocytes are divided into two types:

- **B lymphocytes**
  Are produced in the bone marrow, and migrate to lymphoid (nodes, spleen, MALT) where they are renamed **plasma cells** and produce antibody. Functions include:
  - Production of antibody against specific antigens
  - Presentation of antigen to T-cells to active them
  - Proliferation to form memory cells

- **T lymphocytes**
  Are produced in the bone marrow and migrate to the thymus where they mature. T cells which express antibody to host protein apoptose, resulting in only 2% of immature T cells surviving. Mature T cells then spread to lymphoid tissue. There are five types of T cells, of which two are most important:
  - Helper T-cells
    $2/3^{rds}$ of T-cells are helper cells, are are identified by their **CD4** membrane protein. Functions include:
    - Cytokine production
    - B lymphocyte stimulation
    - Macrophage activation
  - Cytotoxic T-cells

Are identified by their **CD8** membrane protein. Functions include:

- Destruction of virally infected and tumour cells
  All cells **express proteins** that they are producing **on membrane MHC I molecules**, for inspection by immune cells. Infected or tumour cells will express foreign proteins, and cause activation of cytotoxic T cells:
  - **Induce apoptosis** in the target cell
  - **Rapid division** of cytotoxic T cell, which then inspects other cells for infection
- Transformation to memory cells

Adaptive Humoral Immunity

Antibodies Y-shaped immunoglobulins which:

- Are produced in response to a pathogen
- Are specific to that pathogen

Antibody functions include:

- **Opsonisation**
- **Agglutination**
  Each antibody can bind multiple pathogens, increasing target size for leukocytes.
- **Inactivation of pathogen**
  Antibody binding may disable the pathogen.
- **Activation of complement**
  Antibody-antigen complexes cause complement activation.

Primary Immune Response

The process of invasion of a new pathogen to antibody production takes ~5 days, and occurs in a number of steps:

- APC phagocytose a pathogen
  APCs include macrophages and dendritic cells.
- APC express antigen (bits of pathogen) on cell surface
- APC travel to lymphoid tissue and present it to B and T cells
- When an APC finds a B and T cell with a reciprocal antibody:
  - T helper cell becomes activated by APC
  - T helper cell rapidly proliferates ('clonal expansion')
    - Proportion become memory cells
  - B cells are activated by both the **APC *and* a T-helper cell** (requires both)
  - B cells rapidly proliferate
    - Proportion become memory cells
    - Proportion become **plasma cells**
      - Plasma cells produce antibody at a rate of 2000 molecules per *second*, which overrides normal cellular homeostasis, causing death within a week.
      - Antibody produced in a primary immune response is IgM, with some IgG produced later on.

Secondary Immune Response

Repeat invasion by the same pathogen is met with a much more rapid and aggressive immune response:

- APCs phagocytose a pathogen
- APCs express and present antigen
- Memory T and Memory B cells formed during the primary response are activated, and begin rapidly dividing and producing antibody

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Hypersensitivity

> Explain the immunological basis and pathophysiological effects of hypersensitivity, including anaphylaxis.

> Understand the pharmacology of the drugs used in the treatment of anaphylaxis.

Hypersensitivity reactions are **exaggerated immune responses** that cause host injury.

Classification of Hypersensitivity Reactions

The **Gel and Coombs system** classifies hypersensitivity reactions by the mechanism. It is commonly used but fails to classify more complex diseases.

Type	Timing	Mediator	Pathophysiology	Disease example(s)
Type I - Immediate hypersensitivity	Seconds to minutes	IgE	Basophil and mast cell degranulation	Anaphylaxis (systemic), Atopy (local)
Type II - Cellular hypersensitivity	5-8 hours	IgM, IgG	Antibody binding to cell surface antigen, resulting in cell death via complement membrane attack complexes, or phagocytosis by macrophages	Transfusion reactions, hyperacute allograft rejection
Type III - Immune-complex deposition	2-8 hours	IgM, IgG, IgA	Tissue deposition of Ab-Ag complexes. Accumulation of PMNs, macrophages, and complement.	SLE, necrotising vasculitis, post-Strep GN
Type IV - Delayed hypersensitivity	24-72 hours	T-cell	T-cell induced mononuclear cell accumulation. Release of monokines and lymphokines.	TB, Wegener's Granulomatosis, Granulomatous vasculitis

Type I Hypersensitivity

- Antigen simulates a B lymphocyte to produce a specific IgE against it
- This IgE then binds to Fc receptors on mast cells, sensitising them to this exposure
- On re-exposure the antigen binds (**cross-links**) IgE on mast cells, causing degranulation:
  - Histamine, leukotrienes, and prostaglandins are released
  - This may cause local or systemic effects, depending on method of exposure:
    - A systemic reaction is called **anaphylaxis**, and manifests as a combination of:
      - Hypotension
      - Bronchospasm
      - Laryngeal oedema
      - Rashes
    - Local reactions depend on the route of exposure, and include
      - Asthma
        Inhaled.
      - Allergic rhinitis
        Nasopharyngeal mucosa.
- **Non-immune anaphylaxis** (also known as anaphylactoid) reactions are characterised by a immediate generalised reaction clinically indistinguishable from true anaphylaxis, but the immune nature is unknown, or not due to a type I hypersensitivity

reaction

Management of Anaphylaxis

- **Adrenaline** is the drug of choice, as it treats cardiovascular collapse, bronchospasm, and decreases oedema formation.
  - In adults, 0.3-0.5mg IM Q5-15min
  - In children, 0.01mg/kg IM Q5-15min
- **Glucagon** *may* be used in β-blocked patients resistant to adrenaline.
  - In adults, 1-5mg IV over 5 minutes, followed by infusion at 5-15microg/min
  - In children, 20-30mcg/kg up to 1mg over 5 minutes
- Non-pharmacological management includes early intubation to protect against airway obstruction due to angioedema.
- Adjuncts include antihistamines and steroids. They are second line as they do not attenuate cardiovascular collapse, resolve airway obstruction, or have strong evidence behind their use. They include:
  - Diphenhydramine 25-50mg IV (Children: 1mg/kg up to 40mg) up to 200mg in 24/24
  - Salbutamol, for bronchodilation
  - Methylprednisolone 1-2mg/kg, ostensibly to protect against **rebound anaphylaxis** (though there is minimal evidence)

Type II Hypersensitivity

- Antibodies bind to cell surface antigen
- Antibody-Antigen complex **activates complement**
- Complement generates an inflammatory response
- Cell death occurs via:
  - Complement membrane attack complex
  - Phagocytosis

Clinical picture depends on affected organs. Examples include:

- Hyperacute allograft rejection
- Transfusion reactions and haemolytic disease of the newborn
- Goodpasture's syndrome
- Autoimmune cytopaenias
- Myasthenia Gravis

Type III Hypersensitivity

- Immune-complex reaction where Ab-Ag complexes are formed and deposited in tissues
- Subsequent complement activation causes inflammation and neutrophils activation, leading to tissue damage
- There are two subtypes of type III reactions:
  - Formation of complexes in circulation and subsequent deposition in tissues
    - e.g. Serum sickness
  - Formation of complexes in tissues
    Small amounts are typically removed by the reticuloendothelial system, but in this case there are too many, or they are too small, to be cleared effectively.
    - e.g. The Arthus reaction (a localised vasculitis, which may be necrotising)

Type IV Hypersensitivity

- Antigen is presented to T lymphocytes which proliferate and become sensitised
- T-cells then release cytokines, attracting macrophages and leading to local inflammation
- During prolonged exposure, macrophages may fuse to form giant cells and form a granuloma. Examples include:
- TB

- Granulomatous vasculitis

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Classification of Microorganisms

> Describe the classification of micro-organisms, including viruses, bacteria, protozoa and fungi

Microorganisms can be classified as prokaryotes (**bacteria**), **viruses**, or **eukaryotes** (which include **fungi**, **helminths**, and **protozoa**).

Bacteria

- Bacteria are **prokaryotic** organisms
- *Most* clinically relevant bacteria can be classified by **Gram stain** and **shape**[1]
    - Gram stain separates bacteria according to their **cell wall composition**
      It cannot be used on organisms that lack a cell wall, such as mycoplasma.
        - A **crystal violet** followed by an **iodine** solution is applied to the slide, which is then **washed with a solvent**
            - **Gram +ve** organisms will **retain the stain** due to their **thick peptidoglycan cell wall**, whilst gram negative organisms become colourless
        - A **safranin pink stain** is then applied, which stains the **gram -ve** bacteria **pink**
    - Bacteria can also be classified by shape into:
        - **Cocci**
          Appear round on microscopy.
        - **Rods**

Combining of these two systems classifies a large proportion of microbes:

Examples:	Gram Positive	Gram Negative
Cocci	*Staphylococcus Aureus*, *Streptococcus Pneumoniae*	*N. Meningitidis*, *N. Gonorrhoea*
Rods	*Listeria*, *Clostridium difficile*	*Escherichia Coli*, *Pseudomonas aeruginosa*

Bacterial Subclassification

Additional testing can be done to further classify bacteria:

- **Catalase** testing is performed on **Gram positive cocci**
  Hydrogen peroxide is added to a bacterial sample, and in the presence of catalase will produce **oxygen**.
    - Catalase positive indicates Staphylococci
    - Catalase negative indicates Streptococci (and enterococci)

- **Coagulase** testing is performed on Staphylococcal species
  Coagulase is an enzyme which cleaves fibrinogen to fibrin. The staphylococcal colony is added to rabbit plasma and incubated. In the presence of coagulase, fibrin is formed.
    - Coagulase positive strongly suggests *S. Aureus*
    - Coagulase negative examples include *S. epidermidis* or *S. saprophyticus*

- **Haemolytic** testing is performed on Streptococcal species
  Bacterial colonies are added to blood agar, and the colour change (due to haemolysis) is noted.
    - **α haemolytic** organisms produce dark green agar, as methaemoglobin is produced by hydrogen peroxide produced by these organisms. Examples include:
        - *Strep. pneumoniae*
        - *Strep. viridans*
    - **β-haemolytic** organisms produce yellow agar from complete haemolysis. Examples include:

        - *Strep. pyogenes*
        - *Strep. agalactiae*
    - **γ-haemolytic** organisms leave the agar unchanged. Examples include:
        - *E. faecalis*
        - *E. faecium*

- Additionally, gram negative rods should be further classified into **pseudomonal** and **non-pseudomonal** organisms

Viruses

Viruses consist of molecules of either DNA or RNA shielded in a protein coat. They require the use of host cell structures for reproduction and are therefore **obligate intracellular parasites**. They can be classified by **five** properties:

1. **DNA/RNA**
   DNA viruses replicate in the cell nucleus using a host polymerase.
2. Double-**stranded** or single-stranded
    i. *Most* DNA viruses are double-stranded (dsDNA)
    ii. *Most* RNA viruses are single-stranded (ssRNA)
3. Negative-**sense** or positive-sense (**RNA viruses only**)
    i. Positive-sense genomes may be translated directly into mRNA
    ii. Negative-sense genomes require an RNA-dependent RNA polymerase to translate them to a positive-sense strand prior to translation.
4. **Capsid Symmetry**
   The protein coat may be either icosahedral or helical
5. **Enveloped** or non-enveloped
   In addition to a protein coat, viruses may have a lipid membrane (acquired from the host cell) around their protein coat.

Eukaryotic Organisms

Eukaryotic organisms include fungi, protozoa, and helminths, as well as plants and animals. They differ from prokaryotic organisms in a number of ways:

Property	Prokaryotes	Eukaryotes
Chromosomes	Single, circular	Multiple
Nucleus and Organelles	None	Membrane bound nucleus and organelles
Cell wall	Usually	In plants
Ribosome	70S	80S in cell, 70S in organelles
Size	0.2-2mm	10-100mmm

- **Fungi** typically feed on dead/decomposing/the immunocompromised and produce spores. They are subclassified into:
    - **Yeasts**
      Yeasts are unicellular. They are divided into:
        - Candida
            - Albicans
            - Non-albicans More difficult to treat.
        - Cryptococcus
    - **Moulds**
      Moulds are are filamentous.
        - Aspergillus

        - Penicillium
    - **Dimorphous** Have characteristics of both yeasts and moulds.
        - Histoplasma

- **Protozoa** are parasitic single-celled eukaryotes. They can be intracellular or extracellular.

- **Helminths** are parasitic multi-celled eukaryotes. They can be intracellular or extracellular. They are subdivided into tapeworms (cestodes), flukes (trematodes), and roundworms (nematodes).

Footnotes

> [1]. This classification does not capture spirochetes, mycoplasmas, chlamydias, and other less commonly encountered organisms. A more complete classification uses six properties: ↩

1. Cell Wall Structure
    i. Flexible (e.g. Spirochetes)
    ii. Rigid
    iii. Non-existent (e.g. *Mycoplasma spp.*)
2. Morphology
    i. Unicellular
    ii. Filamentous
3. Growth Location
    i. Extracellular
    ii. Obligate intracellular parasites (e.g. *Chlamydia spp.*)
4. Gram Stain
    i. Gram positive
    ii. Gram negative
5. Shape
    i. Cocci
    ii. Rods
6. O_2 tolerance
    i. Aerobes
    ii. Anaerobes (e.g. *Clostridium spp.*)

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Antimicrobial Resistance

> Describe the principles of anti-microbial resistance

Resistance occurs when the **maximal level** of the agent tolerated is **insufficient** to **inhibit growth**.

Resistance can occur broadly via two mechanisms:

- **Genetic Alteration**
  - **Spontaneously**, through mutation and subsequent natural selection of resistant organisms
  - Transferal of resistance genes from organism to organism via **plasmids**
- **Protein Expression**
  Increasing or decreasing expression of proteins with subsequent change in efficacy of antimicrobials.

Mechanisms

Specific mechanisms of resistance (which may be genetic alterations or changes in protein expression) include:

- **Prevent access to target**
  - Decrease permeability
    - Narrowing of porin channels
      e.g. Streptococcal resistance to penicillins typically occurs by reducing access to PBPs.
    - Loss of non-essential transporter channels
      e.g. Anaerobes have no oxygen-transport channel which prevents penetration by aminoglycosides.
  - Active efflux of agent
    Increased efficiency or expression of efflux pumps. Can be:
    - Removed from cell
    - Trapped between cell wall layers
      e.g. Glycopeptide resistance in VRSA.
- **Alter antibiotic target site**
  - Changes in binding site protein will increase resistance to agents with low affinity
  - Over-expression of target protein
  - Synthesis of target-protecting proteins
- **Modification or Inactivation of Drug**
  - Metabolism of drug
    e.g. β-lactamases hydrolyse β-lactam rings
- **Modification of Metabolic Pathways**
  - Development of metabolic pathways to bypass site of action of antibiotic
    e.g. Resistance to Trimethoprim-Sulfamethoxazole by allowing bacteria to synthesis or absorb folic acid.

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Antiseptics

> Outline the pharmacology of antiseptics and disinfectants

Key Definitions

Relevant definitions for antiseptics include:

- Cleaning
  Physical removal of foreign material.
  - Used for **non-critical items**, which come into contact with healthy skin but not mucous membranes (e.g. blood pressure cuff)
- Decontamination
  Destruction of contaminants such that they cannot reach a susceptible site in sufficient number to cause harm.
- Disinfection
  Elimination of all pathological organisms, excluding spores.
  - Used for **semi-critical items**, which are those that contact mucous membranes but do not break the blood barrier (e.g. endoscopes, laryngoscopes)
- Sterilisation
  Elimination of all forms of microbial life, including spores.
  - Used for **critical items**, which are those that enter sterile or vascular tissue and pose a high risk of infection (e.g. surgical instruments, vascular and urinary catheters)

Antiseptic Agents

Drug	Isopropyl Alcohol	Chlorhexidine	Povidone iodine
Pharmaceutics	Typically 60-90% - requires some water to denature protein. Flammable.	May be aqueous or combined with isopropyl alcohol.	Iodine combined with a polymer (povidone) to enhance water solubility
Antiviral Properties	Poor antiviral	Poor antiviral	Good antiviral
Antibacterial Properties	Broad spectrum antibacterial	Broad spectrum antibacterial and antifungal	Broad spectrum including fungi, spores (unlike iodine), and tuberculosis
Toxic	Irritant on mucous membranes and open wounds	Hypersensitivity	Hypersensitivity
Other		Persistent antiseptic effect	Requires continual release of iodine to achieve effect. Inactivated by organic substances. Stains.

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Last updated 2017-08-11

Respiratory Changes of Pregnancy

> Explain the physiological changes during pregnancy, and parturition

Respiratory changes in pregnancy are a function of two things:

- Anatomical compression of the chest
- Increased VO_2 and VCO_2

Anatomical Changes

- Diaphragm pushed upwards by ~**4cm**
- Increased AP and transverse diameter of the chest wall (~2-3cm)
- Large airway dilation, reducing airway resistance by ~35%

Volumes and Capacities

From conception until term:

- V_T increases by 40%
- Inspiratory capacity increases by 10%
- Expiratory capacity decreases by 30%
- Total lung capacity decreases by 5%
- Vital capacity is unchanged

From ~20 weeks until term:

- ERV decreases
- RV decreases
- FRC decreases
  - By 20% erect
  - By 30% supine

Ventilation

Progesterone stimulates respiratory centres, shifting the O_2 and CO_2 response curves to the left which causes hyperventilation and a **respiratory alkalosis**. From conception until term:

- MV increases by 50%
  - 10% increase in RR
  - 40% increase in V_T
- PCO_2 falls to ~26-32mmHg, with a compensatory drop in plasma $[HCO_3^-]$ to 18-21mmol.L^{-1}

Labour and Postpartum

During labour:

- MV increases 70% due to pain and increased oxygen demand
- This causes hypocapnea, so cessation of uterine contractions (and the associated pain and oxygen demand) are followed by a

hypoventilatory period producing desaturation

FRC and RV return to normal within 48 hours of delivery.

References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.

Last updated 2019-07-18

Cardiovascular Changes of Pregnancy

> Explain the physiological changes during pregnancy, and parturition

> Physiological consequences of changes in posture during pregnancy

Pregnancy is a time of increased metabolic demand, which cardiovascular changes reflect. These changes include:

- Increased intravascular volume Occurs via two mechanisms:
  - Increased **oestrogen** causes an **increased plasma volume**
    - This decreases capillary oncotic pressure, predisposing to oedema
      This may be exacerbated by the gravid uterus compressing the IVC, especially near-term
      - Increased **EPO** causes an **increased red cell volume**
- Increased venous return Due to increased intravascular volume and MSFP.
  - The gravid uterus may compress the IVC and impair VR, hence pregnant women are positioned with a left lateral tilt to displace the uterus off the IVC
- Increased VR causes an increase in CO (with both an increase in HR and SV, as well a decrease in SVR)
- Decreased SVR results in SBP, DBP and MAP dropping (despite the increase in CO)

Magnitude of Changes by Trimester

Parameter	Direction	First Trimester	Second Trimester	Third Trimester	Notes
Plasma volume	↑	35%	45%	50%	Peaks between 32-36th week, decreases slightly thereafter
Blood volume	↑	5%	15%	20%	Increases less than plasma volume, resulting in the fall in haematocrit to 33%
HR	↑	15%	18%	25%	Increases progressively throughout
SV	↑	20%	25%	30%	Increases progressively throughout
CO	↑	20%	40%	45%	Increases throughout and dramatically in labour

Changes During Labour

- Uterine contraction boluses ~300ml of blood into the maternal circulation
  Causes an increase in CO by up to 30% during the active phase and 45% during ejection.
  - Associated with corresponding increase in SBP and DBP by 10-20mmHg

- Post-partum CO is up to 80% of pre-labour values due to autotransfusion, and returns to normal within 2 weeks of delivery

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References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.

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Foetal Circulation

> Explain the physiological changes during pregnancy, and parturition

In Utero

The foetal circulation has a number of structural differences:

- Two **umbilical arteries**
  The umbilical artery returns deoxygenated blood to the placenta.
  - PO_2 of 18mmhg (SpO_2 45%)
  - Over 50% of the combined output of both foetal ventricles enters the placenta
- One **umbilical vein**
  The umbilical vein supplies oxygenated blood to the foetus.
  - Has a PaO_2 of 28mmHg (SpO_2 70%)
  - 60% of blood from the umbilical vein enters the IVC
  - 40% of blood enters the liver
- Two ducts:
  - **Ductus venosus**
    Shunts blood from the umbilical vein to the IVC.
  - **Ductus arteriosus**
    Shunts blood from the pulmonary trunk to the descending aorta.
- A **foramen ovale**
  Shunts blood from the right atrium to the left atrium.
- **Immature myocardium**
  Foetal myocardium does not obey Starlings Law, and does not adjust contractility for any given preload. Therefore:
  - SV is fixed
  - CO is HR dependent
    Normal HR at term is 110-160 bpm.

These structural difference alter the pathway of blood circulation:

- Oxygenated blood returns via the umbilical vein
  - 40% flows to the liver
  - 60% is returned to the IVC
- Oxygenated blood in the IVC is directed via the Eustachian valve through the foramen ovale
- Blood returning from the SVC is directed into the RV, and then into the descending aorta by the ductus arteriosus
  - ~10% of RV output flows through the pulmonary circulation

This arrangement has several features:

- Blood with the most oxygen is delivered to the arch vessels to supply the brain
- Blood with the least oxygen is delivered to the umbilical arteries for gas exchange
- Both the RV and the LV eject into systemic circulations, and are of similar size and wall thickness

Changes at Birth

Several changes happen at birth:

- Placental circulation is lost

There is a transition from circulation in parallel to circulation in series.
- An **FRC is established**
  Reversal of hypoxic pulmonary vasoconstriction results in a rapid drop in PVR.
- The cord is clamped
  The systemic vascular bed volume falls, and SVR increases due to the loss of the low-resistance placental circulation.
- The fall in PVR lowers RV afterload
  RAP falls due to the loss of hypoxic pulmonary vasoconstriction.
- The rise in SVR increases LV afterload
  LAP rises as the LV moves up the Starling curve.
- When LAP exceeds RAP, the foramen ovale closes
  A degree (~10%) of residual shunt remains. Shunt is:
  - Bidirectional
    - Left-to-right shunt is unconcerning
    - Right-to-left shunt has usually only minor effects on systemic SpO_2
      Will be increased with ↑ $PaCO_2$, excessive PEEP, ↓ pH.
      - Beware **embolic material**
        Don't forget the bubbles.
- Increased left sided afterload causes **flow reversal** in the ductus arteriosus
  There is progressive closure of the ductus over hours to days, under the influence of prostaglandins and oxygenated blood flowing through the duct.
- The ductus venosus progressively fibroses over a period of days to weeks

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References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
3. Brandis K. The Physiology Viva: Questions & Answers. 2003.

Last updated 2019-06-14

The Placenta

> Outline the functions of the placenta, and determinants of placental blood flow.

The placenta is an organ of maternal and foetal origin which supports the developing foetus.

Physiological Properties

The placenta has three broad functions:

- Interface between foetus and mother for nutrient exchange
- Immunological barrier
- Endocrine

Nutrient and Waste Exchange Functions

The primary purpose of the placenta is **diffusion of nutrients and oxygen**, and **removal of waste**.

As with the lung, diffusion is dependent on Fick's Principle, i.e.:

$\dot{V} = \frac{A \times D \times \Delta P}{T}$, where:

- $\dot{V}$ = Flow of substance across the membrane
- A = Area of the membrane
- D = Diffusion constant for the substance, where $D \propto \frac{Lipid\ Solubility}{\sqrt{Molecular\ Weight}}$
  - Molecules < 600 Da in size more readily diffuse down concentration gradients
- ΔP = Concentration difference across the membrane
  - Maternal placental flow is ~600mL.min^{-1} at term - double that of foetal flow - which improves diffusion by increasing the concentration gradient for solutes
- T = Thickness of the membrane

O_2 Diffusion

At the end of pregnancy, **PO_2 for foetal blood**:

- Entering the placenta via the umbilical artery is **18mmHg** (SpO2 45%)
- Leaving the placenta via umbilical vein is **28mmHg** (SpO2 70%)

The foetus is able to have adequate delivery of O_2 despite the low PO_2 for four reasons:

- **High Cardiac Index**
  Increased cardiac output increases DO_2.

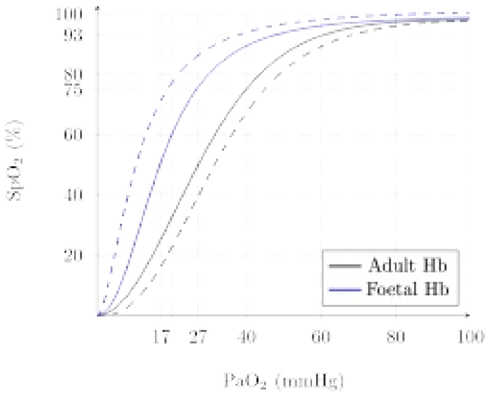
- **Foetal Hb**
  Contains **two gamma subunits** instead of beta subunits. These prevent the binding of 2,3-DPG, which result in a **left-shifted Oxy-Haemoglobin dissociation curve**, favouring oxygen loading at a low PaO_2.

- Foetal [Hb] is 50% greater than maternal [Hb]

- The **Double Bohr** effect:

The Bohr effect states that an **increase** in **$PaCO_2$ right-shifts** the oxyhaemoglobin dissociation curve. Conversely, the affinity of Hb for O_2 increases in alkalaemia. The double Bohr effect describes this happening in opposite directions in the foetal and maternal circulations, favouring transfer of O_2 to the foetus:

- In the placenta, foetal CO_2 diffuses into maternal blood down its concentration gradient
  This makes **foetal blood relatively alkaline, and maternal blood relatively acidic**. Therefore:
  - O_2 unloading of maternal blood is favoured
  - O_2 loading of foetal blood is favoured



CO_2 Diffusion

CO_2 is extremely lipid soluble, and so passes easily across membranes. Foetal $PaCO_2$ is ~50mmHg, and intervillous PCO_2 is ~37mmHg. CO_2 offloading is favoured in the foetus by:

- A high Foetal [Hb] increases the amount of CO_2 that can be carried as carbaminohaemoglobin
- The **Double Haldane** effect:
  The Haldane effect states that deoxygenated Hb binds CO_2 with more affinity than oxygenated Hb. The double Haldane effect describes this happening in opposite directions in the maternal and foetal circulations, favouring CO_2 transfer to the mother:
  - As maternal blood releases O_2, this favours maternal loading of CO_2 without an increase in maternal PCO_2 (Haldane effect)
  - The release of CO_2 from the foetal Hb favours O_2 loading, which in turn favours further maternal O_2 release.

Nutrient Diffusion

In late pregnancy, foetal caloric requirements are high (approximately the same as the mother). **Facilitated diffusion** of **glucose** via carrier molecules occurs in trophoblasts.

Active transport occurs for amino acids, Ca^{2+}, Fe, folate, and vitamins A and C. Other transporters actively remove substances from foetal circulation.

Immunological Function

The placenta is selectively **permeable to IgG** via pinocytosis, which allows maternal antibodies to provide passive immunity to the foetus.

Endocrine Function

Synthesises:

- βHCG
- hPL
- Oestriol

- Progesterone

Development

The placenta develops simultaneously from foetus and mother:

- From the uterine wall, the mother produces **blood sinuses** around the trophoblastic cords
  - These in turn send out **placental villi**
- This creates a sinus of maternal blood invaginated by multiple foetal villi
- Foetal villi are supplied by **two umbilical arteries** and a **single umbilical vein**
- Maternal sinuses are filled from the **uterine arteries**
- The maternal sinuses are supplied by **spiral arteries**

Properties of the Developing Placenta

- Thick(er) membrane impairs permeability
  Placental membrane permeability is small in early-to-mid pregnancy, reaching maximum at ~34 weeks
- Smaller surface area

Properties of the Mature Placenta

- Thick membrane - improved permeability
- Surface area of $14m^2$
- Weight of ~500g
- Blood flow of $600mL.min^{-1}$ at term
  Flow is reduced during contractions due to increased uterine pressure and also with α-adrenergic stimulation.

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Last updated 2019-07-18

Gastric Secretions

> Describe the composition, volumes and regulation of gastrointestinal secretions

The GIT produces a a number of substances which can be classified by region and function:

- Saliva
  - H_2O (98%)
  - Digestive proteins
    - Amylase
    - Lipase
    - Mucin
    - Haptocorrin
      Binds Vitamin B12.
  - Immunological proteins
    - Lysozyme
    - Lactoferrin
    - IgA

- Gastric
  - Digestive
    - HCl
    - Gastrin
    - Pepsin
    - Intrinsic Factor
  - Mucosal Protection
    - Mucous
    - HCO_3^-

- Small Bowel
  - Digestive
    - Pancreatic
      - Lipase
      - Amylase
      - Trypsinogen
    - Endocrine
      - Secretin
      - Somatostatin

Control of Secretions

Secretion occurs in three phases:

- Cephalic
  Thought/sight/taste/smell of food, resulting in vagal-mediated stimulus to release gastrin. Accounts for ~30% of production.
- Gastric
  Stretch of the stomach stimulates HCl secretion and gastrin release. Accounts for ~50% of production.
- Intestinal
  A drop in pH of the proximal duodenum releases **secretin** to stimulate the exocrine pancreas.

Salivary Secretions

Approximately **1L** of saliva is produced by the parotid, submandibular, and sublingual glands each day.

Saliva has four main functions:

- **Lubrication**
  - Mucin
- **Digestion**
  - Amylase
  - Lipase
    Particularly important in neonates who produce little pancreatic lipase.
- **Neutralisation of acid**
  For protection prior to vomiting.
- **Antibacterial**

Gastric Secretions

The stomach produces **~2L** of secretions **per day**:

- **Acid secretion**
  Parietal cells contain an H^+-K^+ exchange pump.
  - H^+ is produced by carbonic anhydrase on CO_2 and water, with 'waste' HCO_3^- removed from the cell in exchange for Cl^-.
    - High levels of acid production result in large amounts of bicarbonate being secreted into blood
      - This creates an **alkaline tide** as portal venous pH increases dramatically
      - Respiratory quotient of the stomach may become negative due to **consumption of CO_2**
  - This pump is activated in response to increased levels of intracellular Ca^{2+} from stimulation by:
    - **ACh**
    - **Histamine** (H_2)
    - **Gastrin**
  - Inhibited by:
    - Low gastric pH
    - Somatostatin

- **Gastric**
  Gastin is a peptide family secreted from antral **G cells**.

  - Secretion is stimulated by:
    - Neural (vagal) stimulation in the cephalic phase of digestion
      Main mechanism.
    - Protein and amino acids in the stomach
    - Drugs
      - Alcohol
      - Caffeine
  - Secretion is inhibited by:
    - Low pH
    - Secretin
    - Glucagon
  - Gastrin has a number of pro-digestive effects:
    - Stimulates gastric acid secretion
    - Stimulates pancreatic secretion

        - Stimulates biliary secretion
        - Increases gastric and intestinal motility
- **Pepsinogens**
  Chief cells secrete pepsinogen I and is released by ACh or β stimulation. Pepsinogen is cleaved to pepsin in the gastric lumen, and breaks down protein.

- **Intrinsic Factor**
  Parietal cells produce intrinsic factor, which forms a complex with B_{12} which facilitates its later absorption in the terminal ileum.

- **Mucous**
  Neck cells produce mucopolysaccharide, glycoprotein, and HCO_3^- in response to stimulus by prostaglandins, which protects mucosa and lubricates food.

- **Pancreatic Secretions**
  Exocrine pancreatic secretions are produced by the **acinar** and **ductal cells**, at the rate of **1.5L per day**.

    - Release is stimulated by:
        - CCK
        - Secretin
        - ACh
          Via vagal stimulation.
    - Consist of:
        - HCO_3^-
          To alkalinise gastric contents.
            - Pancreatic bicarbonate production lowers venous pH, and neutralise's the alkaline tide of the stomach.
        - Water
        - Enzymes
            - Trypsinogen
              Proteolysis.
            - Amylase
              Hydrolysis of glycogen, starch, and complex carbohydrate.
            - Lipase
              Hydrolysis of dietary triglycerides.

Endocrine Function

- Cholecystokinin (**CCK**) is a peptide family secreted by intestinal enteroendocrine cells (I cells) in the mucosa of the duodenum and jejunum. Cholecystokinin:
    - Regulates satiety
    - Regulates leptin release from fat
    - Stimulates secretions from the gallbladder and duodenum
- Secretin stimulates pancreatic release. Secretin is:
    - Released by the proximal duodenum in response to low pH
- Motilin stimulates the migrating motor complex. Motilin is:
    - Released **cyclically** from M cells in the small bowel

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1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.

Last updated 2019-07-18

Oesophagus

> Describe the control of gastrointestinal motility, including sphincter function.

The oesophagus is a muscular tube connecting the pharynx to the stomach. The oesophagus has:

- **Skeletal muscle** in its **upper third**
- **Smooth muscle** in its **lower third**

Lower Oesophageal Sphincter

The LoS is:

- The most distal **2-4cm** of the oesophagus
- Macroscopically indistinguishable from the rest of the oesophagus
    - However it has a higher concentration of nerve cells and is able to constrict at a higher pressure
- Tonically innervated by the vagus
- Important in the prevention of reflux
  Competency of the LoS is required to prevent reflux
    - **Barrier pressure is** the pressure difference between the pressure at the lower oesophageal sphincter and the pressure in the stomach, and is typically **~15-25mmHg**
      Barrier pressure is affected by:
        - Changes in lower oesophageal sphincter pressure
            - Swallowing
              Barrier pressure decreases during swallowing, and transiently increases immediately afterwards.
            - Anatomical
                - Age
                  Sphincter tone is decreased in neonates and the elderly.
                - Diaphragm
                  An external sphincter is formed by the diaphragmatic crura, and exerts a **pinch-cock** action on the oesophagus.
                - Stomach
                  A fold in the stomach wall just distal to the GOJ creates a **flap valve**, which occludes the GOJ when gastric pressure rises.
                - Oesophagus
                  The oesophagus enters the stomach at an oblique angle, limiting retrograde flow.
            - Hormonal
                - Gastrin, motilin, α-agonism **increase** LoS tone
                - Progesterone, glucagon, vasoactive intestinal peptide (VIP) **decrease** LoS tone
            - Drugs
                - ETOH, IV and volatile anaesthetic agents, and anticholinergics **decrease** LoS tone
                - Suxamethonium, metoclopramide, and anticholinesterases **increase** LoS tone
        - Changes in gastric pressure
            - Raised intraabdominal pressure
                - Obesity
                - Pregnancy
        - Disease
            - Hiatus hernia
              GOJ moves into the thorax, causing:

    - Loss of pinch-cock action
    - Negative intrathoracic pressure reduces LoS pressure and therefore barrier pressure

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References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
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Control of Gastric Emptying

> Describe the control of gastrointestinal motility, including sphincter function.

Gastric emptying is a neurally and hormonally mediated process which aims to present food to the small bowel in a controlled manner. Different drugs, hormones, and physiological states can either encourage or inhibit gastric emptying.

Determinants of Gastric Emptying

Rate of gastric emptying is a function of:

- **Antral pressure**
  Main determinant as pyloric resistance tends to be low, and is affected by:
  - Stomach
  - Duodenum
  - Systemic factors
  - Drugs
- **Pyloric resistance**

Stomach

- Gastric **distension**
  Vagal excitation from gastric stretch causes release of **gastrin**, increasing peristaltic frequency.
- Composition of chyme:
  - **Liquids** empty **faster** than **solids**
    - Liquids have a half-time of ~20 minutes, and empty in an exponential fashion
    - Solids have a half-time of ~ 2 hours, with a dwell time of ~30 minutes, and empty in a linear fashion
  - Protein independently stimulates gastrin release

Duodenum

The duodenum has hormonal mechanisms which have a **negative feedback** on gastric emptying. These include:

- **Duodenal distension**
- **Hypoosmolar and hyperosmolar** chyme
- **Acid**ic chyme
  In response to acid the duodenum releases **secretin** and **somatostatin**:
  - Secretin directly inhibits gastric smooth muscle
  - Somatostatin inhibits gastrin release
- **Fat** and **protein**
  Fat and protein breakdown products stimulate release of **cholecystokinin**, which **inhibits gastrin**.
  - Carbohydrate-rich meals empty faster than protein, which empty faster than fat.

Systemic

- **Motilin** released by the small bowel enhances the strength of the **migrating motor complex**, a peristaltic wave of contraction through the whole GIT which occurs every 60-90 minutes
- **Sympathetic** input from the coeliac plexus **inhibits** gastric emptying
- Pregnancy has a number of effects on gastric emptying:
  - Progesterone relaxes smooth muscle and inhibits gastric smooth muscle response to ACh and gastrin, as well as creating

incompetence of the LoS leading to GORD
    - Gastrin production increases
      Some gastrin is produced by the placenta.
    - Gastric acid production is increased during the the third trimester
- **Parasympathetic** input enhances gastric motility

Effect of drugs

Drugs which increase gastric emptying include:

- Metoclopramide
- Erythromycin

Drugs which inhibit gastric emptying include:

- Opioids
- Alcohol
- Anticholinergic agents

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Swallowing

> Describe the control of gastrointestinal motility, including sphincter function

Swallowing is divided into three phases:

- **Oral Phase**
    - Voluntary
    - Food is pushed against hard palate by tongue
- **Pharyngeal Phase**
    - Involuntary
      Coordinated by medulla.
    - Closure of nasopharynx
    - Adduction of vocal cords
    - Hyoid elevation and deflection of epiglottis
    - Pharyngeal contraction
      Propels food bolus towards oesophagus
- **Oesophageal phase**
    - Involuntary
    - Closure of UoS
      Resting **barrier pressure 100mmHg**.
    - Relaxation of LoS
      Resting **barrier pressure 20mmHg**, which is a balance between:
        - LoS pressure (30mmHg)
        - Antral pressure (10mmHg)
    - Oesophageal peristalsis

Impairment of any of these processes increases risk of aspiration:

- Obtundation
  Reduced cough reflex.
- Muscular weakness
- Impaired medullary coordination

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

Last updated 2019-07-18

Physiology of Vomiting

> Describe the control of gastrointestinal motility, including sphincter function

Vomiting is the active, forceful expulsion of gastric contents from the stomach. It is different from regurgitation which is a passive process.

It is a mechanism to expel toxic substances from the GIT.

Stimulation

Stimulants to vomiting can act centrally, or directly in the bowel:

- **Central stimulation**
  Central stimuli may act directly on the vomiting centre. Others act via the CTZ, which is part of the area postrema located outside of the blood-brain barrier, and so it can be stimulated by circulating substances. Central vomiting stimuli include:
  - Direct:
    - Emotion
    - Pain
    - Olfactory
    - Visual
  - Via the CTZ:
    - Vestibular acting on:
      - H_1
      - ACh
    - Drugs/Toxins acting on:
      - 5-HT_3
      - D_2
      - μ-opioid receptors
- **GIT stimulation**
  GIT stimuli travel SNS and PNS afferents to the vomiting centre. The CTZ is not involved and so anti-emetics which act here are not useful in this type of vomiting.

  GIT vomiting stimuli include **distension** and **toxins**. Neurotransmitters include:

  - 5-HT_3 in mucosal stretch receptors
  - ACh in NTS afferents
  - H_1 in NTS afferents

Postoperative Nausea and Vomiting

Central structures involved include:

- Chemoreceptor trigger zone
- NTS
- Multiple pathways exist (similar to those described above), and neurotransmitters involved include:
  - 5-HT_3
  - D_2
  - NK_1
  - H_1
  - mACh

- Risk factors
    - Patient factors
        - Female
        - Non-Smoker
        - Young age
        - History of PONV or motion sickness
    - Anaesthetic factors
        - Volatile use
        - Nitrous oxide use
          Relative risk of 1.4.
        - Opioid use
        - Anaesthesia duration
    - Surgical factors
        - Gynaecological surgery
          Likely not an independent risk factor, and simply confounded by female gender.
        - Strabismus surgery in children

Process of vomiting

Vomiting consists of a set of processes coordinated by the **vomit centre** in the medulla oblongata, and is divided into three phases:

- **Pre-ejection phase**
    - Prodromal nausea
    - Salivation
    - Retrograde intestinal contraction which forces intestinal contents into the stomach
- **Retching Phase**
    - Deep inspiration and breath-holding to splint the chest
    - Epiglottic closure
    - Elevation of the soft palate (prevents nasal soiling)
- **Expulsive phase**
    - Relaxation of oesophageal sphincters
    - Pyloric contraction
    - Violent contraction of the diaphragm and abdominal muscles

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1. Brandis K. The Physiology Viva: Questions & Answers. 2003.
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Last updated 2019-07-18

Functions of the Liver

> Describe the storage, synthetic, metabolic and excretory functions of the liver

Storage

The liver is important in storage and release of:

- Carbohydrates as glycogen
  The adult liver stores ~100g of glycogen.
- Fat as triglycerides
- All fat-soluble vitamins (A, D, E, K)
- Many water soluble vitamins including folic acid and B_{12}
- Iron
- Copper

Synthetic

Synthetic functions include:

- **Bile production**
- Plasma proteins including:
  - Clotting factors
  - Albumin production
    120-300mg.kg^{-1} of albumin is produced per day, dependent on nutritional status, plasma oncotic pressure, and endocrine function.

Metabolic

Metabolic functions include:

- Carbohydrate
- Fat
- Protein
- Bilirubin metabolism
- Drugs and Toxins

Carbohydrates

- Monosaccharides and disaccharides passively diffuse into hepatocytes
  Gradient is maintained by converting glucose to glucose-6-phosphate which is used to produce glycogen. This maintains the gradient for diffusion.
- Glycogen is either synthesised (glycogenesis) or broken down (glycogenolysis) depending on plasma glucose and insulin:
  - Increased blood glucose stimulates insulin release, increasing the formation of glycogen through activation of glycogen synthetase
  - Decreased blood glucose stimulates glycogenolysis and gluconeogenesis from amino acids.

Lipids

- Fat can be:
  - Stored as triglycerides
  - Hydrolysed to glycerol and fatty acids, which is used for ATP production

Proteins and Urea

Amino acids are absorbed from blood to be used for gluconeogenesis and for protein synthesis. In order to produce substrates for the CAC, Amino acids may be:

- Transaminated
- Deaminated
- Decarboxylated

The nitrogenous scrap of these reactions is urea, which is produced in several stages:

- A variety of metabolic processes convert amino acids to **glutamate**
- Glutamate is converted to **ammonia** by glutamate dehydrogenase
- Ammonia then enters the urea cycle to produce (surprisingly) urea, at the cost of **3 ATP**
  - A normal diet of 100g protein per day produces ~30g of urea, and 1000mmol of hydrogen ions

Endocrine

- Produces angiotensinogen
- Produces IGF-1
- Converts T4 to T3

Immunoprotective

- **Kupffer** cells
  Tissue macrophages of the hepatic reticuloendothelial system. They phagocytose harmful substances including:
  - Endotoxins
  - Bacteria
  - Viruses
  - Immune complexes
  - Thrombin
  - Fibrin complexes
  - Tumour cells

Acid-Base Balance

May produce or consume large numbers of hydrogen ions:

- Carbon dioxide production
- Metabolism of organic acid anions
  - Lactate
  - Ketones
  - Amino acids
- Ammonium
- Production of plasma proteins
  Notably albumin

References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
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Laboratory Assessment of Liver Function

> Describe the laboratory assessment of liver function

Synthetic Function

Measures of synthetic function include:

- **Albumin**
  Main plasma protein.
  - Normal range 28-58g.L^{-1}
  - Half-life ~20 days
  - Important in:
    - Maintenance of plasma oncotic pressure
    - Binding
      - Calcium
      - Drugs
  - Decreased in liver dysfunction and malnutrition
- **Coagulation Assays**
  Clotting factors are produced by the liver. Hepatic impairment may result in reduced production and abnormality of clotting assays, although functional clotting function may be normal (as pro-coagulant proteins are affected to a similar extent).
  - INR
    Test of the extrinsic pathway.
  - APTT
    Test of intrinsic pathway.

Metabolic Function

Transaminases are released when liver parenchyma is damaged, and are used to evaluate metabolic function:

- ALT
  Normal range < 54 U.L^{-1}.
- AST
  Normal range < 35 U.L^{-1}.

Obstructive Tests

- ALP (Alkaline Phosphatase)
  Enzyme involved in dephosphorylation of many compounds. ALP is found in all cells, but particularly in the liver, bile duct, bone, kidney, and placenta.
  - Normal range is 30-120 U.L^{-1}
- GGT
  Enzyme found in biliary duct.
  - Normal range:
    - Males: 11-50 U.L^{-1}
    - Females: 7-30 U.L^{-1}
- Bilirubin

Byproduct of haemoglobin metabolism. May be measured as total, or as conjugated and unconjugated bilirubin.

References

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Bile

> Describe the physiology of bile and its metabolism

Bile is a dark green solution produced by the liver to facilitate absorption of fat and fat-soluble vitamins (ADEK) through emulsification. Bile is:

- Produced by the liver at the rate of 1L per day
- Concentrated in the gallbladder
- Important in the absorbance of lipid and fat-soluble vitamins
- Formed from:
    - Water
    - Protein
    - Bilirubin
    - Bile salts
      The sodium and potassium salts of bile acids. Bile acids:
        - Are are produced from cholesterol
        - Are amphipathic, and act as emulsifiers of lipid
          Break up large fat globules into smaller micelles, which can then be absorbed.
        - Major bile acids include:
            - Cholic acid
            - Chenodeoxycholic acid
        - Are absorbed in the terminal ileum, and recycled by the portal circulation
    - Lipids
    - Electrolytes

References

1. Hall, JE, and Guyton AC. Guyton and Hall Textbook of Medical Physiology. 11th Edition. Philadelphia, PA: Saunders Elsevier. 2011.
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Erythrocytes

> Outline the physiological production of blood and its constituents

Erythrocytes:

- Are **7.5μm** in **diameter**
- Are 2um thick
- Have a lifespan of **120 days**
- Have:
  - No nucleus
    Maximises cell volume available for Hb.
  - No mitochondria
    Cannot perform aerobic metabolism - all ATP is generated via glycolysis.
  - No ribosomes Incapable of producing protein
- Have a **biconcave disc** shape
  This maximises surface area (optimising gas transfer) and makes the cells flexible enough to pass through capillary beds (which are narrower than the cell).
- Are important in:
  - Delivering O_2 to the tissues and delivering CO_2 to the lungs
  - Acid-Base balance
  - Metabolism of some drugs
- Carry ~29pg of haemoglobin
- Comprise 40-50% of blood volume

Production

Erythrocytes have a **myeloid progenitor** which differentiates into the myeloid line. EPO (see endocrine functions of the kidney stimulates myeloid progenitor cells to:

- Differentiate
- Proliferate

- Proerythroblasts begin synthesis of Hb, with ongoing production occurring until the cell is mature
- Further differentiation results in successive **loss of organelles**, **increasing Hb content**
- The loss of **ribosomes** and **nucleus** of the reticulocyte are the final stage of erythropoiesis
- The entire process takes ~7-10 days

Function

- Gas Carriage
- Acid-Base Buffering
  - Production of HCO_3^-
  - Binding of H^+ to Hb
- Metabolism
  Esterases (and other -ases) in erythrocytes metabolise many drugs, including:
  - Remifentanil
  - SNP (reacts with Hb to form NO, CN, and Met-Hb)
  - Esmolol

Elimination

Old red cells are removed from circulation via:

- Phagocytosis by macrophages in:
  - Spleen
    Major mechanism.
  - Liver
  - Bone marrow
- Haemolysis
  ~10% of red cell breakdown occurs in circulation, where the Hb dimers are then bound to **haptoglobin** by haemopexin.
  - This is important to prevent glomerular filtration of haeme, and loss of iron

Haemoglobin Metabolism

Haemoglobin is broken down into:

- Globin
  Broken down into constituent amino acids.
- Iron
  Re-enters haemoglobin synthetic pathway.
- Haeme
  Complex metabolic pathway, notable as it is the only metabolic process that produces **carbon monoxide**:
  - Metabolised to **biliverdin** by splenic macrophages in the reticuloendothelial system of the **spleen**
    - Circulating erythrocytes are phagocytosed by splenic macrophages
    - Haptoglobin binds circulating Hb, the Hb-Haptoglobin complex is then phagocytosed by splenic macrophages
  - **Biliverdin** is reduced **to unconjugated bilirubin**
    This is fat soluble, and binds to albumin.
  - **Unconjugated bilirubin** is conjugated in the liver to **conjugated bilirubin**
  - **Conjugated bilirubin** is **secreted in bile** by active transport
    This is impaired during hepatic disease, leading to increased bilirubin levels in plasma.
  - Secreted **conjugated bilirubin** is metabolised **to urobilinogen** by gut bacteria
  - **Urobilinogen** may have a number of fates:
    - Enterohepatic recirculation and elimination in bile (again)
    - Further metabolism by gut bacteria to **stercobilinogen** and then to **stercobilin**
    - Enterohepatic recirculation and urinary excretion, where it is oxidised to **urobilin**

In Disease

	Blood	Urine	Faeces
Prehepatic disease	↑ Unconjugated bilirubin	↑ Urobilinogen, bilirubin not present	Normal
Intrahepatic disease	↑ Conjugated bilirubin, ↑ Unconjugated bilirubin	Bilirubin present	May be pale due to decreased urobilinogen excreted in bile
Posthepatic disease	↑ Conjugated bilirubin	↓ Urobilinogen, bilirubin present	Pale

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Iron Homeostasis

> Describe the normal nutritional requirements

Approximately 3-5g of iron is found in the body as:

- **Oxygen-carrying globin molecules**
  Haemoglobin (~70%) and myoglobin (~5%).
- **Catalyst** for biological reactions (~25%)
  Catalase, peroxidase, and cytochromes all require iron.

Absorption

Dietary iron comes in two forms:

- Haeme groups
  Directly absorbed via specialised transport proteins.
- Dietary iron salts
  - Ferrous (Fe^{2+}) iron is soluble, and is absorbed via facilitated diffusion across the enterocyte membrane
    - Reduced acidity of the stomach will reduce the absorption of ferrous iron
  - Ferric (Fe^{3+}) iron precipitates when pH > 3, and so cannot be absorbed independently by the small bowel.
    - A pathway may exist for absorption of ferric iron from soluble chelates

- Once in the enterocyte, iron can be:
  - Stored, bound to **ferritin**
  - Transported via **ferroportin** out of the enterocyte, where it is then oxidised to ferrous iron and bound to **transferrin**

Regulation

- Excretion is uncontrolled
- Regulation of iron levels is only by absorption
- **Hepcidin** is a liver protein which inhibits the action of ferroportin
  - High hepcidin prevents iron transport from the enterocyte
  - Hepcidin is deficient in haemochromatosis

References

1. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Platelets

> Outline the physiological production of blood and its constituents

> Describe the process and regulation of haemostasis, coagulation and fibrinolysis

Platelets are small cell fragments which are vital in haemostasis via forming a **platelet plug**. They:

- Have a lifespan of **7-10 days**
- Are removed by the reticuloendothelial system in the spleen and liver

Production

Platelets are:

- Anuclear circulating cell bodies, which bud from megakaryocytes
  As the megakaryocyte cell volume increases, the cell membrane invaginates and small platelets bud off.
  - The time from stem cell to platelet is **~10 days**, and is stimulated by **thrombopoietin**
- New platelets are held in the spleen for 36 hours until they mature

Contents

- **α-granules**
  Contain fibronectin, fibrinogen, vWF, PDGF, and Thrombospondin, platelet factor 4.
- **δ-granules**
  Contain 5-HT, ATP, ADP, and Ca^{2+}.
- **Contractile proteins**
  Facilitate platelet deformation when activated.

Activation

- Platelets are activated by:
  - Collagen
    Exposed by damaged endothelium.
  - Adrenaline
  - ADP
  - Thrombin
- Activation results in several events:
  - Exocytosis of granules
  - Activation of membrane **phospholipase A_2** to form **thromboxane A_2**
  - Deformation from a disc to a sphere with long projections
  - Promotion of the coagulation cascade
  - Change in glycoprotein (GP) expression by the action of ADP:
    ADP antagonists (e.g. clopidogrel) prevent expression of the GPIIb/IIIa complex.
    - GP Ib/IIb/IIIa facilitate platelet attachment to vWF
      vWF also binds to sub-endothelial connective tissue.
    - GP IIb/IIIa are also receptors for fibrinogen, which encourages platelet aggregation

References

1. Kam P, Power I. Principles of Physiology for the Anaesthetist. 3rd Ed. Hodder Education. 2012.
2. Krafts K. Clot or Bleed: A Painless Guide for People Who Hate Coag. Pathology Student.

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Transfusion

> Understanding the adverse consequences of blood transfusion, including that of massive blood transfusion

Production and Storage of Blood Products

Red cells, platelets, and FFP have different storage requirements.

Red Blood Cells

- Stored blood decays over time - this is known as a **storage lesion**
  Preservatives are used to extend the time blood can be stored:
    - Kept at ~4°C (balance between freezing and being too warm)
        - Reduces cellular metabolic requirement
        - Inhibits bacterial growth
    - Collected in an aseptic fashion
    - Stored in special solutions:
        - SAGM is currently used by the Australian Red Cross:
            - Saline
            - Adenine
              Substrate for ATP synthesis
            - Glucose
              Substrate for RBC glycolysis
            - Mannitol
        - CPDA1 (citrate-phosphate-dextrose-adenine) was traditionally used
            - Citrate binds calcium, preventing clotting
            - Phosphate acts as a buffer and phosphate source for metabolism
            - Dextrose
            - Adenine

- A **storage lesion** describes the changes that occur in stored blood:
    - Loss of 2,3 DPG
      Less of a factor in CPDA1 blood.
    - Haemolysis
    - Hyperkalaemia
      Typically not clinically relevant as potassium is taken up into red cells when metabolism resumes.
    - Acidaemia
    - Hyponatraemia
      Not clinically significant.

- Blood can be stored for up to 35 days, which corresponds to 70% survival

Platelets

Platelets require particular storage conditions to remain functional:

- Temperature ~22°C
  Below this, platelets deform and become non-functional
- Gas exchange
  Platelets are stored in a bag which allows gas exchange to occur, minimising lactic acid and carbon dioxide production

- Agitation
  Platelets are stored on an agitator which prevents clotting and ensures the platelets are well mixed, which maximises the diffusion gradient for gas exchange
- pH control
  pH is kept between 6.2 to 7.8 to prevent degranulation.

As platelets do not contain antigen, there is not a *strict* requirement for platelets to be type matched. However:

- Rh(+) platelets should be avoided in Rh(-) patients
  The small amount of contaminating red cells may precipitate rhesus disease.
- Plasma incompatibility should be avoided as this may lead to haemolysis of recipient red cells
  - Children are at greater risk due to their proportionally smaller blood volume

Fresh Frozen Plasma

Fresh Frozen Plasma is:

- Prepared either via:
  - Separation from whole blood
  - Apheresis
    Removal of a large volume (typically 800ml) of plasma from a single patient, with return of red cells to the donor.
- Once collected, it is frozen and re-thawed in a water bath prior to use

Cryoprecipitate

Cryoprecipitate is prepared by removing the precipitate from FFP which forms at 1–6°C. Cryoprecipitate contains predominantly:

- Fibrinogen
- Fibronectin
- vWF
- Factor VIII
- Factor XIII

Whole Blood

Whole blood undergoes additional changes:

- White cells become nonfunctional within 4-6 hours of collection, though antigenic properties remain
- Platelets become non-functional within 48 hours of storage at 4°C
- Factor levels decrease significantly after 21 days

Blood Groups

Blood groups refer to the expression of surface antigens by red blood cells, as well as any antibody in plasma. Blood groups can be divided into three types:

- ABO
- Rhesus
- Other antibodies These are additional antibodies that a patient may express in plasma, and include Kell, Lewis, Duffy, etc.

ABO

The ABO blood group is:

- A complex carbohydrate-based antigens series
  These may be either A or B antigen, and patients may express one, both, or neither, giving four blood groups (A, B, AB, O).
- Expressed on the **H-antigen stem** of RBCs, and on the surface of tissue cells.
  - The **Bombay Blood Group** (or **hh** or **Oh** group) describes individuals who do not express the H antigen
    These individuals:
    - Don't express A- or B-antigen (as there is no H-antigen stem) and are 'universal donors'
    - Express H-antibody
      Can only receive blood from other individuals with the Bombay phenotype
- Individuals express IgM antibody to foreign blood groups
  This develops within 6 months of birth, likely due to environmental exposure to similar antigens.
- Associated with a severe hypersensitivity reaction if an ABO-mismatch occurs

Group	RBC	Plasma
A	A-antigen	B-antibody
B	B-antigen	A-antibody
O	-	A-antibody B-antibody
AB	A-antigen B-antigen	-

Rhesus

The Rhesus blood group is the next most important group after ABO. The Rhesus system:

- Consists of ~50 different antigens, the most important of which is **D**
  Rhesus status is therefore expressed as positive (D - 85% of the population) or negative (anything-but-D).
- Rhesus antibody does not naturally occur in Rh(-) individuals
  - This is relevant in Rhesus disease
    A Rh(-) mother exposed to Rh(+) blood will develop Anti-D antibody, which can cross placenta and induce abortion in a future Rh(+) foetus. This can occur with:
    - Incompatible transfusion
    - Foetal-maternal haemorrhage

Compatibility Testing

Donor blood must be tested with recipient blood to avoid a transfusion reaction. This involves three processes:

- Blood Typing (ABO/Rh)
  Blood is typed by mixing it in vitro with plasma (and plasma with erythrocytes) of known groups (containing IgM antibody (Anti-A, Anti-B, Anti-AB)), and observing for agglutination.
- Antibody Screen
  For other antibodies.
  - Testing is similar to ABO screening, except *plasma* is mixed with red cells containing known antigen (e.g. Kell, Duffy), and monitored for agglutination.
- Cross-match
  Involves two processes:
  - Saline test
    Erythrocytes are suspended in saline and mixed with antibodies at room temperature, monitoring for agglutination.
    - This confirms ABO type
  - Indirect Coombs' test

Identifies IgG antibody in host plasma which would cause haemolysis of transfused red cells. This is typically no longer done, as it offers negligible extra safety over the above processes. Doing it involves:

- Incubating
  Binds IgG Ab to antigen on RBC membrane.
- Washing
  Removes serum and unbound IgG.
- Testing with an antibody *to* IgG, known as antiglobulin serum.
  - A positive test will cause clumping of red cells, as each antiglobulin serum will bind two IgG molecules, which have in turn been bound to red cells
  - A negative test will cause no agglutination, as the IgG has not been bound to red cells
    - If negative, the antiglobulin serum is re-used on a control sample to ensure that it is not a false negative

Transfusion Reactions

Transfusion reactions can be classified as either acute (< 24 hours) or delayed (> 24 hours), and as immunological or non-immunological.

Immunological Acute Reactions

Reaction	Incidence	Mechanism
ABO Mismatch	1:40,000	ABO incompatibility causing rapid intravascular haemolysis, which may cause chest pain, jaundice, shock, and DIC. RhD-reactions tend to cause extravascular haemolysis.
Haemolytic (acute)	1:76,000 (1:1.8 million fatal)	Immunological destruction of transfused cells (Type II hypersensitivity). Presents with fever, tachycardia, pain, progressing to distributive shock
Febrile, non-haemolytic	~1:100	Cytokine release from stored cells causing a mild inflammatory reaction, with temperature rising to ≥38ºC or ≥1ºC above baseline (if >37ºC). Benign - but requires exclusion of a haemolytic reaction.
Urticaria	1:100	Hypersensitivity to plasma proteins in the transfused unit
Anaphylaxis	1:20,000	Type I hypersensitivity reaction to plasma protein in transfused unit
TRALI	Variable	Donor plasma HLA activates recipient pulmonary neutrophils, causing fever, shock, and non-cardiogenic pulmonary oedema

Non-Immunological Acute Reactions

Reaction	Incidence	Mechanism
Massive Transfusion Complications	Variable	See below
Non-immune mediated haemolysis	Rare	Due to physicochemical damage to RBCs (freezing, device malfunction). May lead to haemoglobinuria, haemoglobinaemia, tachycardia and fevers.
Sepsis	1:75,000 (platelets), 1:500,000 (RBC)	Contamination during collection or processing. Most common organisms are those which use iron as a nutrient and reproduce at low temperatures, e.g. *Yersinia Pestis*.
Transfusion Related Circulatory Overload (TACO)	< 1:100	Rapid increase in intracellular volume in patients with poor circulatory compliance or chronic anaemia. May result in pulmonary oedema and be confused with TRALI.

Delayed Immunological Reaction

Reaction	Incidence	Mechanism
Delayed haemolytic transfusion reaction	1:2,500	Development of sensitisation with the reaction occurring 2-14 days after a single exposure. Typically Kidd, Duffy, Kell antibodies.
Post-transfusion Purpura	Rare	Alloimmunisation to Human Platelet Antigen causing sudden self-limiting thrombocytopenia
TA-GVHD	Rare	Transfused lymphocytes recognise host HLA as positive causing marrow aplasia, with mortality >90%
Alloimmunisation	1:100 (RBC antigens), 1:10 (HLA antigens)	Previous sensitisation leading to antibody production on re-exposure.
Transfusion-related Immune Modulation	Not known	Transient immunosuppression following transfusion potentially due to cytokine release from leukocytes

Delayed Non-Immunological Reaction

Reaction	Incidence	Mechanism
Iron Overload	Chelation after 10-20 units, organ dysfunction 50-100 units	Each unit of PRBC contains ~250mg of iron, whilst average excretion is $1mg.day^{-1}$.

Complications of Massive Transfusion

A **massive transfusion** is one where:

- Greater than **one-half** of **circulating volume** in **4 hours**
- Whole **circulating volume** in **24 hours**

Risk of complication from a massive transfusion is influenced by:

- Number of units
- Rate of transfusion
- Patient factors

Complication	Mechanism
Air embolism	Inadvertent infusion
Hypothermia	Cooled products
Hypocalcaemia	Consumption with coagulopathy and bound to citrate added to transfused units
Hypomagnesaemia	Bound to citrate in transfused units
Citrate toxicity	Citrate is added to stored units as an anticoagulant
Lactic acidosis	Hyperlactataemia due to anaerobic metabolism in stored units
Hyperkalaemia	Potassium migrates from stored erythrocytes into plasma whilst in storage

References

1. Blood Service. Classification & Incidence of Adverse Events. Australian Red Cross.
2. National Blood Authority. Patient Blood Management Guidelines. Australian Red Cross.
3. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.

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Haemostasis

> Describe the process and regulation of haemostasis, coagulation ~~and fibrinolysis~~

Haemostasis describes the physiological processes that occur to stop bleeding. It involves three processes:

- **Vessel constriction**
  Decreases flow, which limits further haemorrhage and reduces the shear stresses which break up forming clot
- **Platelet plug formation** or Primary Haemostasis
  Platelets adhere to the damaged vessel wall and aggregate
- **Fibrin formation** or Secondary Haemostasis
  Fibrin is formed from fibrinogen (via the coagulation cascade), which stabilises the platelet plug

Primary Haemostasis

Following a vascular injury, the exposure of subendothelial proteins stimulates platelets to form an occlusive plug via several processes:

- **Adhesion**
  Exposed collagen binds to GPIa receptor on platelets.
  vWF also binds to platelets.

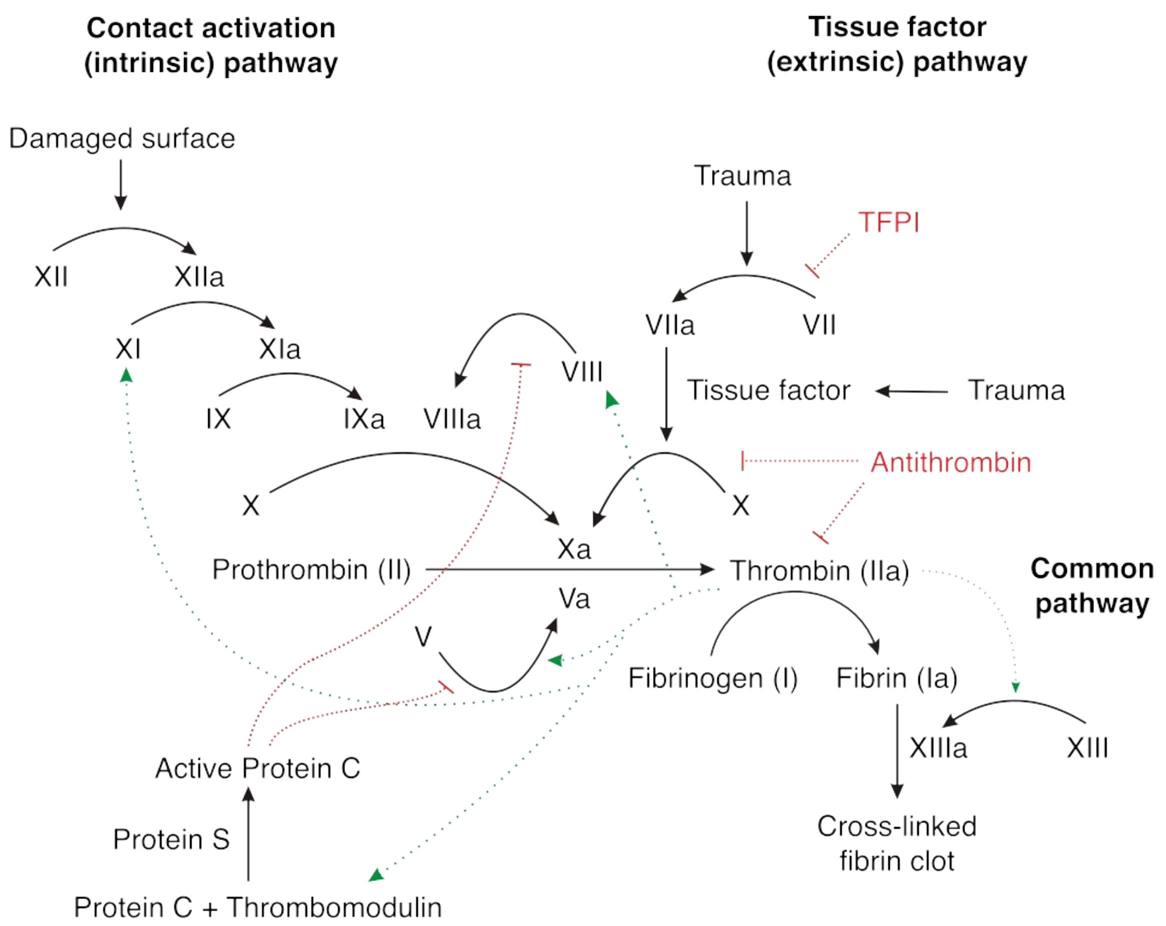
- **Activation**
  Metabolic activation, increasing Phospholipase A_2 and Phospholipase C, increasing platelet intracellular Ca^{2+} and initiating a transformation from a disc to a sphere with long projections.
  - Metabolic activation is stimulated by:
    - Collagen
    - Adrenaline
    - ADP
    - Thrombin
  - Additionally, platelets release ADP and thromboxane A_2 from their **alpha granules** and **dense bodies**, amplifying further platelet aggregation and adhesion

- **Aggregation**
  With other platelets - held together by fibrin - forming a plug.

- **Contraction**
  After some time platelets contract, retracting the clot and sealing the wall.

Secondary Haemostasis

The coagulation cascade is an amplification mechanism which activates clotting factors in order to produce fibrin.



Participating factors in the coagulation cascade can be either **enzymes** or **cofactors**:

- Enzymes circulate in their inactive form, and become active (e.g. VII ⇒ VIIa) when hydrolysed by their precursor factor
- Cofactors amplify the cascade

Pathways

The cascade is divided into the **intrinsic pathway** and **extrinsic pathway**, which join to form the **common pathway**. *In vitro*, the intrinsic and extrinsic pathways operate separately. This is an artifact of lab measurement - *in vivo* **the pathways are co-dependent**.

Extrinsic Pathway

The extrinsic pathway contains two factors, and the process of activation **occurs in seconds**:

- Tissue Factor
  Membrane protein on sub-endothelial cells, which is exposed when the vessel is damaged (it is found in a few other places as well). It binds to factor VII to form VIIa, and thus activates the extrinsic pathway.
- Factor VII

Intrinsic Pathway

The intrinsic pathway is activated **over minutes**, and contains:

- Contact factors
  Only important *in vitro* when conducting lab testing - deficiency of these factors does not cause a coagulopathy.

    - HMWK
      HMWK activates factor XII.
    - Factor XII
      Factor XIIa activates factor IX, as does thrombin.
- Factor XI
- Factor IX
- Factor VIII
  Factor VIII circulates in a complex with vWF, preventing it from degradation. When activated by thrombin, it acts as a cofactor for factor IXa to activate factor X.

The intrinsic pathway is activated by:

- Thrombin
  Main activator of the intrinsic pathway *in vivo*.
- Collagen
- Glass
  In vitro.

Common Pathway

The common pathway contains:

- Factor X
- Factor V
  Cofactor (similar to factor VIII), which when activated by thrombin allows factor Xa to convert prothrombin into thrombin.
- Factor II (prothrombin)
  Has several key roles:
    - Cleaves fibrinogen to fibrin
    - Activates factor XIII
      Factor XIIIa stabilises clot by forming cross-bridges between fibrin in a platelet plug.
    - Amplification of the clotting cascade by activating factors V and VIII
    - Activates protein C
      Thrombin binds with thrombomodulin to form a complex which inhibits coagulation.
- Factor I (fibrinogen)

The Cell-Based Model of Coagulation

- The cascade model (above) accurately describes the process of clotting *in vitro*, but not *in vivo*
- The cell-based model has several changes, noting the central role of the platelet:
    - **Initiation phase**
      Coagulation begins with tissue factor being exposed, which also activates platelets.
    - **Amplification phase**
      A positive feedback loop occurs:
        - Production of Xa causes production of thrombin (IIa), **priming** the system
        - Thrombin then activates factors V, VIII, and IX, accelerating Xa production and further thrombin generation
    - **Propagation phase**
      Platelets bind activated clotting factors, causing high rates of thrombin formation around them.

References

1. Krafts K. Clot or Bleed: A Painless Guide for People Who Hate Coag. Pathology Student.
2. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge University Press. 2015.
3. Clotting Cascade 22/4/2007. (Image). By Joe D (Own work). CC BY 3.0 , via Wikimedia Commons.

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Haemostatic Regulation

> Describe the mechanisms of preventing thrombosis including endothelial factors and natural anticoagulants

Haemostasis must be controlled to prevent rampant clotting of the vascular tree. This involves both endothelial factors and proteins.

Endothelial Regulation

Intact endothelium and the glycocalyx prevent clotting in a number of ways:

- **Minimise stasis**
  - High blood flow
    Especially where flow is turbulent (large arteries).
  - Maximise laminar flow
    Glycocalyx smooths flow.
- **Inhibition of platelet adhesion and activation**
  NO, prostacyclin, and ectonucleotidases (which degrade ADP) inhibit platelet activation.
- **Membrane-bound anticoagulant proteins**
  - **Hepar*an*** (not hepar*in*)
    Activates antithrombin III.
  - **Thrombomodulin**
    Binds thrombin, preventing cleavage of fibrinogen to fibrin. The thrombin-thrombomodulin complex activates protein C (which in turn inactivates factors Va and VIIIa).
- **Prevent exposure of procoagulant protein**
  - Collagen
  - vWF
  - Tissue Factor
- **tPA secretion** (see 'Clot Lysis')

Clot Regulation

- Effect of blood flow
  - Dilutes clotting factors
    Activated clotting factors are washed away and metabolised by the RES.
  - Laminar flow
    Causes **axial streaming** of platelets, minimising endothelial contact and chance of activation.fa
- Activation of anticoagulant factors
  - **Tissue Factor Pathway Inhibitor**
    Inhibits VIIa, antagonising the action of tissue factor
  - **Antithrombin III**
    Inhibits the **serine proteases**, i.e. the non-cofactor factors in all three pathways - IIa, VIIa, IXa, Xa, XIa, XIIa.
  - **Protein C**
    Inactivates protein Va and VIIIa, and is activated by thrombin.
  - **Protein S**
    Cofactor which helps protein C.

Clot Lysis

Clot breakdown is performed by:

- Tissue Plasminogen Activator (**tPA**)
  Binds to fibrin, and then cleaves plasminogen to plasmin. This keeps the plasmin formation in the vicinity of the clot, limiting its systemic spread of.
- **Plasmin** cleaves fibrin into **fibrin degradation products**
  FDPs conveniently inhibit further thrombin and fibrin formation.

References

1. Krafts K. Clot or Bleed: A Painless Guide for People Who Hate Coag. Pathology Student.
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Coagulopathy Testing

> Outline the methods for assessing coagulation, platelet function and fibrinolysis

Coagulation Factors

All these tests measure how long it takes to make fibrin. They evaluate different parts of the coagulation cascade, which help localise where a coagulopathy may be occurring.

In these tests:

- Citrate is added to blood
  Binds calcium and prevents clotting.
- Sample is centrifuged
- Plasma decanted
- Calcium (to replace the calcium lost by binding to citrate) and a reagent is added
- Time taken to clot measured

Prothrombin Time/INR

The prothrombin time measures the **extrinsic pathway**. Tissue factor has to be added to the sample in order start clotting - this is why it is known as the extrinsic pathway as a substance *extrinsic* to the sample must be added. As the PT varies significantly between different labs, the INR is used to allow values to be compared.

Any disorder of the extrinsic or common pathways will prolong the PT, i.e. deficiency or inhibition of:

- Factor VII
- Factor X
- Factor II (prothrombin)
- Factor V
- Factor I (fibrinogen)

Although warfarin affects factors in all three pathways, its clinical effects are measured using INR. This is because:

- Factor VII has the shortest half-life of the clotting factors affected by warfarin
  Therefore so its levels will fall the quickest.
- Therefore a fall in Factor VII levels is the earliest indication of changes in coagulation status due to warfarin
- As factor VII is only in the extrinsic pathway, the PT/INR are the only tests which can evaluate its function

(Activated) Partial Thromboplastin Time

The partial thromboplastin time measures the **intrinsic pathway**, which begins produce fibrin when activated by the addition of phospholipid to the sample (phospholipid is contained in platelets, and so is not technically "extrinsic"). The activated partial thromboplastin time is the same test, except an activating agent is added to speed up the reaction.

Any disorder of the intrinsic or common pathways will prolong the APTT, i.e. deficiency or inhibition of:

- Factor XI
- Factor IX
- Factor VIII
- Factor X
- Factor V

- Factor II (prothrombin)
- Factor I (fibrinogen)

Heparin affects both sides of the pathway (IIa, IXa, Xa, XIa) however typically affects intrinsic factors more than extrinsic.

In addition, **anti-phospholipid antibodies** will also prolong the APTT by binding the added phospholipid.

Activated Clotting Time

Activated Clotting Time is used to for the dosing and reversal of heparin in cardiopulmonary bypass and other extracorporeal circuits.

Fresh whole blood is added to a tube with an activator (e.g. glass beads) to stimulate the intrinsic pathway. The time until clot formation is measured in seconds. Different activators will have different normal ranges, and target ranges for the circuit in use.

Platelet Function

Evaluate how well platelets aggregate in response to factors like ADP, collagen, arachidonic acid, and adrenaline (i.e., endogenous stimulators of platelet aggregation).

In this test, the aggregating agent is added to a tube of platelets, and the change in turbidity measured. Different patterns of response (or non-response) can be diagnostic of different platelet function disorders.

Point of Care Testing

Point of care coagulation testing:

- Involves testing of **whole blood**
  Traditional testing uses plasma only.
  - Therefore includes the **cell-based model** of coagulation
    May **better represent actual clotting function** compared with traditional coagulation factor testing.
- Provides information on all phases of clotting

Viscoelastic Methods

Include:

- **Thromboelastography** (TEG)
  Continuous measurement and display of viscoelastic properties of a blood sample from initial fibrin formation to clot retraction, and ultimately fibrinolysis. Involves:
  - A known volume (typically 0.36ml) of whole blood added to activators in two disposable cuvettes (cups) heated to 37°C
    - Contact activators (such as kaolin) are added to the blood to accelerate clotting
    - A heparinase cuvette is also commonly used so clotting function can be measured during full anticoagulation (e.g. CPB)
  - Pin attached to torsion wire immersed into blood Torsion on the pin is converted (by a transducer) into a TEG tracing.
  - Cuvette rotates through 4°45′ in alternate directions
    Each rotation takes 10s.
  - Pin initially remains stationary as it rotates through the un-clotted blood
    This is represented by a straight line on the tracing.
  - **As blood clots, cup rotation exerts torque on the pin**
  - The stronger the blood clot, the greater the torque exerted on the pin

- **Rotational Thromboelastometry** (ROTEM)

Modified version of TEG:
- A pin fixed to a steel axis is rotated in blood via movement of a spring
  The cuvette remains stationary.
- Two samples are used:
  - Tissue factor is added to measure the extrinsic pathway (known as the ENTEM cuvette)
  - Contact activator is added to measure the intrinsic pathway (INTEM cuvette)
- Impedance to rotation is detected by an optical system:
  - LED
  - Mirror on the steel axis
  - Electronic camera
- **Uses different reference ranges and nomenclature to TEG**

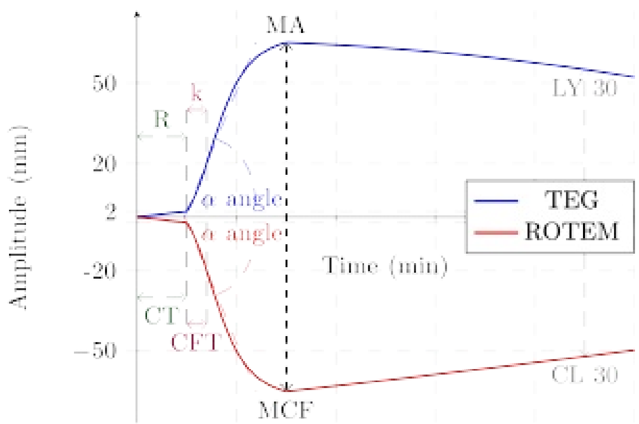
Advantages and Disadvantages of TEG/ROTEM

Advantages	Disadvantages
Rapid compared with traditional testing	Still measures coagulation in artificial conditions
Uses whole blood, providing a more complete picture of plasma-RBC-platelet interaction	Does not measure contribution of endothelium and therefore conditions affecting platelet adhesion (e.g. von Willebrand's disease)
Real-time display of clot evolution	Harder to institute QA outside of laboratory
Reduces non-evidence-based transfusion	Measurement methodology is not yet standardised between institutions
Predictive of post-operative *hyper*coagulable states	Baseline measurement does not predict post-operative bleeding
Very sensitive to heparin effect	Does not measure effect of hypothermia
	Requires training and competency of non-lab staff
	More expensive than traditional testing

Interpreting TEG/ROTEM

Note that reference ranges are not included here, and will vary depending on the:

- Technique (TEG/ROTEM) used
- Activator used
- Adjuvants added
  e.g. Citrated vs. recalcified samples.



Parameter (TEG)	Parameter (ROTEM)	Definition	Relevance

R (reaction) **time**	**CT** (clotting time)	Time until 2mm amplitude	Time until initial fibrin formation, **dependent on plasma concentration of clotting factors**
K time	**CFT** (clot formation time)	Time for amplitude to increase from 2-20mm	Measurement of clot kinetics (clot amplification), **dependent on fibrinogen**
α angle	**α angle**	Angle between the tangent to the tracing at 2mm and the midline	Rapidity of fibrin formation and cross-linking. Alternate measure of clot kinetics, **dependent on fibrinogen**
MA (maximum amplitude)	**MCF** (maximum clot thickness)	Greatest amplitude	Indicates point of maximal clot strength, **dependent *predominantly* on platelets (80%)** and **fibrinogen (20%)**, binding via **GPIIb/IIIa**. Treatment with **platelets** or **DDAVP**.
CL 30 (clot lysis 30)	**LY 30**	Percent decrease in amplitude 30 minutes after MA	Clot stability, dependent on **fibrinolysis**. Reduced CL 30 can be treated with an **antifibrinolytic**, such as TXA

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1. Krafts K. Clot or Bleed: A Painless Guide for People Who Hate Coag. Pathology Student.
2. Activated Clotting Time - Practical Haemostasis.
3. Srivastava A, Kelleher A. Point-of-care coagulation testing. Contin Educ Anaesth Crit Care Pain. 2013;13(1):12-16.

Last updated 2019-07-18

SI Units

The International System of Units (**SI**, or *Système International d'Unités*), is a set of measurement standards which defines (almost) all standards in terms of uniform natural phenomena, and form the base of the metric system.

Base SI Units

There are **seven base SI units**, with **many derived units** made from combinations of these. Base SI units are mutually independent. They consist of:

Quantity	Unit	Abbreviation	Definition
Time	Second	s	Duration of 9,192,631,770 periods of the radiation corresponding to the transition between two hyperfine levels of the ground state of an atom of Cs-133
Length	Metre	m	Distance that light travels in a vacuum in 1/299,792,458th of a second
Current	Ampere	A	The constant current that would produce a force of 2x10^{-7} Newton between two conductors of infinite length and negligible cross section in a vacuum
Temperature	Kelvin	°K	1/273.16th of the triple point of water. The **triple point** is the temperature at which **a substance** exists in **equilibrium** in **all three phases** (solid, liquid, gas).
Amount	Mole	mol	The amount of substance which contains as many elementary entities as in 0.012kg of Carbon 12
Luminous Intensity	Candella	cd	Luminous intensity of a source which emits monochromatic radiation at 540 x 10^{12} Hz at radiant intensity of 1/683 watts per steradian
Mass	Kilogram	kg	Weight of the International Prototype Kilogram (IPK)

Derived Units

Quantity	Unit	Abbreviation	Conversion to Base SI Units	Definition
Area	Square metre	m^2	m^2	
Velocity	Metre per Second	m.s^{-1}	$\frac{m}{s}$	
Acceleration	Metre per Second per Second	m.s^{-2}	$\frac{m}{s^2}$	
Force	Newton	N	$N = \frac{kg.m}{s^2}$	Force required to accelerate 1kg at 1m.s^{-2}
Pressure	Pascal	Pa	$Pa = \frac{N}{m^2} = \frac{kg}{m.s^2}$	Force per area
Energy/Work/Quantity of Heat	Joule	J	$J = N.m = \frac{kg.m^2}{s^2}$	Energy converted when 1N is applied to 1kg over 1m
Dose Equivalence	Sievert	Sv	$Sv = \frac{J}{kg} = \frac{m^2}{s^2}$	Radiation dose per mass

Power	Watt	W	$W = \frac{J}{s} = \frac{kg.m^2}{s^3}$	second
Electromotive Force	Volt	V	$V = \frac{W}{A} = \frac{kg.m^2}{A.s^3}$	Measure of electrical potential energy

References

1. Physical Measurement Laboratory. National Institute of Standards and Technology.
    - And various subpages

Last updated 2017-09-22

Electrical Safety

> Understand the concepts of patient safety as it applies to monitoring involving electrical devices

Electrical Principles

- **Charge** is the property of a subatomic particle which causes it to experience a force when close to other charged particles
  Charge is measured in coulombs (C).
- **Current** is the flow of electrons through a conductor
  Current is measured in amps (A).
- **Voltage** is the strength of the force that causes movement of electrons
  By tradition, voltages are quoted relative to **ground** (or **earth**). If a potential difference exists, a current will flow from that object to the earth via the path of least resistance. If this path contains a person, an electrical injury may result.
- **Resistance** describes to what extent a substance reduces the flow of electrons through it
  Resistance is measured in ohms (Ω).
  - Substances with **high resistance** are **insulators**
  - Substances with **low resistance** are **conductors**
- **Inductance** is the property of a conductor by which a change in current induces an electromotive force in the conductor, and any nearby conductors
- **Capacitance** is the ability of an object to store electrical charge
  Measured in Farads (F), where one farad is when one volt across the capacitor stores one coulomb of charge.
  - A capacitor is an electrical component consisting of two conductors separated by an insulator (called a dielectric)
  - When a **direct current** flows, electrons (a negative charge) build up on one of these conductors (called a plate), whilst an electron deficit (positive charge) occurs on the other plate
    - Current will flow until the build up of charge is equal to the voltage of the power source
    - Current can be **rapidly discharged** when the circuit is changed
  - An **alternating current** can flow freely across a capacitor, and causes no buildup of charge
- **Impedance** describes to what extent the flow of **alternating current** is reduced when passing through a substance
  Impedance can be thought of as 'resistance for AC circuits', and is a combination of **resistance** and **reactance**.
  - Reactance is a function of two things:
    - Induction of voltage in conductors by the alternating magnetic field of AC flow
    - Capacitance induced by voltages between these conductors

Electrical Injury

Potential electrical injuries can be divided into:

- **Ventricular Fibrillation**
  Likelihood is a function of:
  - Current density
  - Frequency
    Lowest current density required is at **50Hz**.
- **Burns**
  Function of current density. Burns typically occur at the entry and exit point as this is where current density is highest.

- **Tetanic Contraction**
  Flexors are stronger than extensors, which may maintain grip on live wire. Death may result from either VF or asphyxiation from sustained respiratory muscle contraction.

Electrical Shock

Electrical shocks are divided into two types, based on their ability to induce VF:

- **Microshock**
  Current required to induce VF when applied directly to myocardium.
  - Typical current is **0.05-0.1mA**
  - This requires **skin breach**
    Potential causes:
    - Guidewire
    - Pacing lead
    - Column of conducting fluid
    - CVC
    - PICC
- **Macroshock**
  Current required to induce VF from surface contact.
  - Typical current is **100mA**
  - This is much higher because most of this current is not going to the ventricle, and so the total current must be greater to achieve sufficient **current density** in the myocardium to induce VF

Other detrimental effects seen at lower currents include:

Current (mA)	Effect
1	Tingling
5	Pain
8	Burns
15	Skeletal muscle tetany
50	Skeletal muscle paralysis & respiratory arrest

Principles of Electrical Safety

Power points contain three wires:

- Active
  240V. Measuring voltage for AC current is not intuitive, as the voltage will be negative half the time. The **root mean square** (RMS) is used instead - each value for the voltage is squared (giving a positive number), and then divided by the number of samples to give an average.
- Neutral
  0V, relative to ground.
- Earth
  Direct pathway into ground.

An electrical circuit is completed between an appliance and the power station by returning current to the station via the earth. This is an **earth referenced power supply**.

Electrical Dangers

- Active wire shorts to equipment casing
    - Principle of earth wire, which provides path of least resistance for current to travel if an individual touches the case
- High current drain through a wire generates heat and starts a fire
    - Principle of fuses which trigger when current drain is >15A

Methods of Electrical Safety

- **Insulation**
  Conductors are coated by a high-resistance substance, preventing current flowing where it shouldn't.

- **Fuses**
  Safety devices which cease all current flow when current exceeds a certain threshold (typically 20A). If there is a fault which greatly lowers resistance (i.e. insulation breaks, causing a device to become live and drain via the earth wire), a high current will flow and the fuse will be triggered.
    - A fault requires:
        - A fault that causes a high current flow
        - The fuse to work correctly

- **Residual Current Devices**
  An RCD measures the current difference between the active and neutral lines.
    - In an non-fault situation, these will be equal
    - In a fault situation, current will be being delivered by the active line but not returned via the neutral
      Current will instead flow to ground via faulty equipment/through the patient.
        - The RCD will detect if there is a >10mA difference between the active and neutral lines, and disconnect power within 10ms if it does so
    - A fault requires:
        - Current to flow
        - A single fault will turn off the circuit
    - Pros: Safe
    - Cons: Will shut off power to the device, which is bad for ECMO/CPB/ventilators without battery backup

- **Line Isolation Supply**, with a **line isolation monitor**
  A line isolated supply is a 'transformer' with an equal number of windings, such that the voltage produced is the same on each side. However, the **powerpoint is not physically connected to the supply**, creating an **earth-referenced floating supply**.
    - A fault requires:
        - **Two** faults
          This makes a failure with potential for shock much less likely.
            - Active wire must be connected to ground
            - Neutral wire must be connected to ground
            - A circuit then exists: active wire - ground - neutral wire, and a current could flow
    - A line isolated supply is paired with a line isolation monitor
      This monitor states how much current *could* flow, *if* a second fault completed the circuit.
        - This is called a **prospective hazard current**
        - The line isolation monitor continuously checks the hazard current by evaluating the impedance between the active wire and ground, and the neutral wire and ground
            - In a no-fault situation, both impedances should be the same and close to infinite
              (Impedance won't be absolutely infinite as there will always be a small current leak from devices).
            - In a single-fault situation, the calculated impedance for the affected line will be significantly lower, and therefore the prospective hazard current will increase
                - An alarm will sound when the prospective hazard current exceeds 20mA
    - Pros: A single fault is not dangerous and will not result in a power loss (important for vital equipment)

- Cons: Two or more faults are dangerous, and will still not result in a power loss

- **Equipotential earthing**
  This is the **only method which prevents microshock**.
  - Ultra-low resistance earth cables are attached to electrical devices and the patients bed
  - These cables are then attached to special wall earth connectors
  - This ensures all equipment is referenced to a common ground, minimising the risk of leakage currents between devices and the patient

Classification of Electrically Safe Equipment

These classifications are designed to limit macroshock:

- **Class I: Earthed**
  Any part that can contact the user is earthed to ground.
  - If a fault develops such that parts of the device that the user can touch are live, then there is a risk of shock
  - If the case is earthed, the path of least resistance should be via the earth wire
    This will cause a large current to flow, and should blow a fuse, ceasing current flow.
- **Class II: Double-insulated**
  All parts of the device that the user can touch have two layers of insulation around them, reducing the chance of the device becoming live.
- **Class III: Low-voltage**
  Device operates at less than 40V DC/24V AC, limiting the severity of shock a device can deliver.

Classification of Electrically Safe Areas

- **B areas**: Protection against macroshock
  - Residual Current Devices
  - Line Isolation Supply
- **BF areas**: Cardiac (microshock) protection
  - Equipotential Earthing
    All devices, and the patient, are earthed to each other by thick copper (i.e. low-resistance), such that any potential difference between devices will be equalised via the path of least resistance (the wire, not the patient).
- **Z areas**: No particular protections

Electrical Devices which Attach to Patients

Devices such as ECG and BIS require an electrical connection to the patient. Risk of electrocution by these devices is reduced by:

- High resistance wires

References

1. Electricity and Electrical Hazards.
2. Alfred Anaesthesia Primary Exam Tutorial Program
3. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

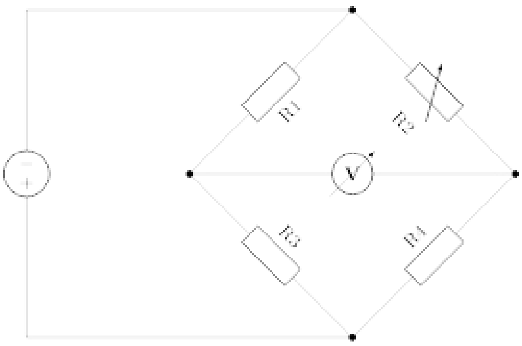
Last updated 2019-07-18

Wheatstone Bridge

The Wheatstone bridge is an electrical device used to accurately measure very small changes in electrical resistance. The Wheatstone bridge is:

- Used in many other medical devices (e.g. invasive pressure monitoring)
- A device with **infinite gain**
- A **null deflection galvanometer**
- **Not an amplifier**
  As it does not increase current amplitude.

Mechanism



The Wheatstone bridge consists of:

- Battery
- Four resistors
  - and R_3 are **known** and **fixed**
  - is **known** and **adjustable**
  - is **unknown**
- Galvanometer

The Wheatstone bridge relies on the ratio of resistances between the known ($\frac{R_2}{R_1}$) and unknown ($\frac{R_4}{R_3}$) legs:

- When $\frac{R_2}{R_1} = \frac{R_4}{R_3}$) equal current flows down either limb and there is **no current flow** across the galvanometer
  At this point the bridge is said to be balanced.
  - The equation can then be re-arranged to solve for R_4:
    $R_4 = \frac{R_2}{R_1} . R_3$
- Very small changes in R_4 lead to a current flow across the bridge
- R_2 can then be adjusted until the bridge is balanced, and the value of R_4 calculated

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References

1. Alfred Anaesthetic Department Primary Exam Tutorial Series

Last updated 2017-10-02

Neuromuscular Monitoring

> Describe the concept of depth of neuromuscular blockade and explain the use of neuromuscular monitoring

> Describe the clinical features ~~and management~~ of inadequate reversal of neuromuscular blockade

The degree of neuromuscular blockade can be assessed:

- Clinically
  Crude compared to electrical assessment. Tests include:
  - Sustained head lift > 5 seconds
    Suggests < 30% blockade.
  - $V_T > 10 ml.kg^{-1}$
  - Tongue protrusion
- Electrically
  Using a nerve stimulator. Can be:
  - Visual/tactile
    Monitoring of twitch height by anaesthetist.
  - Electrical
    Monitoring of twitch height by a device:
    - Accelerometer
      Acceleration is proportional to force for any given mass ($F = ma$), therefore an accelerometer taped to the thumb can be used to assess force of contraction.
    - Mechanical force transducers
      Muscle tension is measured using a strain gauge. Requires control prior to administration.
    - Electromyography
      EMG response is measured using electrodes over the muscle. The AUC of the response curve can be used to calculate degree of blockade.

Nerve Stimulator

A nerve stimulator:

- Consists of two electrodes, a power supply, and some buttons for control
- Produces a monophasic, **square wave** at **constant current**, lasting no more than **0.3ms**
- Generates a **supra-maximal stimulus**
  Ensures every nerve fibre is depolarised, which means a consistently reproducible response will be generated. A supra-maximal stimulus is 25% greater than the maximum required to depolarise all nerve fibres.
- Allows assessment of different muscle groups
  Not all muscle groups are affected equally by neuromuscular blockade.
  - Typically **smaller muscle** groups are **more sensitive**
  - The **positive** (red) lead is placed **proximal**
  - Ulnar nerve
    Electrodes are placed along the ulnar border of the wrist at the flexor crease, and thumb adduction is assessed.
  - Facial nerve
    The positive electrode is placed at the outer canthus, and the negative electrode is placed anterior to the tragus. Eyebrow twitching is assessed.
  - Posterior tibial nerve
    Electrodes are placed posterior to the medial malleolus, and plantar flexion is assessed.

Stimulation Patterns

There are five common stimulation patterns:

- **Train of Four**
  Four single twitches (0.1ms) delivered at 2Hz (i.e. 1.5s for all 4).
  - Number of observed twitches gives an indication of receptor occupancy
    With increasing blockade, the amplitude and number of observed twitches decreases.
    - **Fade** is the reduction of twitch height with repeated stimuli during a partial neuromuscular block
      Occurs due to the effect of non-depolarising agents on the *pre*synaptic membrane, reducing ACh production.
    - Number of observed twitches depends on the degree of blockade:
      - No twitches ≈ 100% blockade
      - One twitch ≈ 90% blockade
      - Two twitches ≈ 80% blockade
      - Three twitches ≈ 75% blockade
        Reversal agents should not be given with a ToF count < 3.
      - Four twitches ≈ < 75% blockade
  - The ratio of the amplitude of T_1 to T_4 (ToF ratio) can also be used as a measure of blockade:
    - ToF ratio > 90% is adequate for extubation
    - ToF ratio > 70% suggests adequate respiratory function
  - Should not be repeated faster than every 10s

- **Tetanic stimulation**
  High frequency (50-200Hz) supramaximal stimulus for 5 seconds.
  - Normal muscle will exhibit tetanic contraction
  - Partially paralysed muscle exhibits fade
    Degree of fade is proportional to degree of blockade, and is very sensitive.

- **Post-tetanic count** (PTC)
  Used in deep blockade when there is no response to ToF. A tetanic stimulus is given, followed 3s later by single twitches at 1Hz.
  - No response may be seen in very deep blockade
  - However, twitches may be seen prior to the return of a ToF response.
    This is called **post-tetanic facilitation**, and occurs due to the tetanic stimulus mobilising ACh vesicles into the pre-junctional area.
    - Typically, a ToF of 1 will occur when the PTC ≈ 9
  - Should not be repeated faster than every 6 minutes
    Due to residual post-tetanic potentiation.

- **Double burst**
  Two 0.2ms 50Hz (tetanic) stimuli are applied 750ms apart.
  - Two identical contractions occur in normal muscle
  - Amplitude of the second burst is reduced in partially paralysed muscle
    DB ratio is similar to the ToF ratio, but is easier to assess clinically.
  - A ratio > 0.9 is required for adequate reversal

- **Single twitch**
  A single stimulus lasting ~0.2ms is applied.
  - > 75% blockade causes a depressed response
  - A twitch must be assessed prior to blockade so a baseline can be established

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1. Leslie RA, Johnson EK, Goodwin APL. Dr Podcast Scripts for the Primary FRCA. Cambridge University Press. 2011.
2. Saenz, AD. Peripheral Nerve Stimulator - Train of Four Monitoring. 2015. Medscape.
3. McGrath CD, Hunter JM. Monitoring of neuromuscular block. Continuing Education in Anaesthesia Critical Care & Pain, Volume 6, Issue 1, 1 February 2006, Pages 7–12.

Last updated 2019-07-18

Pressure Transduction

> Describe the principles of measurement, limitations, and potential sources of error for pressure transducers, and their calibration

> Describe the invasive ~~and non-invasive measurement~~ of blood pressure ~~and cardiac output~~ including calibration, sources of errors and limitations

A **transducer** converts one form of energy to another. Pressure transducers converts a pressure signal to an electrical signal, and require several components:

- Catheter
- Tubing
- Stopcock
- Flush
- Transducer

This system must be calibrated in two ways:

- **Static calibration**
  Calibrates to a known zero.
- **Dynamic calibration**
  Accurate representation of changes in the system.

Static Calibration

Static calibration involves:

- Leveling the transducer (typically to the level of the phlebostatic axis at the right atrium, or the external auditory meatus)
  A change in transducer level will change the blood pressure due to the change in hydrostatic pressure (in cmH_2O).
- **Zeroing** the transducer
  - Opening the transducer to air
  - Zeroing the transducer on the monitor
    A change in measured pressure when the transducer is open to air is due to **drift**, an artifactual measurement error due to damage to the cable, transducer, or monitor.

Dynamic Calibration

Dynamic calibration ensures the operating characteristics of the system (or **dynamic response**) are accurate. Dynamic response is a function of:

- **Damping**
  How rapidly an oscillating system will come to rest.
  - Damping is quantified by the **damping coefficient** or **damping ratio**
    - Describes to what extent the magnitude of an oscillation falls with each successive oscillation
    - Calculated from the ratio of the amplitudes of successive oscillations in a convoluted fashion:
      $D = \sqrt{\frac{(\ln \frac{D_2}{D_1})^2}{\pi^2 + (\ln \frac{D_2}{D_1})^2}}$, where:

- **Resonant Frequency**
  How rapidly a system will oscillate when disturbed and left alone.
  - When damping is low, it will be close to the **natural frequency** (or undamped resonant frequency)

- Damping and natural frequency are used (rather than the physical characteristics) as they are both **easily measured** and **accurate** in describing the dynamic response
- These properties are actually determined by the systems elasticity, mass, and friction, but it is conceptually and mathematically easier to use damping and resonance

Pressure Waveforms and Dynamic Response

- The dynamic response required is dependent on the nature of the pressure wave to be measured
- Accurately reproducing an arterial waveform requires a system with a greater dynamic response compared to a venous waveform

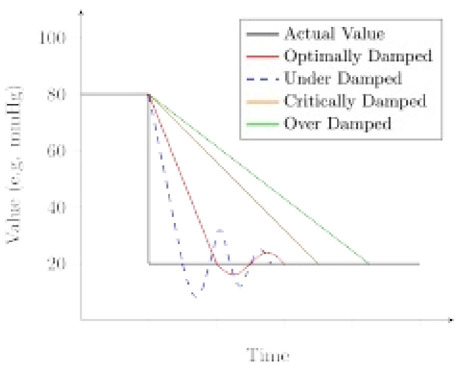
- An arterial pressure waveform is a periodic (repeating) complex wave, that can be represented mathematically by **Fourier analysis**
- Fourier analysis involves expressing a complex (arterial) wave as the sum of many simple sine waves of varying frequencies and amplitudes
  - The frequency of the arterial wave (i.e., the pulse rate) is known as the **fundamental frequency**
  - The sine waves used to reproduce it must have a frequency that is a *multiple* (or **harmonic**) of the fundamental frequency
    - Increasing the number of harmonics allows better reproduction of high-frequency components, such as a steep systolic upstroke
  - Accurate reproduction of an **arterial** waveform requires up to **10 harmonics** - or **10 times the pulse rate**
  - An arterial pressure transducer should therefore have a dynamic response of **30Hz**
    - This allows accurate reproduction of blood pressure in heart rates up to 180bpm (180 bpm = 3Hz, 3Hz x 10 = 30Hz)

Resonance

- If high frequency components of the pressure waveform approach the natural frequency of the system, then the system will resonate
- This results in a distorted output signal and a small **overshoot in systolic pressure**.

Damping

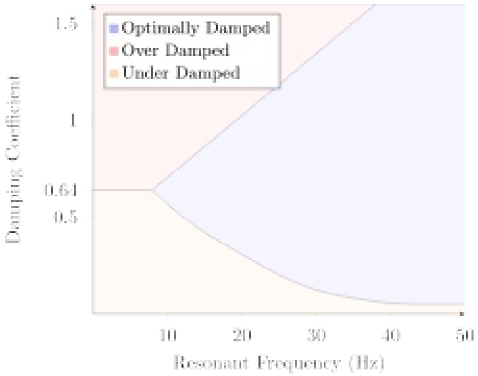
A pressure transduction system should be adequately damped:



- An **optimally** damped waveform has a damping of **0.64**. It demonstrates:
  - A rapid return to baseline following a **step-change**, with **one overshoot and one undershoot**
- A **critically damped** waveform has a damping coefficient of **1**. It demonstrates:

- The most rapid return to baseline possible following a step-change **without overshooting**
- An **over-damped** waveform has a damping coefficient of **>1**. It demonstrates:
  - A slow return to baseline following a step-change with no oscillations
  - Slurred upstroke
  - Absent dicrotic notch
  - Loss of fine detail
- An **under-damped** waveform has a damping coefficient close to 0 (e.g. **0.03**). It demonstrates:
  - A very rapid return to baseline following a step-change with several oscillations
  - Systolic pressure overshoot
  - Artifactual bumps

Optimally damped waveforms are accurate for the widest range of frequency responses:



Testing Dynamic Response

Dynamic response can be tested by inducing a **step-change** in the system, which allows calculation of both the natural frequency and the damping coefficient. Clinically, this is performed by doing a **fast-flush test**.

- Fast flush valve is opened during diastolic runoff period (minimises systemic interference)
- The pressure wave produced indicates the natural frequency and damping coefficient of the system:
  - The **distance between** successive oscillations should be identical and equal to the natural frequency of the system
  - The **ratio of amplitudes** of successive oscillations gives the damping coefficient

Optimising Dynamic Response

The lower the natural frequency of a monitoring system, the smaller the range of damping coefficients which can accurately reproduce a measured pressure wave. Therefore, the optimal dynamic response is seen when the natural frequency is as **high as possible**. This is achieved when the tubing is:

- Short
- Wide
- Stiff
- Free of air
  Introducing an air bubble will increase damping (generally good, since most systems are under-damped), however it will lower the natural frequency and is detrimental overall.

Footnotes

Fundamentals of Pressure Measurement

Pressure exerted by a static fluid is due to the weight of the fluid, and is a function of:

- Fluid density (in kg.L^{-1})
- Acceleration (effect of gravity, in m.s^{-2})
- Height of the fluid column

This can be derived as follows:

- $Pressure = \frac{Force}{Area} = \frac{Mass \times Acceleration}{Area}$
- $Density = \frac{Mass}{Volume}$, therefore $Mass = Volume \times Density$
- Combining the above equations:
  $Pressure = \frac{Density \times Volume \times Acceleration}{Area} = Density \times Length \times Acceleration$
  - This is usually expressed as: $Pressure = \rho . h . g$
- Note that this expression does not require the mass or volume of the liquid to be known
- This is why pressure is often measured in height-substance units (e.g. mmHg, cmH_2O)

References

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Last updated 2019-07-18

Pressure Waveform Analysis

> Describe the invasive and non-invasive measurement of ~~blood pressure and~~ cardiac output including calibration, sources of errors and limitations

Analysis of arterial pulse contour is:

- **Real-time** and **continuous**
- Used to **estimate** cardiac output
  Less accurate but also less invasive (e.g. thermodilution) or technically demanding (e.g. echocardiography) than other methods.
  - Therefore also calculate (and often display) stroke volume variation and pulse pressure variation

Principles

All models recognise that the **amplitude of the systolic upstroke** is:

- Directly proportional to **stroke volume**
- Inversely proportional to **arterial compliance**

Other principles used by some (but not all) devices include:

- **Three-element Windkessel model**
  Characterises the arterial tree as having three major features:
  - Aortic Impedance
  - Arterial Compliance
    Predicted using patient characteristics.
  - Systemic Vascular Resistance
- **Conservation of Mass**

Devices

Devices can be **classified based on** whether they are:

- Calibrated/Uncalibrated
  - **Calibrated**
    Initial estimation is refined using a dilution technique.
    - Dilutions may be by:
      - Thermodilution
        - Cold saline injected into SVC
          Using an IJV or SCV CVC.
        - Temperature changed measured at the femoral artery
      - Lithium dilution
        - Small amounts of lithium chloride injected into a central vein
        - Change in lithium concentration measured in radial artery
        - CO by calculated Stewart-Hamilton equation
    - Periodically recalibrated to correct for drift
  - **Uncalibrated**
    Not corrected for a measured 'true' cardiac output.
    - Inaccurate for short term changes in arterial properties

    - Not validated in:
        - Shock
        - ARDS
        - Hepatic surgery
          Due to changes in arterial tone.
        - Cardiac surgery
- Invasive/Non-invasive
  - Invasive
    Rely on a (usually femoral) arterial catheter.
  - Non-invasive
    Rely on the **volume clamp** method:
    - Inflatable cuff wrapped around finger
    - Plethysmograph estimates blood volume in the digital arteries
    - Cuff inflates and deflates throughout the cardiac cycle, keeping the volume of the arteries constant
      Arterial pressure is proportional to cuff pressure.
    - **Inaccurate** in:
      - Peripheral oedema
      - Vasoconstricted states

Common Devices in Use

- PiCCO/VolumeView/FloTrac
  - Calibrated
  - Invasive
  - 3-element Windkessel
  - Mechanism:
    - Calculates area under systolic part of the arterial curve
    - Divides calculated area by aortic compliance
      Compliance estimated by proprietary algorithm each time the device is calibrated.
  - SVR is continuously estimated from calculated CO and measured BP
- LiDCO
  - Calibrated
  - Invasive
  - Conservation of mass
  - Compliance inferred from biometric data
- Clearsight/CNAP
  - Uncalibrated
  - Non-invasive
- T-Line
  - Calibrated
    Proprietary, *non-validated* auto-calibrating algorithm.
  - Non-invasive
  - Uses radial applanation tonometry

References

1. Jozwiak M, Monnet X, Teboul J-L. Pressure Waveform Analysis. Anesth Analg. 2017.
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Last updated 2019-07-18

Non-Invasive Blood Pressure

> Describe the ~~invasive and~~ non-invasive measurement of blood pressure ~~and cardiac output~~ including calibration, sources of errors and limitations

Non-invasive blood pressure measurements is performed with either a:

- **D**evice for **I**ndirect **N**on-invasive **A**utomatic **M**ean **A**rterial **P**ressure (DINAMAP)
  Automatic blood pressure cuff.
- Von Recklinghausen's oscillotonometer
  "Manual" blood pressure cuff.
  - Uses two cuffs, and therefore two tubes

DINAMAP

Components:

- One cuff
  Performs both arterial occlusion and measurement.
- Tubing
- Device for inflating the occlusive cuff and gradually deflating it
- Pressure transducer
- Display

Method:

- Cuff is inflated above SBP
- Cuff deflates at a rate of 2-3mmHg.s^{-1}
  When cuff pressure equals:
  - SBP
    Turbulent flow occurs past the cuff, creating pressure oscillations. The pressure at which these are **first detected** is the **SBP**.
  - MAP
    The pressure at which **amplitude** of oscillations is maximal.
- DBP is calculated from MAP and SBP

Cons

- Requires an appropriately sized cuff
  Cuff should be ~20% greater than arm diameter.
  - Cuffs that are too small will over-read
  - Cuffs that are too wide will under-read
- Requires a regular rhythm
- Inaccurate at extremes of blood pressure
- Inaccurate when used more frequently than once per minute
- Inaccurate when the vessel is incompressible
  - Heavily calcified vessels
  - When applied to forearm/foreleg
- May cause neuropraxia

Von Recklinghausen's Oscillotonometer

Components:

- Two cuffs
  - Occlusive cuff
  - Measurement cuff
- Tubing
- Device for inflating the occlusive cuff and gradually deflating it
- Aneroid barometer for transducing pressure
- Display

Process:

- Cuff is inflated until the radial pressure is no longer palpable
  This is approximates SBP.
- Cuff is deflated, and re-inflated to 20mmHg above the estimated SBP
- Cuff is deflated at a rate of 2-3mmHg.s^{-1} whilst auscultating the brachial artery
  When cuff pressure equals:
  - SBP
    Turbulent flow occurs past the cuff, turbulent flow causes the first of the **Korotkoff sounds** (clear tapping pulsations) to be heard.
  - DBP
    The cuff no longer compresses the vessel at all, so no turbulent flow occurs and nothing is auscultated.

References

1. ANZCA July/August 2000
2. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.
3. Leslie RA, Johnson EK, Goodwin APL. Dr Podcast Scripts for the Primary FRCA. Cambridge University Press. 2011.

Last updated 2019-07-18

Cardiac Output Measurement

> Describe the invasive and non-invasive measurement of ~~blood pressure and~~ cardiac output including calibration, sources of errors and limitations
>
> Explain the derived values from common methods of measurement of cardiac output (i.e. measures of vascular resistance)

Cardiac output measurement can be performed:

- Invasively
  - Pulmonary Artery Catheter
    - Thermodilution
    - Fick Principle
  - TOE
  - Arterial waveform analysis
    - PiCCO
    - Vigileo
- Non-invasively
  - TTE
  - MRI
  - Thoracic impedance

Thermodilution

Thermodilution remains the gold standard of cardiac output measurement.

This technique:

- Requires a pulmonary artery catheter
  Various different designs exist. For CO measurement, they require:
  - A proximal port at the RA/SVC
  - A temperature probe at the tip
    Typically a silicon oxide thermistor.
  - A balloon at the tip
    To float it into position.
  - A distal (PA) port is required for measuring PAP and the PCWP, but is not required for CO calculation

Method for Intermittent Cardiac Output Measurement by Thermodilution

- A known volume of (typically dextrose) at a known temperature (classically cooled, but this is not required) is injected into the proximal port
- The temperature of blood is measured at the tip
  This produces a temperature-time curve.
- The area under the curve can be used to calculate cardiac output, as per the modified Stewart-Hamilton Equation:
  $Q = \frac{V(T_B - T_I)k_1k_2}{\int_{t_1}^{t_2} \Delta T dt}$, where:
  - = Cardiac output
  - = Volume of injectate
  - = Temperature of blood

- = Temperature of injectate
- = Density constant
  Relates to the specific heat and specific gravity of both injectate and blood.
- = Computation constant
  Accounts for catheter dead space and heat exchange during injection.
- = Area under the change in temperature-time curve

Errors in Thermodilution

- Natural variability
  Cardiac output varies up to 10% with changes in intrathoracic pressure during respiration. Therefore:
  - A mean of 3-5 measurements should be taken
  - Measurements should be taken at end-expiration
- Incorrect volume of injectate
  - Too much underestimates CO
  - Too little overestimates CO
- Warm fluid
  The closer the temperature of injectate is to blood, the greater degree of error introduced to the measurement.
  - Colder injectate is more accurate, but carries the risk of inducing bradyarrhythmias
- Poorly positioned PAC
  The PAC must be positioned in West's Zone 3 for blood flow to occur past the tip, and for the measured temperature to be accurate.
- Tricuspid regurgitation
  Results in retrograde ejection of injectate back past the valve.
- Arrhythmia

Fick Principle

Cardiac Output can also be measured using the Fick Principle. This technique:

- Uses the Fick Principle
  The flow of blood to an organ is equal to the uptake of a tracer substance divided by the arterio-venous concentration difference.
  - In this case, the tracer substance is oxygen
  - The 'organ' is the whole body
  - This produces the equation: $CO = \frac{VO_2}{C_a - C_v}$, where:
    - CO is Cardiac Output
    - VO_2 is the patients oxygen consumption
      Typically estimated as 3.5ml.kg^{-1}.min^{-1}
    - C_a is arterial oxygen content
    - C_v is mixed venous oxygen content
- Relies on mixed venous blood sampled from the pulmonary artery, and arterial blood sampled from a peripheral arterial line

References

1. Moise, S. F., Sinclair, C. J. and Scott, D. H. T. (2002), Pulmonary artery blood temperature and the measurement of cardiac output by thermodilution. Anaesthesia, 57: 562–566.
2. Nishikawa, T. & Dohi, S. Errors in the measurement of cardiac output by thermodilution. Can J Anaesth (1993) 40: 142.

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Pulse Oximetry

> Describe the principles of pulse and tissue oximetry, ~~co-oximetry and capnography,~~ including calibration, sources of errors and limitations

Pulse oximetry relies on several principles:

- Oxygenated and deoxygenated haemoglobin **absorb light of different wavelengths** to different extents
  Light of **660nm** and **940nm** is used.
  - Deoxyhaemoglobin has a greater absorbance of red (660nm) light than oxyhaemoglobin
  - Oxyhaemoglobin has a greater absorbance of infrared (940nm) light than deoxyhaemoglobin
  - The relative absorbance of each allows determination of the proportions of oxygenated and deoxygenated haemoglobin

- The **Beer-Lambert Law(s)**:
  Absorption of light passing through a substance is directly proportional to both the distance it travels through the substance and the concentration of attenuating species within the substance. It is a composite of:
  - **Beer's Law**
    Absorption of light is proportional to the concentration of "attenuating species"
  - **Lambert's Law**
    Absorption is proportional to the thickness of the solution, or more precisely, that each layer of equal thickness absorbs an equal proportion of radiation that passes through it

- **Blood flow is pulsatile**

Method

A pulse oximeter consists of:

- Two diodes of the desired wavelengths
- Photocell
- Microprocessor

- During pulsatile flow, the expansion and contraction of the blood vessels alters the distance and haemoglobin concentrations, changing the absorption spectra of blood (as per the Beer-Lambert Law).

- Non-pulsatile elements are due to tissues and venous blood

- These are subtracted from the total, leaving the pulsatile element which represents the arterial component
- The **ratio of absorbance** of the **pulsatile** elements and the **non-pulsatile elements** is called **R**, and is calculated as:
  $$R = \frac{Pulsatile_{660}/Non-Pulsatile_{660}}{Pulsatile_{940}/Non-Pulsatile_{940}}$$
  - R is compared with a set of standardised values to deliver a calculated SpO_2
    - An R of 1 gives an SpO_2 of 85%
    - An R of 0.4 gives an SpO_2 of 100%
    - An R of 2 gives an SpO_2 of 50%

The Isobestic Point

- The **isobestic point** is the wavelength at which light is absorbed equally by both haemoglobin species
- Light absorption is therefore **independent** of saturation, and is instead a function of **haemoglobin concentration**
- This can be used to correct for haemoglobin concentration
- There are two isobestic points for oxygenated and deoxygenated haemoglobin, at **590nm** and **805nm**

Limitations

- Requires detectable pulsatile flow
  - Limited by poor peripheral perfusion (shock, hypotension, hypothermia) and non-pulsatile flow (ECMO, CPB)
  - Body movements confound readings (shivering, seizing)
- Low saturations
  Inaccurate below 70%, and completely unreliable below 50%.
- Venous pulsation
  Detected as pulsatile flow, and erroneously interpreted by the microprocessor as arterial flow.
- Confounded by ambient light
  The diodes are cycled at several hundred times per second which allows the detector to compensate for the effect of ambient light (the values when the diodes are off give the effect of ambient light).
- Absorption spectra confounded by:
  - Haemoglobinopathies
    - Carboxyhaemoglobin causes the pulse oximeter to read artificially high due to as it also absorbs 660nm light
    - Methaemoglobinaemia causes the SpO_2 to trend towards 85%, as though it absorbs 660nm light is also absorbs 940nm light to a greater degree
  - Dyes
    - Methylene blue will cause the SpO_2 to read $< 65\%$ for several minutes
    - Indocyanine green will also cause a decreased SpO_2

References

1. Davis PD, Kenny D. Basic Physics and Measurement in Anaesthesia. 5th Ed. Elsevier. 2003.
2. Mardirossian G, Schneider RE. Limitations of Pulse Oximetry. Anesth Prog 39:194-196 1992.
3. CICM March/May 2014
4. Tremper KK, Barker SJ. Pulse oximetry. Anesthesiology. 1989 Jan;70(1):98-108.
5. Williams GW, Williams ES. Basic Anaesthesiology Examination Review. Oxford University Press. 2016.

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Oxygen Analysis

> Describe the principles of measuring oxygen concentration

As oxygen is a molecule containing two similar atoms, its partial pressure cannot be determined using infrared techniques (unlike CO_2). Oxygen content of a gas is instead determined using:

- Paramagnetic analyses
- Fuel Cells

Paramagnetic Analysis

Principles of paramagnetic analysis:

- Oxygen is paramagnetic
  This means it is attracted by magnetic fields, but does not propagate the field.
  - This is because its two unpaired valent electrons have the same spin.
- Many other gases weakly repelled by magnetic fields (diamagnetic)
- The attraction of a gas mixture to a magnetic field is therefore proportional to its oxygen content
- Many different methods exist which use this property to determine oxygen content

Pressure Method

- Gas tested flows into a tube
- A reference gas flows into a parallel tube
- Both gases then pass through:
  - Flow restrictors
  - Magnetic field
    This is being turned on and off at ~100Hz.
- The gases combine in the magnetic field
- The greater the oxygen content of the gas, the more it will move into the magnetic field
  This movement creates a negative pressure behind the gas.
- The pressure difference between the tested gas and the reference gas is proportional to the oxygen content of the test gas.

Temperature Method

Used in many modern devices.

- Gas flows through a magnetic field, causing the particles to align
  This changes the thermal conductivity of the oxygen molecules.
- The change in thermal conductivity of the gas mixture is proportional to the oxygen content
- This is detected by measuring current passing through a heated wire

Pros

- Accurate
- Rapid response time
  Modern analysers can identify breath-to-breath variation in FiO_2.
- Don't require regular calibration

Cons

- Water vapour reduces accuracy
- Interference from other paramagnetic gases
    - Nitric oxide
      Effect is minimal as nitric is delivered in far smaller volumes than oxygen, and is only weakly paramagnetic.

Fuel Cells

Fuel cells rely on reduction of oxygen to measure oxygen partial pressure. They consist of:

- Oxygen permeable membrane
- KOH solution
  This contains:
    - Lead anode
      Lead is consumed as the fuel cell operates.
    - Gold cathode

Method

- Oxygen diffuses across the membrane into the potassium hydroxide solution
- At the cathode:
  $O_2 + 4e^- + 2H_2O \rightarrow 4OH^-$
- At the anode:
  $Pb + 2OH^- \rightarrow PbO + H_2O + 2e^-$
- The oxygen consumption is proportional to the current generated, which is measured with an ammeter

Pros

- No power required
- Small
- Accurate

Cons

- Will accumulate nitrogen in the presence of N_2O
  Results in an under-reading of PO_2.
- Must be replaced after 6-12 months
- Requires regular two-point calibration
  21% and 100% oxygen are used.
- Relatively slow response time compared to paramagnetic analysers
  ~20s.

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

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End-Tidal Gas Analysis

> Describe the principles of ~~pulse and tissue oximetry, co-oximetry and~~ capnography, including calibration, sources of errors and limitations

Principles

Several mechanisms for E_TCO_2 measurement exist:

- Infrared Spectroscopy
- Colourimetric Methods
- Rayman Scattering
- Gas Chromatography

Infrared Spectroscopy

Infrared spectroscopy relies on the fact that:

- Gases with two or more different atoms will **absorb infrared radiation**
- **Different gases absorbing different wavelengths** to different degrees
- Measuring the absorbed wavelengths and comparing with the **likely composition** of a mixture, a system can be designed using a specific wavelength to measure gas concentrations and avoid interference

End-tidal gas analysis using infrared light is used in the measurement of:

- CO_2
  Capnography is the continuous measurement and graphical display of the partial pressure of CO_2 in expired gas. This is the most common method to measure E_TCO_2.
- Anaesthetic agents

Measurement of CO_2

Components:

- Sapphire sampling chamber containing gas sample
  - CO_2 absorbs infrared radiation at a peak wavelength of 4.28μm
  - The sapphire lens only allows 4.28μm light through
- Emitter
- Detector
- Microprocessor
- Display

Method:

- Light is emitted and passes through the sampling chamber
  A lens is used to focus emitted light.
- Levels of radiation are measured on the other side of the chamber
- Levels correspond to the amount of gas present in the sample
- The less radiation that reaches the detector, the more gas there is in the sample absorbing it

Equipment Errors

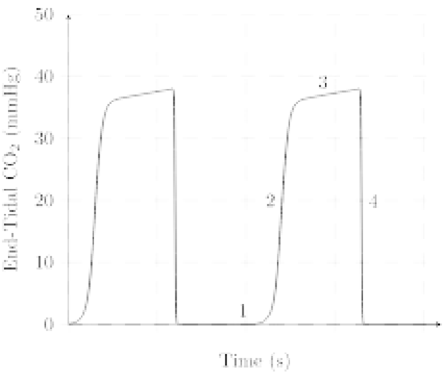
Errors can be classified into:

- Specific to technique
    - The **collision broadening effect**
      Intermolecular forces vary depending on their proximity to other molecules in the gas mixture. A change in intermolecular forces may alter their bond-energy and the frequencies at which they absorb radiation. It can be overcome by:
        - Correcting for the presence of other gases
        - Manually adjusting the obtained values
    - Crossover with other gas mixtures
      CO_2 and N_2O have similar absorbance spectra, and may lead to error when a device is not designed to measure both wavelengths.

- Failure of equipment
  These can be overcome by use of **double-beam capnometer**. This uses a reference chamber which contains CO_2-free air, and the same emitter-detector system. All absorption from this system must occur due to artifact (as no CO_2 is present). The artifactual component is then subtracted from the value detected in the main chamber. This corrects for:
    - Variable amount of infrared radiation released
    - Variable sensitivity of the detector
    - Variable efficacy of the crystal window and lens system

- Relating to type of capnometer used
  E_TCO_2 may be either **side-stream** or **in-line**.
    - Side-stream CO_2 involves a length of narrow tubing drawing gas from the expiratory limb of the breathing circuit (typically from the HME filter) to the capnograph
        - Side-stream requires a flow of 150 ml.min^{-1}
        - Has a (pretty insignificant) delay (<1s) in measurement
        - May be blocked by water vapour, and require use of a water trap to remove condensation
    - In-line systems have a sampling chamber attached in-line with the ETT
        - The sampling chamber slightly increases the dead-space of the circuit
          May be relevant in children or very difficult to ventilate patients.
        - Adds weight to patient end of the breathing circuit
        - Require heating to 41°C to avoid condensation

Normal E_TCO_2 Waveform

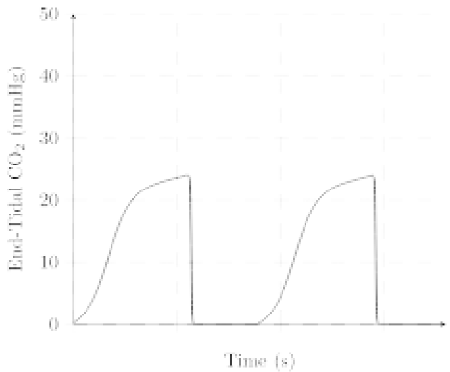


The normal trace consists of four components:

1. The **baseline**
   This consists of:
    - Inspiratory time

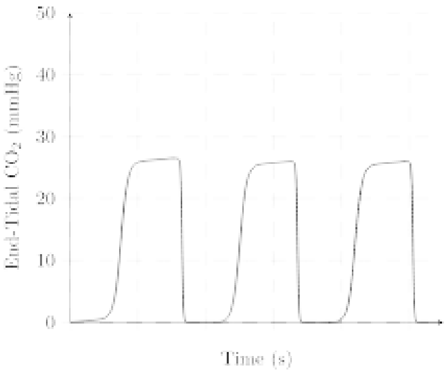
- Early **dead-space exhalation**
  This is the period immediately before phase 2, where some gas with a PCO_2 of **0** is exhaled.
2. **Alveolar exhalation**, where PCO_2 **rises rapidly**
3. **Alveolar plateau**, where PCO_2 **flattens**
   The highest-point of this curve is labeled E_TCO_2.
4. **Inspiration**, where PCO_2 returns to **0**

E_TCO_2 Waveform Variations



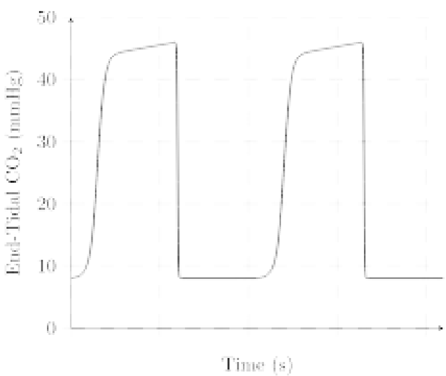
Airway obstruction:

- Occurs due to uneven emptying of alveoli with different time-constants



Hyperventilation:

- Lower E_TCO_2 with shorter baseline
- Plateau phase may not occur at very high respiratory rates



Rebreathing:

- Baseline increases as inspired CO_2 is measured from gas analyser

Changes in E_TCO_2

Normal E_TCO_2 is 32-42 mmHg, whilst normal $PaCO_2$ is 35-45 mmHg.

High E_TCO_2

This may be from:

- Decreased ventilation
    - Decreased RR
    - Decreased V_T
    - Increased V_D and therefore a greater V_D:V_T ratio
- Increased production of CO_2
    - Increased metabolic rate
        - Sepsis
    - Tourniquet release
    - ROSC following arrest
- Increased inspired
    - Rebreathing (i.e. equipment/ventilator malfunction)
    - External source of added CO_2

Low E_TCO_2

Rapid Loss of E_TCO_2

- Failure of ventilation
    - Circuit disconnect
    - Airway obstruction
    - Bronchospasm
- Failure of circulation
    - Cardiac arrest
    - Shock

Gradual Loss of E_TCO_2

- Increased V_A (i.e. increased MV)
- Decreased CO_2 production
    - Hypometabolic state
        - Hypothermia
- Increased V_D, i.e. V/Q mismatch
    - Increased West Zone I physiology:
        - Hypotension
        - Increased RV Afterload:
            - PE
            - High PEEP
- Sampling error
    - Air entrainment into the sample chamber
    - Inadequate V_T

Discrepancy between E_TCO_2, P_ACO_2, and $PaCO_2$

The normal gradient between $PaCO_2$ and E_TCO_2 is 0-5 mmHg. Healthy and awake individuals should have essentially no (<1ml) alveolar dead space, and so essentially no gradient. This gradient is increased in patients with:

- V/Q mismatch
    - E_TCO_2 will underestimate arterial CO_2 as gas from un-perfused alveoli (with negligible CO_2) will dilute CO_2 expired gas

Colourimetric Methods

Litmus paper which changes colour when exposed to hydrogen ions (produced by CO_2) can be used to confirm endo-tracheal intubation, though they may generate false-positive results due to gastric pH.

References

1. Cross ME, Plunkett EVE. Physics, Pharmacology, and Physiology for Anaesthetists: Key Concepts for the FRCA. 2nd Ed. Cambridge University Press. 2014.
2. Davis PD, Kenny D. Basic Physics and Measurement in Anaesthesia. 5th Ed. Elsevier. 2003.
3. Leslie RA, Johnson EK, Goodwin APL. Dr Podcast Scripts for the Primary FRCA. Cambridge University Press. 2011.

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Blood Gas Analysis

> Describe the methods of measurement of oxygen and carbon dioxide tension in blood and blood pH

Blood gas machines directly measure three variables and calculate the remainder. Measured variables are:

- PO_2
- CO_2
- pH

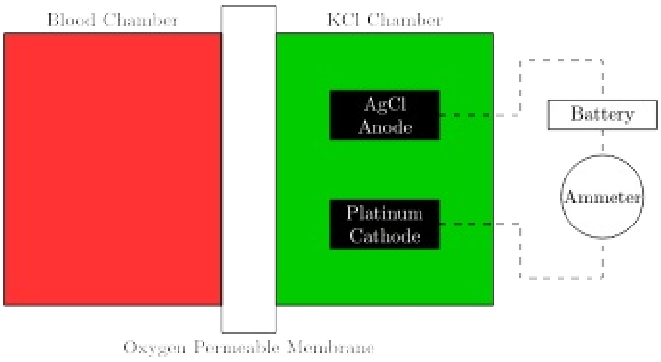
Calculated variables include:

- Bicarbonate
  Using the pH, CO_2 and the Henderson-Hasselbalch equation.
- Base Excess
  Calculated using the Henderson-Hasselbalch and Siggaard-Anderson equation. Can be expressed in two ways:
  - Base Excess
    The amount of alkali that must be added to the sample to return it to a normal pH, at a temperature of 37°C and a $PaCO_2$ of 40mmHg.
  - Standardised Base Excess
    As base excess, but calculated for blood with a Hb concentration of 50g.L^{-1}. This is thought to better represent the ECF as a whole.

Oxygen Tension

Oxygen tension is measured with a **Clarke electrode**. This consists of:

- A chamber for the blood sample
- A chamber containing a potassium chloride solution, which:
  - Is separated from the blood chamber by an oxygen-permeable membrane This prevents blood being in direct contact with the cathode, which would lead to protein deposition on the cathode and incorrect measurement.
  - Contains a platinum cathode
  - Contains a silver/silver Chloride anode
- A battery applying 0.6V across the electrodes



Method

- A voltage of **0.6V** is applied across the electrodes, causing the silver to reactive with chloride in the solution to produce electrons:
  $$Ag + Cl^- \Rightarrow AgCl + e^-$$

- This potential difference is required to start the reaction
- 0.6V is chosen because it is enough to start the reaction but will have minimal effect on measured current flow
- At the cathode, oxygen combines with electrons and water to produce hydroxyl ions:
  $O_2 + 4e^- + 2H_2O \Rightarrow 4OH^-$
- For each oxygen molecule present at the cathode, four electrons can be consumed
- Increasing the oxygen available at the cathode increases the number of electrons consumed, and therefore increases **current flow**
  - Oxygen will move from the sample chamber to the measuring chamber according to its partial pressure
- Measured current flow is therefore proportional to oxygen tension in blood

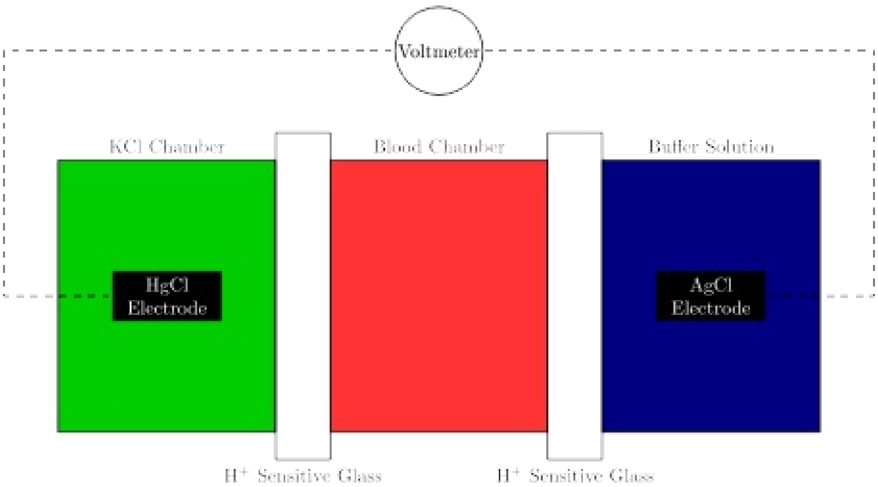
Calibration, Limitations, and Accuracy

- Calibration is performed with standard gas mixtures
  Requires regular two-point calibration.
- Cathode must be kept clean from protein and not damaged
- Cathode must be kept at 37°C
- May read falsely high with halothane

pH Measurement

pH is a measure of the hydrogen ion concentration[1] in solution, and is defined as the negative logarithm to the base 10 of the $[H^+]$:

- $pH = -log_{10}[H^+]$
- A pH of **7.4** is a $[H^+]$ of **40nmol.L^{-1}** at 37°C
  - A change in a pH unit of 1 is equivalent to a 10-fold change in the $[H^+]$
  - A change in pH of 0.3 is equal to doubling or halving the $[H^+]$



The pH electrode consists of:

- A chamber for the blood sample
- A measuring chamber, separated from the sample by H^+-permeable glass, which contains:
  - A buffer solution
  - A silver/silver chloride measuring electrode
- A reference chamber, also separated from the chamber by H^+-permeable glass, which contains:
  - A KCl solution
    Has no buffering properties.

- A mercury/mercury chloride reference electrode

Method

- Relies on the principle that two solutions with different H^+ activities will develop a potential difference between them (proportional to the concentration gradient)
- H^+ passes through the glass along a concentration gradient:
  - A variable potential difference is generated in the measuring chamber, as H^+ ions are buffered and the concentration gradient is maintained
  - A constant potential difference is generated in the reference chamber, as there is no buffer of H^+ ions in the KCl solution
- Once H^+ has equilibrated between blood and the KCl solution, the potential difference between the measuring and reference electrodes is proportional to the H^+ concentration in blood

Calibration, Limitations, and Accuracy

- Calibration is performed with two phosphate buffer solutions containing two different (known) $[H^+]$
- Must be kept at 37°C

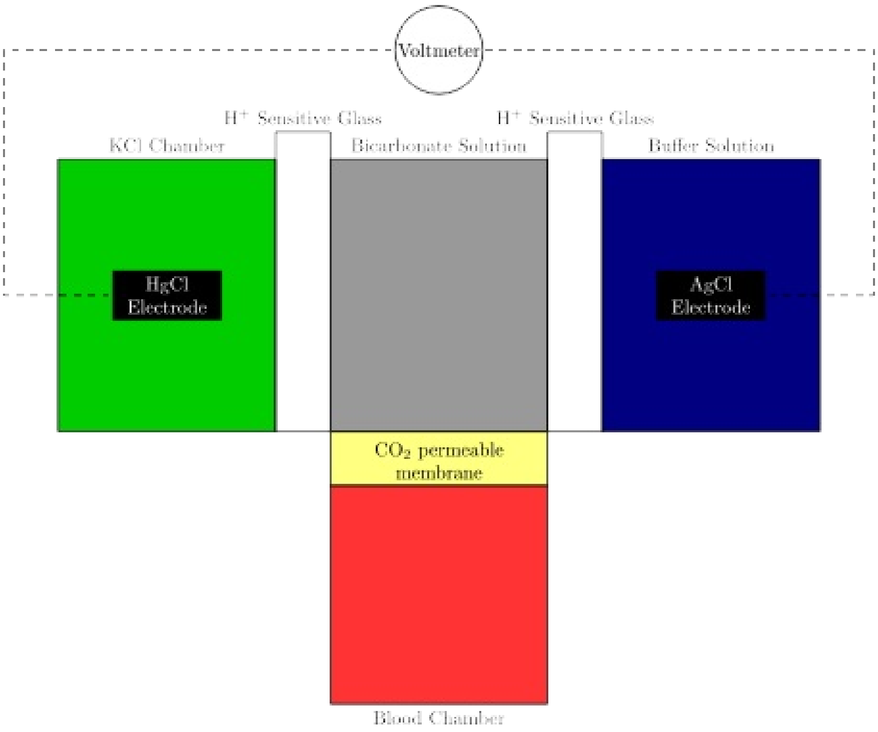
  Hypothermia increases solubility of CO_2 and therefore *lowers* $PaCO_2$

  A reduced partial pressure of CO_2 is required to keep the same number of molecules dissolved (as per Henry's Law)
  - Therefore, as blood cools its pH will increase
- Electrodes must be kept clean from protein and not damaged

Carbon Dioxide Tension

Carbon dioxide tension is measured with a **Severinghaus electrode**, which is based on the pH electrode, as PaCO2 is related to $[H^+]$. The Severinghaus electrode consists of:

- A chamber for the blood sample, separated from the bicarbonate chamber by a CO_2 permeable membrane
- A chamber containing bicarbonate solution in a nylon mesh, and separated from both the measuring and reference chambers by H^+-permeable glass
- A measuring chamber containing:
  - A buffer solution
  - A silver/silver chloride measuring electrode
- A reference chamber containing:
  - A KCl solution
  - A mercury/mercury chloride reference electrode



Method

- CO_2 diffuses from blood into the bicarbonate chamber
- CO_2 reacts with water in the bicarbonate chamber to produce H^+ ions
- From here, the process is identical to the pH electrode, except bicarbonate takes the place of blood:
  - H^+ ions diffuse into the reference chamber until the H^+ ion concentration has equilibrated
  - H^+ ions continually diffuse into the measuring chamber (as they are buffered)
    - This establishes a constant pH gradient
      This gradient is proportional the H^+ ion concentration in the bicarbonate chamber, which is proportional to the CO_2 content of blood.

Calibration, Limitations, and Accuracy

- Calibration is performed with solutions of known CO_2 concentration
- Must be kept at 37°C
  Hypothermia decreases solubility of CO_2 and therefore decreases pH
- Electrodes must be kept clean from protein and not damaged
- Slow response time relative to pH electrode due to time taken for CO_2 to diffuse and react
  This can be accelerated with carbonic anhydrase

Footnotes

> 1. Technically pH is defined as the **activity** of H^+ in a solution. Clinically, activity is identical to concentration, so in medicine these definitions are functionally the same. ↩

References

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2. (FRCA - Measurement of pO2, pCO2, pH, pulse oximetry and capnography)[http://www.frca.co.uk/article.aspx?articleid=100389]
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Last updated 2018-09-21

Gas Flow

> Describe the measurement of flow, pressure and volume of gases

Types of Flow:

- Laminar flow
  Fluid moving in a steady manner without turbulence.
- Turbulent flow
  Irregular fluid movement in radial, axial, and circumferential axes.
  - Laminar flow is more efficient than turbulent flow, as it requires a smaller pressure gradient to generate the same flow
  - For two fluids moving at the same speed, the velocity of individual particles in laminar flow will be both higher and lower
- Transitional flow
  Mixture of laminar and turbulent flow. Flow is typically turbulent in the centre, and laminar at the edges.

Devices used to measure gas flow include:

- Variable-Orifice Flowmeters
- Fixed-Orifice Flowmeters
  Pneumotachograph.
- Hot wire flowmeter

Note orifice based flowmeters rely on the **Hagan-Poiseuille Equation**:
$Q = \frac{\Delta P r^4 \pi}{8 \eta l}$

- Viscosity (η) and length (l) are fixed by both devices
- Fixed orifice flowmeters also fix radius (r), such that the change in pressure must therefore be proportional to flow:
  $Q = \Delta P \pi k$, where k is a constant
- Variable orifice flowmeters also fix pressure (ΔP), such that flow can be calculated from the radius:
  $Q = r^4 \pi k$

Flowmeters

Constant pressure, variable orifice flowmeters are found on wall and cylinder gases. They consist of:

- An inverse conical tube (i.e. narrower at the bottom, and wider at the top)
- A needle valve
- A bobbin
  May have a groove which causes the bobbin to spin, confirming it is not stuck.

Method:

- Gas flows from the bottom to the top of the tube
- The bobbin obstructs flow
  Therefore there is a **pressure difference** across it.
  - Remember: $Pressure = \frac{Force}{Area} = \frac{Mass \times Acceleration}{Area}$
  - **At equilibrium**, the pressure exerted by the bobbin on the flow of gas ($P = \frac{Gravity \times Bobbin\ Mass}{Bobbin\ Cross-Sectional\ Area}$)

is equal to the pressure exerted by the gas on the bobbin

- As flow is increased, the bobbin is pushed further up the flowmeter due to the increased pressure
- The bobbin will reach a new equilibrium position when the orifice of the flowmeter has become wide enough for the pressure on the bobbin to equal the pressure of gravity

- Flowmeters are calibrated for individual gases as:

    - Laminar (typically low flows) flow is proportional to viscosity
    - Turbulent (typically high flows) flow is proportional to density

Pros

- Cheap
- No additional power supply required
- Accurate
  Readings may be altered by:
    - Change in temperature affects viscosity and density of gas
    - Change in pressure affects density of gas

Cons

- Must be vertical
- Bobbins can become stuck

Pneumotachographs

Constant orifice, variable pressure flowmeter. Several different designs exist, and include:

- Fleisch pneumotachograph
    - Consists of several fine bore parallel tubes placed in the gas circuit
      Decreased radius and increased resistance reduces gas flow velocity, improving laminar flow.
    - A **differential pressure transducer** is placed at either end of the tubes
    - The pressure drop across the tubing is directly proportional to flow
- Pitot tubes
    - Consists of two tubes placed into the gas circuit:
        - One faces into the gas flow
        - The other faces away from the gas flow
    - The pressure difference between tubes is proportional to flow

Pros

- Accurate
- Continual measurement
- Allow calculation of volumes
  $Volume\ (L) = Flow\ (L.s^{-1}) \times Time\ (s)$

Cons

- Increased resistance
- Increased dead space
- Require laminar flow

Inaccurate when:
- Flows are higher than what the system is designed for
- Alteration in gas density
    - Change in gas mixture
- Alteration in gas temperature

Hot Wire Flowmeter

Components:

- Two fine platinum wires in the gas circuit
    - One heated to 180°C at $OL.min^{-1}$
    - One at 0°C
- Ammeter

Method:

- As gas flows, the wire cools
- Rate of heat dissipation is proportional to gas flow
- The amount of current required to return the wire to 180 is measured, and is proportional to flow

Pros

- Accurate
- Fast

Cons

- Fragile

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

Last updated 2019-07-18

Principles of Ultrasound

> Describe the physical principles of ultrasound and the Doppler Effect.

Ultrasound is an imaging technique where high-frequency sound waves (2-15MHz) are used to generate an image. An ultrasound wave is produced by a probe using the **piezoelectric effect**:

- Certain crystalline structures will vibrate at a particular frequency when a certain voltage is applied across them
  The conversion of electrical energy to kinetic energy is how the ultrasound probe creates an ultrasound wave.
- Similarly, they can generate a voltage when a vibration is induced in them
  This is how the probe interprets reflected waves.

Basic Principles

- **Spatial resolution**
  How close two separate objects can be to each other and still be distinguishable. It is divided into:
  - **Axial resolution**, how far apart two objects can be when one is above the other (in the direction of the beam)
  - **Lateral resolution**, how far apart two objects can be when side side-by-side
- Contrast resolution is how similar two objects can appear (in echogenic appearance) and still be distinguishable
- **Higher frequency** settings offer greater spatial resolution but decreased penetration
- **Lower frequency** settings offer reduced spatial resolution but increased penetration
  They are used for visualising deep structures.

Affect of Tissues on Ultrasound

At tissue interfaces, the wave may be:

- **Absorbed**
  Sound is lost as heat, and increases with decreased water content of tissues.
- **Reflected**
  Sound bounces back from the tissue interface, and returns to the probe.
  - Reflection is dependent on the:
    - **Difference in sound conduction** between the two tissues
    - **Angle of incidence** (close to 90° improves reflection)
    - **Smoothness** of the tissue plane
  - The amplitude of sound returning to the probe determines echogenicity, or how white the object will be displayed
  - The time taken for the sound to return determines depth
    - The time taken for a wave to return is proportional to **twice** the distance of the object from the probe
    - Depth can be calculated using $d = vt$, where:
      - d is Depth
      - v is the speed of sound in tissue, and is assumed to be 1540 ms^{-1}
      - **t** is Time
- **Transmitted**
  Sound passes through the tissue, and may be reflected or absorbed at deeper tissues.
- **Scattered**
  Sound is reflected from tissue but is not received by the probe.
- **Attenuated**

Attenuation describes the loss of sound wave with increasing depth, and is a function of the above factors.
- Attenuation is managed by increasing the **gain**
  Gain refers to amplification of returned signal.
- **Time-gain compensation** refers to amplification of signals which have taken longer to return, which amplifies signals returned from deep tissues

Modes

Ultrasound modes include:

- **B-Mode** (brightness mode)
  The standard 2D ultrasound mode, and plots the measured amplitude of reflected ultrasound waves by the calculated depth from which they were reflected.
- **M-Mode** (movement mode)
  Selects a single vertical section of the image and displays changes over time (i.e. depth on the y-axis, and time on the x-axis).

Doppler Effect

The doppler effect is the change in observed frequency when a wave is reflected off (or emitted from) a moving object, relative to the position of the receiver. In medical ultrasound, this is the change in frequency of sound reflected from a moving tissue (e.g. an erythrocyte). It is given by the equation:

$V = \frac{\Delta F s}{2F_0 cos\theta}$ where:

V = Velocity of object
F = Frequency shift
s = Speed of sound (in blood)
F_0 = Frequency of the emitted sound
θ = Angle between the sound wave and the object

Reflected frequencies are **higher towards the probe** and **lower away**.

Calculation of Cardiac Output

Remember, $CO = HR \times SV$.

- Heart rate is measured
- Stroke volume is calculated by:
  - Measuring the **cross-sectional area** of the **left ventricular outflow tract**
    Obtained by measuring the diameter using ultrasound.
  - Measuring the **stroke distance**
    Obtained via integrating the velocity-time waveform for time across the left ventricular outflow tract (LVOT VTI).
    - The integral of flow ($m.s^{-1}$ and time (s)) for time (s), produces a distance (m)
  - Multiplying the LVOT cross-sectional area (m^2) by the stroke distance (m), produces a volume (m^3)
    This is the stroke volume.

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1. Cross ME, Plunkett EVE. Physics, Pharmacology, and Physiology for Anaesthetists: Key Concepts for the FRCA. 2nd Ed. Cambridge University Press. 2014.
2. CICM July/September 2007.

Last updated 2019-07-18

Temperature and Humidity

> Describe the measurement of temperature and humidity

Temperature is the tendency of a body to transfer heat energy to another body, and is measured in degrees. It is distinct from **heat**, which is the kinetic energy content of a body, and is measured in Joules. The two are related by the **specific heat capacity**, which describes how much energy (J) must be applied to a body to raise its temperature from 14°C to 15°C, without a change in state.

Humidity may be either **absolute** or **relative**:

- **Absolute Humidity** is the mass of water vapour in a volume of air
- **Relative Humidity** measures the percentage saturation of air at *current temperature*, or more formally:
$$Relative\ Humidity = \frac{mass\ of\ water\ vapour\ in\ volume\ of\ air}{mass\ of\ water\ vapour\ if\ air\ was\ fully\ saturated} = \frac{absolute\ humidity}{mass\ of\ water\ if\ air\ was\ fully\ saturated}$$

Measurement of Temperature

Temperature is measured by a number of methods:

Liquid Expansion Thermometry

This is used in mercury thermometers. These consist of:

- A graduated **evacuated capillary** of negligible volume, attached to
- A mercury reservoir, of much greater volume, separated by
- A constriction ring
  Prevents travel of mercury up the capillary by gravity.

Mechanism:

- When heated, the kinetic energy of the mercury increases and it expands, forcing it up the capillary
  As the thermal expansion coefficient for all liquids is very small, the capillary must be of a very small volume to create a usable device.
- The speed that this occurs is related to the **time-constant** of the system
  This is typically 30 seconds. Measurement therefore takes ~4 time-constants, or 2 minutes.

Pros

- Easy to use
- Accurate
- Reusable
- Sterilisable
- Cheap

Cons

- Slow response
  Only accurate once it has reached thermal equilibrium.
- Glass can break
  May cause release of mercury or alcohol.
- Inaccurate at:

    - Low temperatures with mercury
      Freezes at -38.8°C.
    - High temperatures with alcohol
      Boils at 78.5°C.

Electrical

Electrical methods include:

- **Resistance thermometer**
  Platinum wire increases electrical resistance with increasing temperature.
    - Therefore the voltage drop across the wire will correspond to the temperature of the wire
    - Change in resistance is linear across the temperature range
    - However, these are expensive.
- **Thermistor**
  Metal (e.g. SiO_2) semiconductor which changes its resistance in a **predictably non-linear fashion** (run-away exponent) with temperature.
    - Can be manufactured so that change is linear over the clinical range
    - Much cheaper than wire resistance methods
    - The degree of voltage drop is usually very small, however this can be amplified using a **Wheatstone bridge**
- **Thermocouple**
  At the junction of two dissimilar metals, a potential difference will be produced proportional to their temperature. This is known as the Seebeck effect.
    - Non-linear (wash in exponent)
    - Degrade over time

Measurement of Humidity

Humidity can be measured by a number of methods:

- **Hair Hygrometer**
  Hair (actual hair) changes elasticity depending on the humidity of air. Changes in elasticity can be related to changes in humidity.

- **Wet and Dry Bulb**
  This system measures both temperature and relative humidity.

    - Two thermometers are used
        - One is wrapped in a wick, which is attached to a water reservoir
          This is the wet thermometer.
        - The dry thermometer gives a measurement of surrounding air temperature
    - The wet thermometer is cooled due to evaporative cooling from the wick
      High energy water molecules become vapour, leaving only low energy molecules behind.
    - The **temperature difference** between the thermometers is a function of:
        - Latent heat of vapourisation of water
        - How much evaporative cooling is occurring
          This is function of humidity.
            - At 100% relative humidity, no evaporative cooling will take place and the temperatures will be equal
            - As humidity decreases, evaporative cooling will cool the wet thermometer, and the temperature difference allows humidity to be determined

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.
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Last updated 2019-07-18

Electrocardiography

> Describe the principles behind the ECG

The ECG is a graphical representation of the electrical activity of the heart, as measured by the sum of electrical vectors at the patients skin.

Components

An ECG consists of:

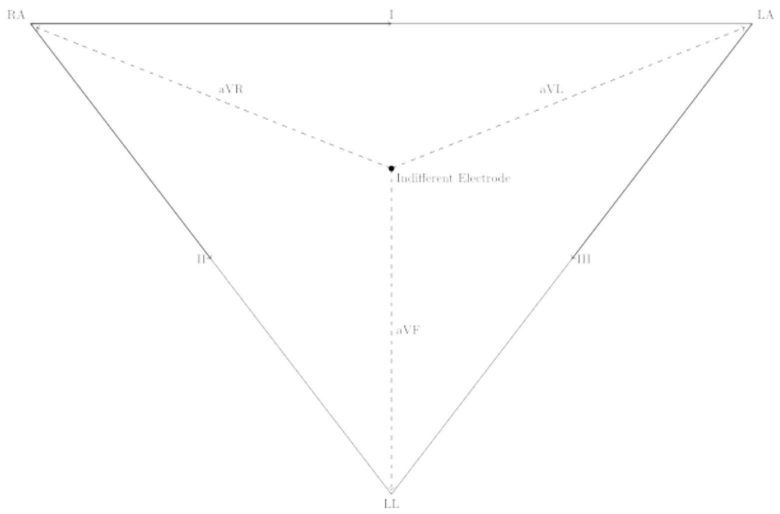
- Electrodes
  Disposable, sticky components which act as conductors due to a silver/silver chloride coating. To reduce electrode impedance, skin should be:
    - Hairless
    - Dry
    - Clean
- Cables
  Shielded to prevent currents being induced and electrocuting the patient.
- Processor
- Monitor

ECG Leads

ECG **leads** are created by taking the **potential difference** between two electrodes, which varies by **0.5-2mV** through the cardiac cycle as myocardium depolarises. ECG leads are divided into:

- Limb leads
  Potential difference between limb electrodes:
    - I: RA to LA
    - II: RA to LL
    - III: LA to LL
- Augmented leads
  Potential difference between the average of the limb leads (called the **indifferent electrode**) and each individual limb lead.
    - Augmented leads are of much lower voltage and must be amplified
    - Three augmented leads exist (one for each limb electrode)
- Precordial leads
  Potential difference between the indifferent electrode and one of the six additional electrodes placed on the chest wall.

The relationship between electrodes and leads is described with **Einthoven's Triangle**:



Method

- As the myocardial membrane potential changes across the cardiac cycle, a potential difference can be measured at the skin.
    - A depolarisation wave traveling towards the positive electrode (or a repolarisation wave traveling away) will cause an upward deflection in the ECG
- These potential differences are very small, and therefore need to be:
    - Distinguished from background interference
      Several techniques exist:
        - **Common mode rejection**
          Identical electrical activity occurring in multiple electrodes is likely due to interference rather than cardiac activity, and is removed from the measured signal.
            - A ground electrode is typically used for this purpose
        - ECG modes
          ECGs can be set to varying levels of sensitivity.
            - Diagnostic mode
              Responds to higher range of frequencies, but is at greater risk of interference.
            - Monitor mode
              ECG responds to a lower range of frequencies, reducing interference but also resolution. This is common on 3-lead ECG.
        - High input impedance
          Minimises signal loss.
    - Amplified
      Frequencies in the desired signal range are amplified.

Sources of Error

- Improve signal detection
    - Good adherence
    - Optimal skin contact
      Ensure dry and hairless.
- Minimise external electrostatic forces
    - Earthed
    - Diathermy
    - Shivering

Risks

- ECG electrodes can act as an exit electrode for surgical diathermy

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.
2. CICM February/April 2016

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Humidifiers

Humidifiers add water vapour to inspired gas, taking the place of normal body mechanisms which are bypassed or impeded by invasive and non-invasive ventilation. Maintaining adequate humidity of inspired gas is important in:

- Reducing metabolic load
  Humidification of inspired gas accounts for ~15% of basal heat expenditure.
- Maintaining function of the mucociliary elevator
  Inspiration of dry gas increases viscosity of mucous.
- Reducing water loss
  Water will be absorbed from mucosa to humidify gas.

Humidifiers can be classified into active or passive.

Passive Humidifiers

Passive humidifiers:

- Do not require power
- Do not require water

The Heat and Moisture Exchange (HME) filter is the classic passive humidifier:

- Placed between the patient and the patient Y-piece
- Consists of:
  - A moisture exchange layer
    Pleated, hygroscopically coated foam or paper.
    - Expired gas cools as it passes, condensing onto the foam, with condensation promoted by hygroscopic coating (usually this is NaCl)
    - The latent heat of vapourisation results in a decreased temperature of expired gas
  - A filter layer
    Typically a electrostatic or hydrophobic material.
- Expired gas is cooled and dried
- Inspired gas is then heated and humidified
- An HME takes up to 20 minutes to be fully effective, and can achieve a relative humidity up to 70%
- Efficacy depends upon the patient's core temperature and the condition of the airway

Pros

- Cheap
- Lightweight
- Straightforward
- May contain anti-bacterial filter

Cons

- May be blocked with vomit and secretions
- Increase airway resistance
- Increase dead space
- Not as effective as powered active systems
- Only last 24 hours

- Takes 15-20 minutes to become fully effective

Active Humidifiers

Active Humidifiers:

- Require either:
  - Power
    Unpowered humidifiers are typically less effective, and only operate well at lower flow rates.
  - Water
  - (Or both)
- Consist of:
  - A water bath
    Typically sterile water.
  - A heating element
    To heat the water bath.
  - A gas pipe
    Inspired gases are bubbled through the water bath to humidify them.
  - A water trap
    To trap condensed water. Should be changed regularly to minimise infection risk.

Pros

- Greater humidification
- Appropriate for long-term ventilation

Cons

- Bulky
- Expensive
- Require power
- Infection risk from water bath

References

1. McNulty G, Eyre L. Humidification in anaesthesia and critical care. Continuing Education in Anaesthesia Critical Care & Pain, Volume 15, Issue 3, 1 June 2015

Last updated 2019-07-18

Supplemental Oxygen

> Describe different systems to deliver supplemental oxygen and the advantages and disadvantages of these systems

Devices for delivery of oxygen can be classified into:

- Variable performance devices
- Fixed performance devices

Variable Performance Devices

Variable performance devices:

- Do not deliver a fixed FiO_2
    - This is because respiratory flow is non-uniform
      Although minute ventilation may be 5-6L.min^{-1}, peak inspiratory flows are substantially higher.
    - Delivered FiO_2 is dependent on oxygen flow and inspiratory flow
        - Increasing oxygen flow rate will increase FiO_2, but the effect will vary depending on the device (volume, seal) and the patient
- Include:
    - Nasal Cannulae
      Prongs delivering gas at 1-4L.min^{-1}.
        - Higher flows may dry mucosa, and lead to epistaxis
        - Nasopharynx acts as an oxygen reservoir, somewhat increasing FiO_2
        - Well tolerated
            - Allow eating, drinking, and talking
    - Hudson Mask
      Simple unsealed mask, allowing gas flow up to 15L.min^{-1}.
        - Cheap
        - Less well tolerated
        - Rebreathing may occur
    - Non-Rebreather Mask
      Modified version of the Hudson mask, containing a reservoir bag.
        - Reservoir bag is filled during expiration
        - Gas is drawn from the reservoir bag during inspiration, increasing FiO_2
          Some air is entrained from around the mask and so FiO_2 is < 1.

Fixed Performance Devices

Fixed performance devices:

- Theoretically deliver a fixed FiO_2
  These are usually flow limited as well, and so FiO_2 may decrease at higher inspiratory flows.
- Include:
    - Venturi
      Consists of a cone through which oxygen flows. Apertures on the side of the cone entrain room air.
        - Air is entrained via:
            - Frictional drag of molecules
            - The venturi effect (though this is controversial)

The widening of the cone leads to an increase in fluid velocity and therefore a decrease in pressure, as per the Bernoulli principle.

- Entrained air is proportional to flow rate, so the ratio of oxygen to air is constant for any given aperture size
  This is known as the **entrainment ratio**.
- Will deliver the specified FiO_2 provided oxygen flow is above the minimum rate
  Therefore become variable performance devices when inspiratory flow greatly exceeds oxygen flow.

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

Last updated 2019-07-18

Bispectral Index

> Describe the principles behind the BIS

Bispectral Index (BIS) is a proprietary signal-processed EMG and EEG monitor used to estimate depth of anaesthesia.

The BIS outputs four values:

- BIS
  Dimensionless index between 0 and 100 where:
  - 0 represents cortical electrical silence
  - 85-100 represents normal awake cortical activity
  - 40-60 is consistent with general anaesthesia
- Signal Quality Index (SQI)
  Dimensionless index between 0 and 100 which gives an indication of the accuracy of the BIS value.
- Electromyography
  Gives an indication of the influence of muscle activity on BIS values.
- Suppression Ratio (SR)
  Percentage of previous 63 seconds where EEG is isoelectric.

Method

Proprietary, but involves:

- Multivariate logistic regression of EEG features that correlate with clinical levels of sedation
- Initial validation on a cohort of healthy volunteers, not undergoing surgery
- Use of four frontotemporal EEG monitors

Analytic techniques:

- **Compressed Spectral Array**
  - The signal over a short period (e.g. 5-10 seconds) of EEG recordings are analysed together
    Each period is known as an epoch.
  - A Fourier transformation is performed
    This breaks the EEG signal down into the sine waves used to produce it.
  - A histogram of each frequency is plotted
  - As anaesthesia deepens, lower frequencies begin to dominate
  - The **spectral edge frequency** is the frequency greater than 95% of the frequencies in the compressed spectral array
    It is an indicator of anaesthetic depth, but not of drug concentration.
- **Coherence**
  Under anaesthesia, the electrical activity in different sections of the brain falls out of phase.

Pros

- Reduced anaesthetic awareness in high risk patient groups
  Trauma, GA caesarian section, cardiac surgery.
- Non-invasive
- Use appears to result in reduced anaesthetic use and more rapid emergence

Cons

- Proprietary algorithm
- Expensive
- May be inaccurate with:
    - Hypothermia
    - Hypercarbia
    - Hypoxia
    - Muscle relaxants
      BIS may fall inappropriately.
    - Non-GABAergic agents (e.g. ketamine, nitrous oxide)
      May not fall appropriately.

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

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Medical Gas Supply

> Describe the supply of medical gases (bulk supply and cylinder) and features to ensure supply safety including pressure valves and regulators and connection systems

Production

Fractional Distillation

Oxygen is produced on the industrial scale by fractional distillation of atmospheric air. This process:

- Relies on the fact that **different gases** have **different boiling points**
  By liquefying air and then heating it gradually, each gas can be removed separately as it boils.
- Occurs in stages:
  - Atmospheric air is filtered
    Removes dust and other contaminants.
  - Air is **compressed** to **6 atm** and **then cooled** to below ambient temperature
    Water vapour condenses and is removed.
  - Compressed air passed through a **zeolite sieve** which removes CO_2
  - Compressed air is allowed to re-expand
    As it does so it loses heat energy as per **Gay-Lussac's Law**, and liquefies.
    - Air must be cooled below the boiling point of the desired gases
      This requires getting gases very cold, and so the process may be mechanically assisted using a turbine, and/or a heat exchanger. Key boiling points (at 1 atm):
      - Nitrogen: 77°K
      - Oxygen: 90°K
      - Helium: 4°K
        Helium *can* be produced by fractional distillation, but liquefying it is understandably difficult given the very, very low boiling point. Helium can also be mined, as helium produced by alpha decay of radioactive materials may be trapped in gas pockets under the earth.
  - Liquid air is then **fractionally distilled**
    Temperature of liquid air is raised slowly.
    - As the boiling point of each gas is reached (e.g. 77°K for nitrogen), that gas will begin to vapourise from the liquid, and can be collected
    - The remaining liquid can then be further heated, until the boiling point for the next gas is reached
    - This process can be repeated until all the desired gases have been separated

Oxygen Concentrator

Oxygen concentrators:

- Produce up to 95% oxygen from air by removing nitrogen
- Built using two **zeolite lattices**
  - Pressurised air is filtered through one lattice
    - Nitrogen and water vapour are retained in the lattice
    - Oxygen and **argon** are concentrated
      Produces a 95% oxygen/5% argon mixture.
  - The unused column is heated to release the bound nitrogen and water

Pros

- Cheap
- Reliable
- Avoid need for oxygen delivery

Cons

- Result in an accumulation of argon when used at low flows on a circle system
- Require continuous power
- Fire and explosion risk

Storage

Medical Gas Cylinders

Gas cylinders are:

- Made from chromium molybdenum or aluminium
- Used as:
  - Backup for a piped supply
  - When a piped supply is not available (transports)
  - When the gas is uncommonly used (e.g. nitric oxide)
- The common cylinder used in hospital is **CD**
  This contains **460 L** of oxygen at 15°C and 137 bar.
- Cylinders are not completely filled, to reduce risk of overpressure and explosions if the temperature rises
  - The **filling ratio** is the weight of liquid in a full cylinder compared to the weight of water that would completely fill the cylinder
    - In cool climates, the filling ratio is ~0.75
    - In warmer climates, the filling ratio is reduced to ~0.67
- Cylinders are tested for safety every 5-10 years
  Tests include:
  - Endoscopic examination
  - Tensile tests
    1% of cylinders are destroyed to perform testing on the metal.

Pros

- Portable
- Reusable

Cons

- Heavy
- Limited supply

Cylinder Manifolds

Cylinder manifolds are formed of sets of large gas cylinders used in parallel.

- All cylinders in a group are used together

- When the pressure falls below a set level, a pressure valve will switch and gas will be drawn from another cylinder group
- The first (now empty) cylinder group is exchanged for full cylinders

Pros

- Cheap
- Useful as a backup supply

Cons

- Less capacity than a VIE
- Fire and explosion risk

Vacuum Insulated Evaporator

The VIE:

- Stores **liquid oxygen**
  It is **vacuum insulated** as it must keep oxygen below its critical temperature (-119°C). The VIE typically stores oxygen between -160°C and -180°C, and at 700kPa.
  - The gas is stored below its critical temperature and above its boiling point
  - The amount of oxygen remaining is calculated from its mass
- Does not require active cooling
  Instead it is cooled by:
  - Insulation
  - Evaporation
    Heat entering the VIE causes liquid oxygen to evaporate. Oxygen vapour is drawn off the VIE to the pipeline supply, so the VIE remains cool and at a steady pressure provided oxygen is being drawn from it.
- Has a pressure relief valve to prevent explosions if oxygen is not being used
- Has an evaporator to evaporate large volumes of oxygen rapidly if demand is high
  - This is simply an uninsulated pipe exposed to the outside temperature

Pros

- Cheapest option for oxygen delivery and storage
  - Storing oxygen as a liquid is much more efficient than as a gas
  - Does not require power

Cons

- Set-up costs are expensive
- Requires a back-up setup
- Will waste large volumes of oxygen if not being used continuously
- Fire and explosion risk

Safety in Medical Gas Supply

Many systems exist to ensure safety:

- Colour coding of cylinders and hoses
  - Oxygen is white
  - Nitrogen is black

        - Air is black with white shoulders
    - Nitrous oxide is blue
    - Helium is brown
        - Heliox is brown with white shoulders
    - Carbon dioxide is grey-green
- Labeling of connections
- The **pin index system**
  Used to prevent the wrong gas yoke being connected to a cylinder.
    - Pins protrude from the back of the yoke
    - Holes exist on the valve block
    - Pins and holes must line up for the cylinder to be connected
    - There are six positions, divided into two groups of three
      Common combinations include:
        - Oxygen: 2-5
        - Air: 1-5
        - Nitrous oxide: 3-5
- **Sleeve Index System**
  Used in Australia when connecting pipeline gases.
    - Wall block contains a sleeve when prevents fitting the incorrect gas hose to the wall
    - Screw thread is identical in all cases
- **Non-Interchangeable Screw Thread** (NIST)
  Used (but not in Australia) when connecting pipeline gases.
    - NIST connectors have a probe and a nut
    - Probe diameter is gas-specific, preventing the wrong gas from being connected

- **Testing**
    - Must demonstrate
        - Correct oxygen concentrations
        - Absence of contamination
        - Delivery of adequate pressure when several other systems on the same pipeline are in use
    - Testing must be performed twice on a new installation:
        - First by engineers
        - Second by a medical officer
          In theatres, this should be the director of the anaesthetic department or their delegate, who should hold fellowship of ANZCA.

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.
2. ANZCA August/September 2016
3. The Essential Chemical Industry Online - Oxygen, Nitrogen, and the rare gases.
4. Thompson, C. The Anaesthetic Machine - Gas Supplies. University of Sydney.

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Vapourisers

> Describe the principles and safe operation of vapourisers

Delivery of gas that is fully saturated with anaesthetic agent would result in lethal doses being administered. The use of a vapouriser allows a safe dose of anaesthetic agent to be given. Vapourisers can be divided into:

- Variable bypass vapourisers
  Air that is fully saturated with gas is mixed with a 'bypass' stream of gas, diluting the delivered concentration. Further subdivided into:
    - Plenum
      Requires supra-atmospheric pressure to operate.
        - More accurate
    - Draw-over
      Driven by the patients inspiratory effort.
        - Portable

Variable Bypass Vapouriser

Variable bypass vapourisers aim to deliver the same concentration of anaesthetic agent over a range of flows. They achieve this by:

- Flow management
    - Baffles and wicks increase the surface area of the liquid/gas interface, increasing the rate of vapourisation.
        - Excessively high flow rates may result in gas not being fully saturated with agent when it exits the vapouriser stream
        - These are less effective in draw-over vapourisers, as resistance must be minimised
- Temperature management
  The SVP of volatile agents increases non-linearly as temperature increases. Temperature changes:
    - Occur through:
        - Changes in ambient temperature
        - Loss through latent heat of vapourisation
          Liquid agent from the vapouriser will cool over the course of an anaesthetic.
    - Are managed with:
        - Temperature stabilisation
          Use of materials with both a high thermal conductivity and specific heat capacity, allowing the vapourising chamber to buffer changes in surrounding temperature.
        - Temperature compensation
          Adjusts flow into either the vapourising chamber or bypass chamber to account for changes in environmental temperature. Methods include:
            - Bimetallic strip
              Metal strip which bends in response to environmental temperature, adjusting the amount of gas entering the vapourising chamber.
            - Aneroid bellows
              Connect to a cone in the opening of the bypass chamber. As temperature decreases, the bellows contract and the cone partially obstructs the bypass channel.

Difference Between Plenum and Draw-Over Vapourisers

Plenum vapourisers are:

- More accurate
  Designed to deliver accurate agent concentrations over a wide range (0.25-15L.min^{-1}) of flow rates
  - Below 250ml.min^{-1} the resistance of the flow splitting valve becomes more significant, causing the amount of gas in the bypass stream to be higher than intended
  - Above 15L.min^{-1} gas may not be fully saturated
- Heavier
  Typically built of metals such as copper to maximise thermal stability.
- High internal resistance
  - Must be used out-of-circle
  - Must be used with positive-pressure

Draw-Over Vapourisers are:

- Less accurate
  - Less use of baffles and wicks to minimise inspiratory resistance
- Less thermally stable
  - Oxford Minature Vapouriser does not have a bimetallic strip
  - Oxford Minature Vapouriser uses glycol as a thermal buffer

Measured Flow Vapourisers

Measured flow vapourisers have a separate stream of agent-saturated gas that is added to the gas flow. This requires the device to:

- Measure fresh gas flow rate
- Adjust vapour-gas flow rate so the desired concentration is delivered

This system is used for the delivery of desflurane, as desflurane:

- Has a very high SVP
  Requires high bypass flow rate to dilute to a clinically useful concentration.
- Has a low boiling point
  Intermittently boils at room temperature, which will cause large fluctuations in delivery:
  - Excessive agent delivery during boiling
    This will lead to cooling due to the latent heat of vapourisation.
  - Cooled desflurane will have a much lower saturated vapour pressure
    Significant under-delivery will then occur.

The Tec6 vapouriser:

- Heats desflurane to 39°C
  SVP of desflurane at this temperature is 1500mmHg.
- Gaseous desflurane is then added to the fresh gas flow
  The amount added depends on:
  - Desired concentration
  - Fresh gas flow rate
    As flow increases the resistance to flow of desflurane vapour decreases.

General Safety Features of Vapourisers

Agent specificity:

- Key indexed filling
- Pin indexed safety system connectors

- Colour coding of unit and agent containers

Single agent administration:

- Interlock mechanism
  Prevents multiple vapourisers being turned on.
- Single cartridge slot (Aladdin system)

Tipping and overfilling:

- Long vapourisation chamber inflow
- Heavy construction
- Transport modes
- Side filling and overflow ports

Anti-pumping:

- Check valves and long vapourisation chamber inflow prevent entrainment of vapouriser gas in the inflow of the bypass channel

Agent depletion:

- Filling gauges
- Low pressure alarms (Tec 6)

Other Factors Affecting Vapourisers

Carrier Gas Composition:

- Nitrous oxide and air are more viscous than oxygen
- This leads to decreased flow through the vapourising chamber when FiO_2 is low
  This effect is not clinically significant.

Altitude:

- Clinical effect of volatile agent is a function of their partial pressure in tissues
- As SVP is independent of atmospheric pressure, this is unchanged at altitude
- A vapouriser set at 2% will deliver 4% gas at 0.5atm pressure, however as the atmospheric pressure is reduced the same partial pressure of vapour is delivered

- The delivered concentration of an agent at altitude is given by the equation:
  $Delivered\ Concentration\ (\%) = Intended\ Concentration \times \frac{P_{cal}}{P_{alt}}$, where:

- $Actual\ Delivered\ Concentration$ is the concentration of agent in the gas delivered to the patient
  This must be multiplied by the atmospheric pressure to find the partial pressure of agent delivered to the patient.
- $Intended\ Concentration$ is the concentration dialed up on the vapouriser
- P_{cal} is the atmospheric pressure where the vapouriser was calibrated
- P_{alt} is the atmospheric pressure where the vapouriser is being used

References

1. Miller RD, Eriksson LI, Fleisher LA, Weiner-Kronish JP, Cohen NH, Young WL. Miller's Anaesthesia. 8th Ed (Revised).

Elsevier Health Sciences.
2. Boumphrey S, Marshall N. Understanding vapourizers. Continuing Education in Anaesthesia Critical Care & Pain. Volume 11, Issue 6, 1 December 2011, Pages 199–203,

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Breathing Systems

This provides a general overview of anaesthetic breathing systems. The circle system in particular is covered elsewhere.

Classifications:

- Open
  Anaesthetic gases not confined to the circuit.
  - Limited current practical application
    Expensive, environmental contamination.
  - e.g. Ether masks
- Non-rebreathing
  No expired gas is re-inspired; requires a one-way valve.
  - Limited practical application
  - Requires a low-resistance draw-over vapouriser
  - e.g. Tri-service apparatus
    - Robust
    - Inexpensive
- Rebreathing systems
  Expired gas is re-inspired.
  - Absorption systems
    Requires method for CO_2 absorption.
    - Circle
      Common anaesthetic circuit, covered in detail under. Can be:
      - Vapouriser Out-of-Circuit
        Common system, covered in detail under circle system.
        - $$[Alv_{agent}] \propto \frac{FGF}{MV}$$
      - Vapouriser in-circuit
        Uncommon system.
        - $$[Alv_{agent}] \propto \frac{MV}{FGF}$$
        - In a spontaneous ventilation mode, the patient will increase agent concentration as minute ventilation ↑
          This means that as surgical stimulus ↑, depth of anaesthesia also ↑.
    - Waters
      Mapleson B or C with a CO_2 absorption canister between bag and FGF.
  - Non-absorption Rebreathing expired gas is part of circuit design.
    - Mapleson Systems

Mapleson System

Properties:

- Rebreathing of expired gas **does not necessarily equate to CO_2 retention**, provided the FGF is above a certain multiple (circuit dependent) of the patients MV
  - $PaCO_2$ is a function of FGF and CO_2 production **only**
    Increasing MV without increasing FGF will result in re-breathing of CO_2 and unchanged $PaCO_2$.
- In any spontaneous ventilation mode, patients will hyperventilate if FGF is inadequate

Types:

- Mapleson A
  - Setup
    - APL valve close to mask
    - Tubing between bag and mask
    - FGF close to bag
  - Flow requirements
    - Spontaneous ventilation: $0.7 \times MV$
      APL valve is set low. Initial exhalation (which is mostly **dead space**, and not containing CO_2) will fill bag until bag pressure exceeds APL valve opening pressure. Provided the APL valve is set *low*, the majority of CO_2 containing exhalation will exit through the APL valve, and FGF required to clear CO_2 from the circuit is low.
    - Controlled ventilation: $> 3 \times MV$
      APL valve is set high. More of the exhalation will fill the bag, and so a greater FGF is required to prevent re-breathing.
- Mapleson B & C
  - Setup
    APL valve and FGF are situated close to the mask.
    - Mapleson B has long tubing between the mask and bag
    - Mapleson C has short tubing between the mask and bag
  - Flow requirements
    Spontaneous and controlled ventilation are similar, at $3 \times MV$.
- Mapleson D
  - Setup
    - FGF is is close to mask
    - Valve is close to bag
    - Tubing between FGF and APL valve
      Co-axial versions exist, but are functionally similar.
  - Flow requirements
    Overall, generally the best circuit to maximise efficiency across both spontaneous and controlled ventilation.
    - Spontaneous ventilation: $2 \times MV$
    - Controlled ventilation: $0.8 - 1 \times MV$
      Best circuit for controlled ventilation.
- Mapleson E/Ayre's T-piece
  - Setup
    - T-shaped circuit with no valve or bag
- Mapleson F/Jackson-Rees modification to the Ayre's T-piece
  - Setup
    - Bag (with hole) added to the stem of the T of a Mapleson E
      Allows monitoring of ventilation, and occluding the hole of the bag allows controlled ventilation.
    - Functionally identical to a Mapleson D, with an operator-controlled APL valve
  - Flow requirements
    As per Mapleson D.
    - Spontaneous ventilation: $2 \times MV$
    - Controlled ventilation: $0.8 - 1 \times MV$

References

1. Westhorpe, R. Paediatric Breathing Systems. RCH Anaesthetic Tutorial Program. 2019.

Last updated 2019-07-20

Circle System

This covers the circle breathing system. A general overview of anaesthetic breathing systems is covered under anaesthetic circuits.

The circle breathing system is a highly efficient system which:

- Has several key advantages
  - Preserves anaesthetic gases making volatile anaesthesia cost-effective
  - Preserves medical gases (oxygen) which is useful in resource-limited settings (e.g. prehospital)
  - Preserves heat and moisture
  - Reduces fire risk
    Particularly with older agents.
- Requires **re-breathing** of expired gases
  CO_2 is actively removed.
- Is a closed-circuit system
  - The only gases which must be replaced are those:
    - Consumed by the patient
      - Oxygen
      - Absorbed and metabolised volatile agents
    - Lost via leak

Principles

A circle circuit consists of:

- A Y-piece, connecting the circuit to the patient
- Expiratory and inspiratory valves, ensuring unidirectional flow
- A means of generating pressure
  In most systems this consists of both a ventilator and a reservoir bag with APL valve attached, with a bag/vent switch to swap between circuits.
  - These are typically placed on the expiratory limb so that gas can be removed via scavenging prior to passage through soda lime
    This reduces soda lime consumption, as some CO_2 will be scavenged.
- Soda lime
  To absorb CO_2.
- Fresh gas flow
  - Includes oxygen, air and nitrous oxide
  - Oxygen enters the back-bar last
  - When the vapouriser is out-of-circuit, all fresh gas flow will pass through the vapouriser prior to entering the circle
- A separate high-pressure high-flow oxygen flush, which bypasses the vapouriser

Soda Lime

Soda lime:

- Consists of granules of:
  - 81% $Ca(OH)_2$
  - 4% $NaOH$
  - 15% H_2O
  - Silicates

Hardens granules.
- pH indicator
  Visual representation of uptake of CO_2 by soda-lime.
  - Phenolphthalein
    Red to white.
  - Ethyl violet
    White to purple.
- Granules are 4-8 mesh in size
  - Will pass through a mesh with 4 holes per square inch, but not 8
  - Balance between surface area (speed/efficacy of reaction) and resistance to flow
- Absorbs CO_2 by following reaction:

$$CO_2 + H_2O \rightarrow H_2CO_3$$
$$H_2CO_3 + 2NaOH \rightarrow Na_2CO_3 + 2H_2O + Heat$$
$$Na_2CO_3 + Ca(OH)_2 \rightarrow CaCO_3 + 2NaOH + Heat$$

  - This increases the pH of the soda lime, causing the pH indicator to change colour
- 100g of soda lime can absorb ~26L of CO_2

Pros

- Cheaper to operate
- Conserves gases, heat, and moisture
- Low dead space
- Reduced greenhouse effects

Cons

- Gas mixture settings are not delivered to the patient
  Settings affect the fresh gas flow mixture, whilst the patient respires gas from the circuit. These are not identical, especially at low flows.
- Nitrogen may build up in the circuit during low-flow anaesthesia, and potentially lead to delivery of a hypoxic gas mixture
- Less portable than open-circuit systems
- Increased circuit resistance
- Requires soda lime, which can be toxic
  - Produces Compound A-E from sevoflurane
  - Produces carbon monoxide from desflurane, isoflurane, and enflurane
  - Dangerous if aspirated

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

Last updated 2019-07-18

Scavenging

> Describe the hazards of anaesthetic gas pollution and the methods of scavenging anaesthetic gases

Scavenging is the removal and safe disposal of waste anaesthesia gases from the breathing circuit to avoid contamination of the theatre environment. This is important as continuous exposure of staff to anaesthetic gases has been implicated in:

- Cognitive impairment
- Spontaneous abortion
- Infertility
- Haematological malignancy

Methods of Scavenging

A scavenging system consists of:

- Gas collection assembly
  - Connects to the APL valve and ventilator relief valve
    Collects gas vented from the circuit.
  - Uses a 30mm connector
    Prevents accidental connection to the breathing system.
- Transfer tubing
- Scavenging interface
  The structure of the scavenging interface depends on the type of scavenging system.
  - Open interface
    Active scavenging systems use a pump to generate a pressure gradient drawing gas to the disposal assembly. The scavenging interface is **open** to air to prevent the negative pressure being transmitted to the patient.
  - Closed interface
    Passive scavenging systems use a series of positive and negative pressure relief valves.
    - When gas pressure in the collection assembly exceeds **5cmH$_2$O**, the positive relief valve opens and gas enters a reservoir bag
    - When gas pressure in the disposal assembly falls below **0.5cmH$_2$O**, the negative relief valve opens and gas enters the disposal assembly
- More transfer tubing
- Disposal assembly

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

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Diathermy

> Discuss the principles of surgical diathermy, its safe use and the potential hazards

Diathermy is the use of an electrical current to cut tissue and coagulate blood via localised heating. Diathermy:

- Uses **high frequency**, **alternating current** passing between two electrodes
  Frequencies between 300kHz and 2MHz are used, which have a negligible risk of inducing arrhythmia.
- Heat energy produced is proportional to electrical power dissipated ($I^2 R$)
- Relies on the principle of current density
  $$Current\ Density = \frac{Current}{Area}$$
  - A high current density at the electrode causes tissue damage
  - A low current density (e.g. at the plate of a unipolar electrode) causes heating without damage

Diathermy Types

Diathermy can be either:

- **Unipolar**
  Consists of a probe containing one electrode, and a large plate (placed elsewhere on the patient) containing the other probe.
- **Bipolar**
  Consists of a pair of forceps with each point containing a separate electrode. Minimises the current passing between probes, and is used when using diathermy on electrically sensitive tissues (e.g. brain).

Diathermy Modes

Diathermy modes include:

- Cutting
  Low-voltage mode producing a high current in the shape of a continuous sine wave.
- Coagulate
  High-voltage mode producing a damped sine wave response.
- Blended
  Mixture of cutting and coagulate on different tissues.

Risks

- Burns
  From incorrectly applied unipolar plate.
- Electrocution
  May injure patient, staff, or damage equipment and implants.
- Electrical Interference
  May inhibit pacing in certain pacemakers, or trigger ICDs.
- Smoke production
  Respiratory irritant, dissemination of viral particles, and may be carcinogenic.
- Tissue dissemination
  Potential source of metastatic seeding.

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

Last updated 2017-09-16

Lasers

> Describe the principles of surgical lasers, their safe use and the potential hazards

A laser is a device for **l**ight **a**mplification by **s**timulated **e**mission of **r**adiation. Laser light is:

- Non-divegent
  All photons move in parallel.
- Coherent
  All photons are in phase.
- Monochromatic
  All photons have the same wavelength.

Lasers are used clinically for:

- Precise incisions
  Destruction of cells by localised vapourisation of water.
- Destruction of chemicals
  Tattoos, oncological drugs.
- Tissue destruction without heating
  Opthalmology.

Principles

Method:

- An energy source is passed through a **lasing medium**, housed in a **resonator** made of mirrors
- As the lasing medium is excited, electrons enter a higher energy level
  When more than 50% of electrons are at a higher energy level, **population inversion** has occurred.
- As electrons fall back to their resting state, they release a photon
  - A spontaneous emission occurs when an electron enters its resting state spontaneously
  - A stimulated emission occurs when an electron enters its resting state after being struck by a photon released from a spontaneous emission
    - Stimulated emissions result in amplification of light release
- The mirrors in the resonating chamber ensure most light is reflected back into the chamber, causing more stimulated emissions
- The exit from the chamber can be be adjusted so only certain polarities of light are emitted
- A lens may be used to focus the laser beam

- Lasers may be:
  - Pulse wave
    Uses short bursts of laser light to minimise collateral damage.
  - Continuous wave
    May lead to excessive heating.

Pros

- Precise surgery and haemostasis

Cons

- Require multiple safety precautions
  - Laser safety officer
  - Eye protection
  - Warning signs on doors
  - Cover theatre windows
  - Non-combustible drapes
  - Matte finish on equipment to minimise chance of reflection
- Additional risks in airway surgery
  - Use lowest FiO_2 possible
  - Avoid N_2O
  - Consider use of heliox
  - Use specialised laser tubes
    Normal PVC ETTs are combustible.

References

1. Aston D, Rivers A, Dharmadasa A. Equipment in Anaesthesia and Intensive Care: A complete guide for the FRCA. Scion Publishing Ltd. 2014.

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Subclavian Vein

> Describe the anatomy relevant to central venous access (including ~~femoral, internal jugular, external jugular,~~ subclavian ~~and peripheral~~ veins)

The subclavian vein:

- Is a continuation of the axillary vein as it crosses the **upper surface** of the **first rib**
- Travels posterior to the clavicle, separated from the subclavian artery by the anterior scalene
- **Joins** with the **internal jugular vein** to form the **brachiocephalic vein**

Borders

- Anteriorly by the clavicle, subclavius muscle, and pectoralis major
- Posteriorly by anterior scalene muscle and subclavian artery
- Inferiorly by first rib and lung apex
- Superiorly by skin, subcutaneous tissue, and platysma
- Medially by the brachiocephalic vein
- Laterally by the axillary vein

Surface Anatomy

The needle is placed in the deltopectoral groove, inferior and lateral to the middle third of the clavicle. The needle is inserted at a shallow angle, passing under the middle third of the clavicle aiming at the sternal notch.

References

1. McMinn, RMH. Last's Anatomy: Regional and Applied. 9th Ed. Elsevier. 2003.

Last updated 2019-07-18

Internal Jugular Vein

> Describe the anatomy relevant to central venous access (including ~~femoral,~~ internal jugular, ~~external jugular, subclavian and peripheral~~ veins)

The internal jugular vein:

- Originates at the **jugular bulb**
  This is a dilatation formed by the confluence of the inferior petrosal sinus and the sigmoid sinus.
- Exits the skull via the **jugular foramen**
- Descends laterally to the internal carotid (and later the common carotid) in the **carotid sheath**
- Terminates behind the sternal end of the clavicle, where it joins with the **subclavian vein** to form the **brachiocephalic vein**

Borders

- Anteriorly by SCM
- Posteriorly by the lateral mass of C1, scalene muscles, and lung pleura
- Medially by the internal carotid

Relationships

- Vagus nerve lies behind/between the carotid and IJV
- Cervical sympathetic plexus lies posterior to the carotid sheath
- Deep cervical lymph nodes lie close to the vein
- External jugular crosses the sternomastoid belly of SCM, running posteriorly and more superficial to the IJV, later perforating deep fascia to drain into the subclavian vein
- Pleura rises above the clavicle, and is close to the vein at its termination
- Thoracic duct passes lateral to the confluence of the left IJV and SCV, and may be injured during **left** IJV cannulation
  - The right lymphatic duct may be injured during right IJV cannulation, but due to its smaller size this is less common

Surface Anatomy

Identify the triangle formed by the two heads of SCM and the clavicle. Palpate the artery, and ensure the site of entry is **lateral** to the carotid. Aim:

- Caudally, at a 30 angle to the frontal plane
- Parallel to the sagittal plane
- Towards the ipsilateral nipple

Ultrasound Anatomy

Identify the vein deep to SCM, noting that it is (unlike the adjacent ICA):

- Non-pulsatile
- Thin walled
- Compressible

Approaches

- Anterior
  At the medial border of SCM, 3-4cm above the clavicle. Requires retraction of the carotid medially.
- Central approach
  At the apex of the triangle formed by each muscle belly of SCM and the clavicle.
- Posterior approach
  At the posterior edge of SCM, just superior to where the EJV crosses the sternomastoid.

References

1. Lasts
2. http://radiopaedia.org/articles/internal-jugular-vein
3. http://www.frca.co.uk/article.aspx?articleid=100030
4. Internal jugular vein catheterisation: Posterior and Central Approach

Last updated 2019-07-18

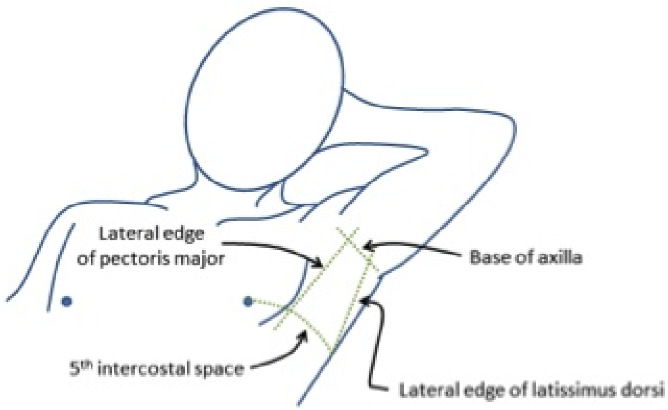
Intercostal Catheter

> Describe the anatomy relevant to the insertion of an intercostal catheter

An intercostal catheter drains the intrapleural space.

Surface Anatomy

An ICC should be placed in the **safe triangle**:



This is bordered:

- **Anteriorly** by pectoralis major
- **Posteriorly** by latissimus dorsi
  Too far posterior will injure the long thoracic nerve.
- **Superiorly** by the base of the axilla
- **Inferiorly** by the 5th intercostal space
  Too far inferiorly risks placement in the liver or spleen.

Layers of Dissection

- Skin
- Subcutaneous tissue
- External intercostal
- Internal and innermost intercostal muscles
  Note the **neurovascular bundle** which sits on the inferior aspect of the ribs, therefore aim to place the ICC at the bottom of the intercostal space - "above the rib below".
- Parietal pleura

References

1. LITFL - Chest Drain

Last updated 2017-09-18

Antecubital Fossa

> Describe the anatomy relevant to central venous access (including ~~femoral, internal jugular, external jugular, subclavian and~~ peripheral veins)

The antecubital fossa is a **triangular space** on the anterior aspect of the forearm.

Borders

The triangular borders are formed:

- Medially by pronator teres
- Laterally by brachioradialis
- Superiorly by an imaginary line between the medial and lateral epicondyles
- The roof of the fossa is formed by subcutaneous tissue
- The floor is formed by brachialis and supinator

Contents

From medial to lateral:

- Median nerve
- Brachial artery
- Biceps tendon and aponeurosis
- Radial and posterior interosseous nerves
- Veins
  - Basilic vein
  - Cephalic vein
  - Venous variations:
    - A median cubital vein connecting the basilic and cephalic veins
    - A median vein of the forearm, which divides into a median basilic and median cephalic vein which drain into the basilic and cubital veins

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References

1. FRCA - The Cubital Fossa

Last updated 2019-07-18

Tracheostomy

> Describe the anatomy relevant to the performance of a ~~naso, or endo, tracheal intubation, a cricothyroidotomy or~~ tracheostomy

Trachea

The trachea is fibrocartilagenous tube which:

- Extends from the larynx superiorly to the Plane of Louis inferiorly
- Terminates by division into the right and left mainstem bronchi
- Runs at 15 degrees parallel to the surface of the neck, such that the distal trachea is deeper than the proximal trachea
- Has a D-shaped cross section
    - Anterior wall is formed by 18-22 incomplete cartilaginous rings which maintain tracheal patency
    - Posterior wall of the trachea is spanned by longitudinal smooth muscle known as trachealis
- Is typically:
    - **10cm long**
    - **2.3cm wide**
    - **1.8cm in AP diameter**

Relationships

- Lateral to the trachea are the:
    - Carotid sheaths
      Contains the carotid artery, internal jugular vein, and vagal nerves.
    - Thyroid lobes (and inferior thyroid arteries)
    - Recurrent laryngeal nerves.
- Inferior to the thyroid isthmus lies the thyroid veins
- Posterior to the trachea are the:
    - Oesophagus
    - Vertebral column

Surface Anatomy

Midline neck structures are relevant surface anatomy:

- Laryngeal structures
  Including: Hyoid, thyroid cartilage, cricothyroid membrane, cricoid cartilage.
- Sternal notch
- Thyroid lobes
  Lie lateral to trachea.

Layers of Dissection

- Skin
- Subcutaneous fat
- Superficial and Deep Pretracheal fascia
- Tracheal wall

    - Ideally between 1st and 2nd rings

References

1. McMinn, RMH. Last's Anatomy: Regional and Applied. 9th Ed. Elsevier. 2003.

Last updated 2019-07-18

Toxic Alcohols

Alcohols include:

- **Ethanol**
- **Methanol**
- **Ethylene Glycol**

In toxicity:

- All present with symptoms of alcohol intoxication
- All contribute to the osmolar gap
- Different toxicities occur due to the different metabolites

Ethanol

Ethanol is a weak alcohol with a complicated mechanism of action similar to volatile anaesthetic agents:

- Enhanced GABA-mediated inhibition
  This is **reversible with flumazenil**.
- Inhibition of Ca^{2+} entry
- Inhibition of NMDA function
- Inhibition of adenosine transport

Property	Drug
Dosing	One unit is ~8g/10ml of pure ethanol
Absorption	Rapid PO absorption
Metabolism	Saturatable kinetics at >4mmol.L^{-1} due to high doses requiring extensive NAD^{+} for oxidation, limiting metabolism to ~1 unit per hour. Low (0.2) extraction ratio, so high portal vein concentrations from rapid absorption (e.g. shots) causes a greater pharmacological effect. Ethanol is metabolised by **alcohol dehydrogenase** to acetylaldehyde, which is metabolised by aldehyde dehydrogenase to **acetyl CoA**.
Elimination	10% eliminated unchanged in air and urine
Resp	Respiratory depression
CVS	Vasodilatation increasing heat loss, reduced cardiovascular disease mortality due to increased HDL and inhibition of platelets. Alcoholic cardiomyopathy in abuse.
CNS	Slurred speech, intellectual impediment, motor impediment, euphoria, dysphoria, increased confidence. Dementia, encephalopathy, peripheral neuropathy, and cerebellar atrophy with chronic use.
Endocrine	Stimulates ACTH release and 'pseudo-Cushing's syndrome'. Inhibits testosterone release. May cause lactic acidosis and hypoglycaemia in toxicity.
Renal	Inhibition of ADH release, causing diuresis. Ethanol is osmotically active and contributes to the **osmolar gap**.
GIT	Gastritis. Fatty liver, progressing to hepatitis, necrosis, fibrosis and cirrhosis
GU	Tocolytic effect
Haeme	Inhibition of platelet aggregation
Metabolic	High energy content comparable with fat (29kJ.g^{-1})
Other	Synergistic with other CNS depressants. Metabolic interactions with warfarin, phenobarbitone, and steroids

Methanol

- Metabolised by alcohol dehydrogenase to formaldehyde and then formic acid
- Formic acid is neurotoxic
  Damages retina and the optic nerve.

Ethylene Glycol

- Metabolised by alcohol dehydrogenase to glycoaldehyde, and (via several intermediate steps) to oxalic acid
- Oxalic acid binds calcium, which causes:
  - Hypocalcaemia
    - Long QT
  - Acute renal failure

References

1. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.
2. Holford NH. Clinical pharmacokinetics of ethanol. Clin Pharmacokinet. 1987 Nov;13(5):273-92.
3. LITFL- Toxic Alcohol Ingestion

Last updated 2019-07-18

Naloxone

Pure MOP antagonist used for:

- Treatment of opioid overdose
- Reducing constipation
  In combination with PO oxycodone.

Property	Drug
Class	**μ**-selective opioid receptor competitive antagonist
Uses	Opioid overdose, neuraxial opioid side effects (e.g. pruritus), prevention of constipation in combination with oral opioids
Presentation	Clear, colourless solution at $400mcg.ml^{-1}$
Route of Administration	IV, IM, PO
Dosing	0.1-0.4mg Q5min, $0.5mg.kg^{-1}.hr^{-1}$ by infusion
Absorption	Very high first pass metabolism leading to ~2% PO bioavailability
Distribution	50% protein bound. V_D $2L.kg^{-1}$, highly lipid soluble.
Metabolism	Rapid hepatic glucuronidation
Elimination	Renal elimination
Resp	Reversal of opioid-induced respiratory depression (↑ RR, ↑ V_T)
CVS	↑ SVR & ↑ BP, arrhythmia due ↑ in SNS tone
CNS	↓ Analgesia, ↓ sedation, ↓ miosis. Antanalgesic in opioid naive patients. Precipitation of opioid withdrawal.
Other considerations	Duration of action is ~30-40 minutes is shorter than some opioids, which may lead to re-narcosis if not given subsequent doses or by infusion

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

Last updated 2019-07-18

Flumazenil

Competitive antagonist and inverse agonist of the benzodiazepine receptor.

Property	Action
Class	Imidazo-benzodiazepine
Uses	Reversal of BZD
Route of Administration	IV
Dosing	0.1mg boluses up to 2mg
Onset	Within 2 minutes
Distribution	Moderate lipid solubility, 50% protein bound. $t_{1/2}\beta$ < 1 hour - may require infusion.
Metabolism	Hepatic to inactive metabolites
Elimination	Renal of metabolites
CNS	May precipitate seizures or BDZ withdrawal due to inverse agonist effect
GIT	N/V

References

1. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

Last updated 2017-09-17

Oxygen

Property	Action
Class	Naturally occurring gas
Uses	Improve FiO_2, CO poisoning, hyperbaric O_2 therapy
Pharmaceutics	Clear, colourless, odourless gas at STP. Critical temperature **-119°C**, manufactured by fractional distillation. Highly flammable.
Route of Administration	Inhaled
Dosing	0.21-1.0 FiO_2
Absorption	Diffusion across the alveolar capillary membrane in proportion to membrane area and partial pressure gradient, and inversely proportional to membrane thickness
Distribution	Bound to plasma Hb, and dissolved in plasma
Metabolism	Metabolised in mitochondria of cells during the citric acid cycle to produce ATP, creating CO_2
Elimination	Exhalation as CO_2, or combined with H_2O to produce HCO_3^- and eliminated in urine
Resp	↓ Respiratory drive in all individuals. May result in a fatal ↓ in those dependent on hypoxic drive. **Pulmonary toxicity** due to free radial formation when PiO_2>0.6bar - pneumonitis/ARDS due to lipid peroxidation of the alveolar-capillary membrane. Absorption atelectasis.
CVS	Improvement in all CVS parameters in the setting of hypoxia. However, hyperoxia ↓ CO, ↓PVR, ↓PAP, and causes coronary vasoconstriction with prolonged administration
CNS	CNS O_2 toxicity, typically at pressures >1.6 bar though this is variable. Presents with a variety of neurological symptoms, progressing to disorientation and seizure. Retrolental fibroplasia in neonates exposed to high FiO_2.
Other	Fire risk

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. RAH Advanced Diving Medicine Course Notes: Chapter 6 Oxygen and Carbon Dioxide Toxicity

Last updated 2019-07-18

Helium

Helium is an inert gas which is used to reduce the specific gravity of inhaled gas mixtures. It is typically provided as a 0.79/0.21 Helium-Oxygen (Heliox) mixture (though other dilutions exist).

	Helium	**Heliox (0.79/0.21)**	**Oxygen**
Specific Gravity (as compared to air)	0.18	0.34	1.09

Reduced specific gravity results in a proportional reduction in Reynolds Number, improving laminar flow within the airways.

Property	Action
Class	Inert Gas
Uses	Obstructive lung disease, deep water diving
Presentation	Clear, colourless solution
Route of Administration	Inhaled
Dosing	Typically as Heliox: 79% He/21% O_2
Absorption	Diffusion across the alveolar capillary membrane in proportion to membrane area and partial pressure gradient, and inversely proportional to membrane thickness
Distribution	Distributes proportionally to solubility and tissue partial pressures
Metabolism	Not metabolised
Elimination	Respiratory exhalation along a pressure gradient
Resp	Significantly decreases the specific gravity of inhaled gas mixtures
Toxic Effects	High Pressure Neurologic Syndrome at >16 atm

References

1. RAH Advanced Diving Medicine Course Notes: Chapter 6 Oxygen and Carbon Dioxide Toxicity

Last updated 2017-12-22

Beta Agonists

This covers the inhaled β-agonists used for bronchodilation. Information on catecholamines and sympathomimetics with activity on β-receptors is covered under adrenergic vasoactives.

Common Features

Pharmacodynamic Effects	β-agonists
Resp	Bronchodilatation, ↓ HPV causing ↑ shunt and potential ↓ PaO_2 if O_2 is not co-administered.
CVS	↑ HR (β_1 with higher doses), ↓ BP (β_2 with lower doses)
GU	Tocolytic.
Metabolic	Hypokalaemia from β_2 stimulation of Na^+/K^+ ATPase, hyperglycaemia.
Other	Potentiates non-depolarising muscle relaxants

Differences

Property	Salbutamol	Salmeterol
Class	Synthetic sympathomimetic amine	Synthetic sympathomimetic amine
Uses	Acute asthma/bronchospasm, hyperkalaemia	Nocturnal and exercise-induced asthma
Presentation	MDI (100µg), solution at 2.5-5mg.ml^{-1} for nebulisation	MDI
Route of Administration	Inhaled, IV	Inhaled
Dosing	1-2 puffs via MDI, 5mg nebulised. 0.5mcg.kg^{-1}.min^{-1} as IV infusion.	
Onset	Rapid	Slow
Distribution	Low protein binding	
Metabolism	High first pass hepatic to inactive metabolites, $t_{1/2}\beta$ 6 hours.	Extensive hepatic via CYP3A4
Elimination	Urinary elimination of active (30%) drug and inactive metabolites	Renal of metabolites

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

Last updated 2017-09-07

Antimuscarinics (Respiratory)

Antimuscarinics with predominantly cardiac effects are covered at Antimuscarinics (Cardiac), whilst atropine is covered separately.

These agents competitively antagonise ACh at M_3 receptors in bronchial smooth muscle, preventing parasympathetic mediated bronchoconstriction.

Property	Ipratropium	Tiotropium
Class	Muscarinic antagonist	Muscarinic antagonist
Uses	Bronchodilatation	Bronchodilatation
Presentation	MDI or solution for nebulisation	MDI
Route of Administration	Inhaled	Inhaled
Dosing	18mcg MDI, 500μg nebuliser	
Absorption	5% bioavailability via inhaled route	
Metabolism	Hepatic to inactive metabolites	
Elimination	Equal renal and faecal elimination	
Resp	Bronchodilation	Bronchodilation
GIT	Decreased GI secretions in large doses	Decreased GI secretions in large doses
CNS	Mydriasis if deposited in eye	Mydriasis if deposited in eye

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

Last updated 2017-08-02

Phosphodiesterase Inhibitors / Methylxanthines

Methylxanthines non-selectively inhibit phosphodiesterase, which results in reduced levels of cAMP hydrolysis and therefore increased intracellular cAMP, and subsequent smooth muscle relaxation. This effect is synergistic with β_2 agonists, which also increase cAMP by increasing production.

Property	Theophylline
Class	Methylxanthine/Non-selective phosphodiesterase inhibitor
Uses	Asthma and COAD
Route of Administration	IV or PO
Dosing	4-6mg.kg^{-1} IV load, then at 0.4mg.kg^{-1}.hr^{-1} targeting serum concentration of 10mcg.ml^{-1}
Absorption	High oral bioavailability
Distribution	V_D 0.5L.kg^{-1}, 40% protein binding.
Metabolism	Hepatic via CYP450 to active metabolites (caffeine and 3-methylxanthine), low hepatic extraction ratio
Elimination	Highly variable elimination affected by age, renal disease, hepatic disease
Resp	Bronchodilation, ↑ Diaphragmatic contractility
CVS	↑ Inotropy, ↑ chronotropy. Narrow therapeutic range due to arrhythmogenic (VF) properties
CNS	↓ Seizure threshold
Renal	Natriuresis and hypokalaemia
Toxic Effects	Low therapeutic index, with toxicity manifested as tachyarrhythmias including VF, tremor, insomnia and seizures

References

1. Lexicomp. Theophylline: Drug Information. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2017.
2. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
3. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

Last updated 2019-07-18

Leukotriene Antagonists

Selectively inhibit the cysteinyl leukotriene receptor, increased activity of which is involved in airway oedema and bronchial smooth muscle constriction.

Property	Montelukast
Class	Leukotriene Antagonist
Uses	Asthma, allergic rhinitis
Route of Administration	PO
Dosing	10mg daily
Absorption	64% PO bioavailability
Distribution	$t_{0.5}$ 5 hours, >99% protein bound
Metabolism	Hepatic by CYP3A4
Elimination	Predominantly faecal
Resp	Bronchodilatation

References

1. . Lexicomp. Montelukast: Drug information. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2017.

Last updated 2017-09-20

Corticosteroids

Glucocorticoids are endogenous (hydrocortisone) and synthetic (prednisolone, methylprednisolone, dexamethasone) steroid hormones with **metabolic**, **anti-inflammatory**, and **immunosuppressive** effects. They bind to specific intracellular receptors and translocate into the nucleus, where they regulate gene expression in a tissue-specific manner.

Corticosteroids have multiple indications including:

- Replacement in adrenal suppression or other cortisol-deficient states
- Autoimmune disorders
- Anaphylaxis and atopic disorders, including asthma
- Hypercalcaemia
- Chemotherapy
- Immunosuppression following transplantation

Common Features

System	Effect
Resp	↑ Bronchial smooth muscle response to circulating catecholamines, ↓ airway oedema
CVS	↑ Inotropy, ↑ vascular smooth muscle response to circulating catecholamines (↑ receptor expression), ↑ BP secondary to mineralocorticoid effects
CNS	Mood changes, sleep disturbance, psychosis
MSK	Atrophy, thinning of skin
Renal	Glycosuria, Na^+ and fluid retention (mineralocorticoid effect), hypokalaemia
GIT	Gastric ulceration
Metabolic	↑ Gluconeogenesis, diabetes, ↑ protein catabolism, fat redistribution, adrenal suppression (negative feedback on ACTH), ↑ lipolytic response to circulating catecholamines
Immune	↓ Transudate production, ↓ production of inflammatory mediators, ↓ macrophage function, ↓ transport of lymphocytes, ↓ T-cell function, ↓ antibody production, ↑ susceptibility to infection,
Toxic Effects	Relative steroid deficiency in adrenal suppressed individuals with infection or surgery

Comparison of Corticosteroids

Property	Hydrocortisone	Prednisolone	Methylprednisolone	Dexamethasone
Route of Administration	IV/PO	PO	PO/IV/IM	IV
Relative Dose Equivalents	100mg	25mg	20mg	4mg
Absorption	50% PO bioavailability	100% PO bioavailability		60% PO bioavailability
Distribution	Variable protein binding depending on concentration, V_D 0.5 $L.kg^{-1}$	Variable protein binding depending on concentration, V_D 0.5 $L.kg^{-1}$	V_D 1 $L.kg^{-1}$	

Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Elimination	Elimination $t_{0.5}$ is 2 hours	Elimination $t_{0.5}$ is 3 hours	Elimination $t_{0.5}$ is 3 hours	Elimination $t_{0.5}$ is 4 hours
Relative mineralocorticoid effect	+++	++	+	+

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
3. Nieman LK, Lacroix A, Martin KA. Pharmacologic use of glucocorticoids. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2017.
4. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

Last updated 2019-07-18

Pulmonary Vasodilators

Property	Nitric Oxide	Iloprost	Sildenafil
Class	Inorganic gas	Synthetic eicosanoid with prostacyclin activity	
Uses	ARDS, RVF, PHTN	PHTN	PHTN, erectile dysfunction
Presentation	Aluminium cylinders with 100/800ppm NO/N_2	Synthetic analog of epoprostenol	
Route of Administration	Inhaled	Inhaled	PO
Dosing	1-40ppm, via inspiratory limb of ventilator		20mg TDS
Absorption			40% PO bioavailability
Distribution	Avidly bound to Hb		95% protein bound, V_D of 100L
Metabolism	Metabolised to methaemoglobin and nitrite prior to reaching systemic circulation - $t_{1/2}$ of < 5s		Hepatic by CYP450
Elimination			Faecal
Mechanism of Action	Stimulates cGMP which reduces intracellular Ca^{2+}	Stimulates cAMP which reduces intracellular Ca^{2++} and smooth muscle growth	Inhibits cGMP
Resp	Inhibits HPV, improves V/Q matching		
CVS	↓ vascular resistance, ↓ PVR in ventilated alveoli and improving V/Q matching. ↑ Capillary permeability.	↓ BP with compensatory ↑ HR	↓ PVR
CNS	↑ CBF		
Haeme	Inhibits platelet aggregation. MetHb	Inhibits platelet aggregation	
Other	Rebound pulmonary HTN on abrupt cessation		

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

Last updated 2019-07-18

Adrenergic Vasoactives

This covers the pharmacology of specific catecholamines and sympathomimetics. The synthesis of endogenous catecholamines is covered under adrenal hormones, whilst specifics of catecholamine receptor function is covered under adrenoreceptors.

Adrenergic drugs:

- Act via:
  - Dopamine (D)
  - Adrenoreceptors (α and β)
- Can be:
  - **Direct-acting**
    Stimulate the receptor.
  - **Indirect-acting**
    Stimulate the release of noradrenaline to cause effects.
- Classified as either:
  - **Naturally-occurring catecholamines**
  - **Synthetic catecholamines**
  - **Synthetic sympathomimetics**
    Drugs which act on adrenoreceptors but are not classified as catecholamines due to their chemical structure.

Comparison of Commonly Used Adrenergic Agents

Properties	Noradrenaline	Adrenaline	Phenylephrine	Metaraminol	Ephedrine
Class	Natural Catecholamine	Natural Catecholamine	Sympathomimetic phenylethylamine derivative	Synthetic sympathomimetic	Synthetic sympathomimeti
Uses	↑ SVR	Cardiac arrest, anaphylaxis, inotropy, chronotropy, adjunct in local anaesthetics	↑ SVR	↑ SVR	↑ SVR without ↓ in HR
Dosing	Start at 0.05μg/kg/min	Infusion starts at: 0.01μg/kg/min	Bolus start at 50-100mcg	Bolus 0.5-2mg	3-6mg bolus
Route	IV	IV/IM/ETT/SC	IV/IM/SC	IV	IV
Presentation	Clear, colourless, light-sensitive solution. Sodium metabisulfite as excipient.	A clear, colourless solution typically at 0.1-1mg/ml	Clear, colourless solution at 100mcg/ml	Clear, colourless solution in ampoule at 10mg/ml, typically reconstituted to 0.5mg/ml	Clear, colourless solution in 30mg/ml ampoule
Absorption	IV only	Variable ETT and SC absorption	IM onset 15 minutes, duration up to 1 hour	IV only	IV or IM
	$t_{1/2}$ 2min. Metabolised by mitochondrial MAO and	$t_{1/2}$ 2min. Metabolised by mitochondrial MAO and		Some uptake into	Hepatic (not metabolised by MAO and COMT), giving

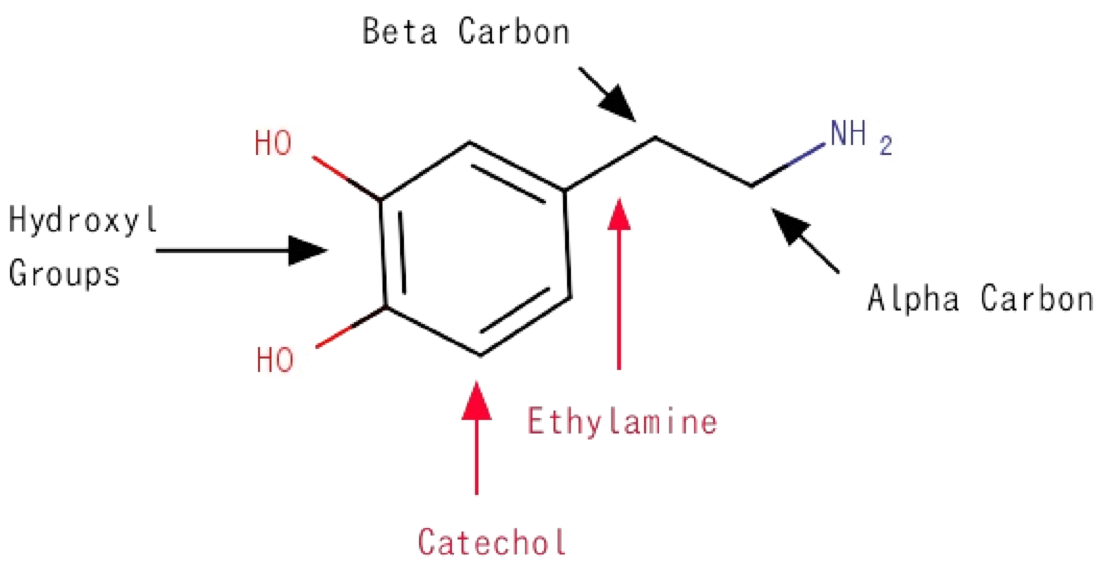
Metabolism	COMT in liver, kidney, and blood to VMA and metadrenaline.	COMT within liver, kidney, and blood to VMA and metadrenaline.	Hepatic by MAO	adrenergic nerve endings	longer (10-60 minute) duration of action and a $t_{1/2}\beta$ of 3-6 hours
Elimination	Pulmonary uptake of up to 25%. Urinary excretion of metabolites	Urinary excretion of metabolites	Renal of metabolites, $t_{1/2}\beta$ 2-3 hours		50% unchanged in urine
Mechanism of action	α>>β	β>α at lower doses. At high doses α_1 effects dominate.	Direct α_1	Direct and indirect (via ↑ NA release) α_1 agonism	↑ NA release (indirect α_1) and direct α and β agonism
Respiratory	↑ MV, bronchodilation	↑ MV, bronchodilation			Bronchodilation
CVS	↑ SVR, ↑ Myocardial O_2 consumption, ↑ Coronary flow.	↑ Inotropy, ↑ HR, ↑ SVR and PVR, ↑ BP, ↑ CO, ↑ myocardial O_2 consumption. Coronary vasodilation. Arrhythmogenic.	↑ SVR and BP, potential reflex bradycardia. Not arrhythmogenic.	↑ SVR/PVR, reflex bradycardia. Indirect ↑ in coronary flow.	Direct and indirect (via NA release) ↑ in HR, BP, and CO. Arrhythmogenic
CNS		↑ Pain threshold, ↑ MAC			↑ MAC, mydriasis.
MSK	Necrosis with extravasation	Necrosis with extravasation			
Renal	↓ RBF	↓ RBF and ↑ in sphincter tone	↓ RBF	↓ RBF	↓ RBF
Metabolic		↑ BMR, ↑ lipolysis, ↑ gluconeogenesis and BSL, ↑ Lactate. Initially ↑ insulin secretion (β), then ↓ (α)			
GU	↓ Uterine blood flow and foetal bradycardia		↓ Uterine blood flow	↓ Uterine blood flow	

Comparison of Less Common Adrenergic Agents

Properties	Dopamine	Isoprenaline	Dobutamine
Class	Natural Catecholamine	Synthetic Catecholamine	Synthetic Catecholamine
Uses	Haemodynamic support	Severe bradycardia	Stress testing, increasing CO
Dosing	Start 1μg/kg/min	Infusion from 0.5-10μg/min	0.5-20μg/kg/min
Route	IV	IV	IV

Presentation	Clear, colourless solution with 200mg or 800mg in water	Clear solution at 1mg/ml	250mg dobutamine in 20ml water
Metabolism	$t_{1/2}$ 3 min. 25% of dose converted to noradrenaline. Remainder is metabolised by MAO and COMT similar to nor/adrenaline.	Hepatic by COMT	$t_{1/2}$ 2 min. COMT to inactive metabolites.
Elimination	Renal, $t_{1/2}\beta$ 3 minutes		Urinary excretion of unchanged drug and metabolites
Mechanism of action	D_1, D_2; β>α at lower dose	$\beta_1>\beta_2$	$\beta_1>>\beta_2$, D_2
Respiratory		Potent bronchodilation	Bronchodilation
CVS	↑ Inotropy, ↑ HR, ↑ CO, coronary vasodilation. At high doses, ↑ SVR and PVR, ↑ VR.	↑ SVR, potential reflex bradycardia. Not arrhythmogenic.	↑ HR, CO, contractility, and automaticity. B_2 effects may ↓ SVR and BP.
CNS	Inhibits prolactin. Nausea.	Stimulant	Tremor
MSK	Necrosis with extravasation		
Renal			↑ RBF and ↑ urinary output with no improvement in renal function
GIT	Mesenteric vasodilation		

Structure-Activity Relationships of Sympathomimetics



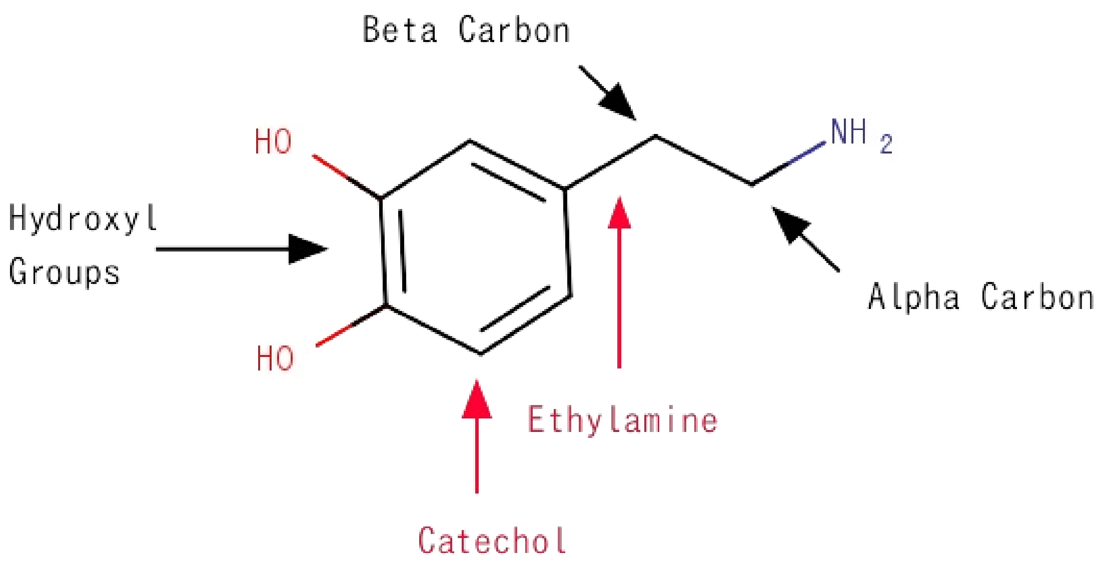
Catecholamines consist of:

- A catechol ring

  A benzene ring with two hydroxyl groups in the 3 and 4 position.
  - Losing one hydroxyl group
    - Increases lipid solubility and decreases the potency 10-fold

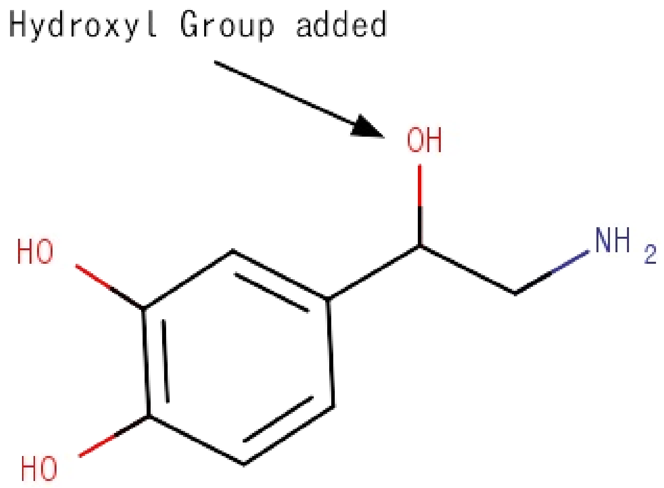
        - Prevents metabolism by COMT, prolonging duration of action
    - Losing both hydroxyl groups decreases the potency 100-fold
        - Changing the hydroxyl groups to the 3 and 5 position increases beta-2 selectivity when there is also a large substitution present on the amine group
- An ethylamine tail
  Consists of:
    - Beta carbon
      The first carbon.
        - Adding a hydroxyl group decreases lipid solubility and CNS penetration
        - Adding any group increases alpha and beta selectivity
    - Alpha carbon
      The second carbon.
        - Adding a group prevents metabolism by MAO, prolonging duration of action
        - Methylation increases indirect activity
    - Amine group
      The terminal nitrogen.
        - Addition of a methyl group generally increases beta selectivity
          As the chain length increases, so does the beta selectivity.

Dopamine



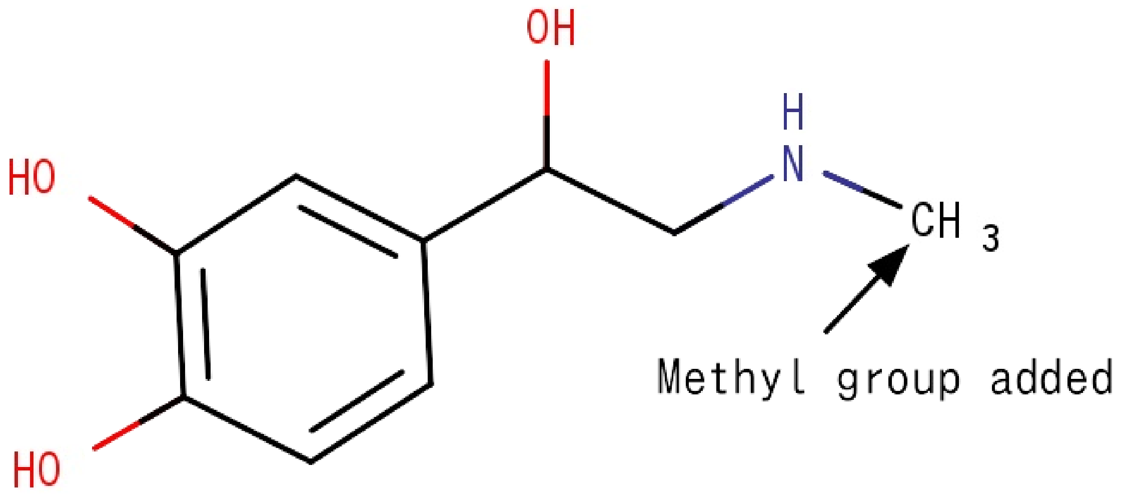
- Dopamine is the prototypical catecholamine, to which others are compared

Noradrenaline



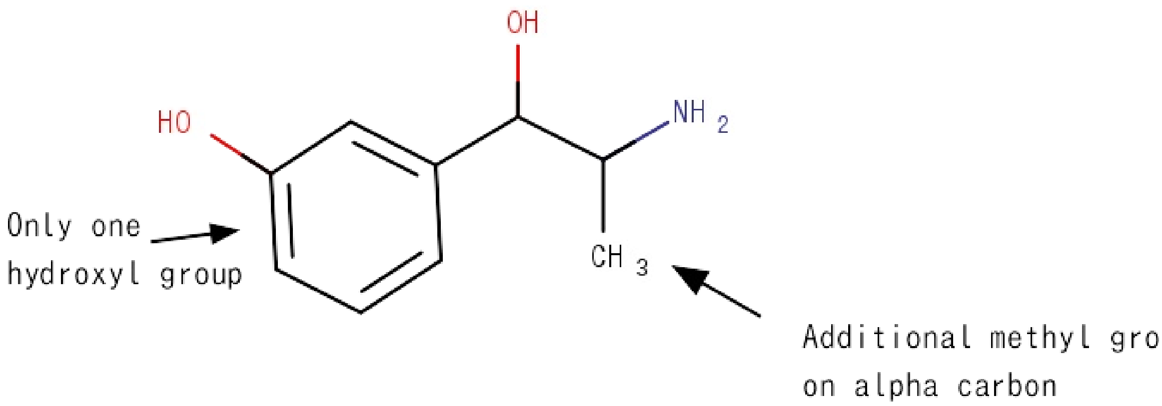
- Noradrenaline has a hydroxyl group added to the beta carbon, increasing its alpha selectivity

Adrenaline



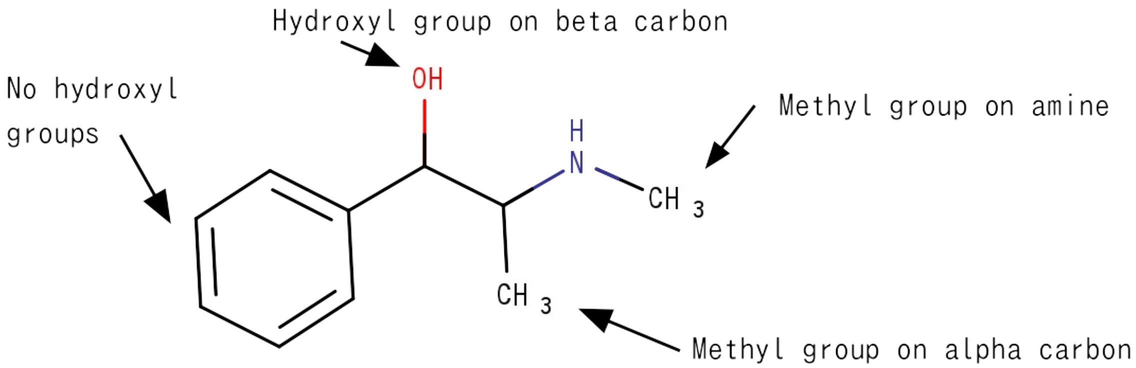
- Adrenaline is similar to noradrenaline with an additional hydroxyl group on the beta carbon
- Adrenaline also has a methyl group added to the terminal amine, increasing beta selectivity

Metaraminol



- Metaraminol has an additional hydroxyl group on the beta carbon
- Metaraminol has only one hydroxyl group on the phenol ring, so:
  - It is no longer classified as a catecholamine
  - It is not metabolised by COMT, prolonging its duration of action
  - It has reduced potency, requiring administration in higher doses
- Metaraminol has an additional methyl group on the alpha carbon, preventing metabolism by MAO and further prolonging its duration of action

Ephedrine



- Like metaraminol, ephedrine has a hydroxyl group on the beta carbon and a methyl group on the alpha carbon
- Ephedrine has no hydroxyl groups on the phenol ring, further reducing its potency and increasing its elimination half-life
- Ephedrine has a methyl group on the amine, increasing its beta selectivity

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Non-Adrenergic Vasoactives

Key non-adrenergic cardiovascular drugs include **vasopressin** (and its analogues, **terlipressin** and **ornipressin**), **phosphodiesterase III inhibitors** such as milrinone, and **calcium sensitisers** such as levosimendan.

Property	Vasopressin (ADH)	Milrinone	Levosimendan
Class	Natural nonapeptide	Phosphodiesterase III inhibitor	Calcium sensitiser and phosphodiesterase inhibitor
Uses	Haemorrhage, DI, catecholamine-sparing vasopressor	Refractory CCF and low CO states	Severe acute heart failure
Dosing	5-10 units IV bolus, up to 4U/hr infusion		Load 12-24mcg/kg over 10min, then infusion at 0.05-2mcg/kg/min
Route	IV/SC/IM	IV	IV
Presentation	Clear solution	Yellow solution at 1mg/ml	2.5mg/mL in 5ml & 10ml vials
Distribution		70% protein bound	Very high protein binding >90%
Metabolism	$t_{1/2}$ 10 minutes. Metabolised by tissue peptidases and renal elimination.	$t_{1/2}$ 1-2.5 hours	$t_{1/2}$ 1 hour. Hepatic to active metabolite with a $t_{1/2}$ ~70 hours
Elimination		80% of drug is excreted unchanged	
Mechanism of action	V_2 receptors (kidney, platelets) are adenylate cyclase mediated. V_1 (vascular smooth muscle) and V_3 receptors (pituitary) are phospholipase C/inositol triphosphate mediated	Inhibits phosphodiesterase breakdown of cAMP, increasing intracellular Ca^{2+} levels. Also increases speed of Ca^{2+} uptake into cardiac muscle, increasing lusitropy.	Binds to troponin C increasing myofilament Ca^{2+} sensitivity. Also opens K^+ channels causing vasodilation. It may also have some PD III inhibition effect.
CVS	↑ SVR through vasoconstriction	Increased inotropy, increased lusitropy, decreased SVR and PVR (PVR decreases more than SVR). Increased dysrhythmias.	Increased CO without increased O_2 demand, vasodilation, prolonged QTc with risk of arrhythmia
GIT	GIT smooth muscle contraction		
Renal	↑ Aquaporin insertion into the apical membrane of collecting ducts which ↑ water reabsorption		
Haematological	↑ Coagulation factor mobilisation and ↑ platelet aggregation		
Metabolic	Hyponatraemia		

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Last updated 2019-07-18

Centrally Acting Anti-Hypertensives

Property	Clonidine	Methyldopa
Class	Central α_2-agonist (200:1 α_2:α_1)	Phenylalanine derivative
Uses	Analgesia, sedation, anti-hypertensive	Antihypertensive (especially in pregnancy)
Presentation	Clear colourless solution at 150µg.ml^{-1}	Tablets - not appropriate for urgent blood pressure reduction
Route of Administration	PO/IV at 10-200mcg up to QID. Can be added to neuraxial blockade at 1-2mcg.kg^{-1} to decrease opioid requirement.	PO/IV.
Dosing	50-200µg QID.	250-500mg PO BD/TDS.
Absorption	100% PO bioavailability with rapid absorption	Highly variable PO bioavailability
Distribution	20% bound, V_D 2L.kg^{-1}	50% protein bound, V_D 0.3L.kg^{-1}
Metabolism	50% hepatic to inactive metabolites, $t_{1/2}\beta$ 9-18 hours	Intestinal and hepatic
Elimination	50% renal elimination unchanged	40% renal elimination unchanged
Mechanism of Action	Agonist of central α2 receptor, ↓ SNS tone via decreased NA release from peripheral nerve terminals.	Metabolised to α-methyl-noradrenaline in the CNS, which agonises central α2 receptors.
CVS	Initial ↑ in BP due to α_1 stimulation, evident with bolus dosing. Followed by prolonged ↓ in BP, ↑ PR, ↓ AV conduction, ↑ baroreceptor sensitisation (lower HR for a given increase in BP). Cessation may cause rebound HTN.	↓ SVR with unchanged HR or CO
CNS	Sedation, analgesia due to ↓ NA release which ↓ opioid requirement. Adjunct in chronic pain and in opioid withdrawal. Anxiolysis at low doses. Central antiemetic effect.	May ↓ MAC
Metabolic	Stress response to surgical stimulus is inhibited	
Renal	Diuresis secondary to inhibition of ADH	

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1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

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Calcium Channel Blockers

Ca^{2+}-channel blockers:

- Have affinity for L-type calcium channels
  L-type channels exist in myocardium, nodal, and vascular smooth muscle.
  - Variable affinity for each causes a preference for either nodal and inotropic, or vascular effects
- Prevent Ca^{2+} entry into cells in a use-dependent fashion

Class	Chemical Structure	Drugs
Class I	Phenylalkylamines	Verapamil
Class II	Dihydropyridines	Nifedipine, amlodipine, nimodipine
Class III	Benzothiazepines	Diltiazem

Comparison of Calcium Channel Blockers

Property	Verapamil	Amlodipine	Diltiazem
Class	Phenylalkylamine	Dihydropyridine	Benzothiazepine
Uses	SVT, excluding AF with WPW	HTN, Angina	Angina, HTN, SVT, Raynaud's, migraine, oesophageal dysmotility
Presentation	20-240mg tablet, PO solution, IV at $2.5mg.ml^{-1}$	Tablet	Tablet
Isomerism	Racemic preparation. The D-isomer also has some local anaesthetic activity		
Route of Administration	PO/IV	PO	PO
Dosing	80-160mg BD/TDS	2.5-10mg daily	30-120mg TDS
Absorption	20% bioavailability	60% bioavailability	40% bioavailability
Distribution	90% protein bound	90% protein bound, lipid insoluble.	80% protein bound
Metabolism	Hepatic to active norverapamil	Hepatic to inactive metabolites	Hepatic to active metabolites
Elimination	Renal elimination of active metabolites	Renal of inactive metabolites	Renal of active metabolites. $t_{1/2}$ 2-7 hours
CVS	↓ HR via ↓ SA and ↓ AV nodal conduction, ↓ inotropy, ↓ SVR, ↓ BP, arrhythmia including HB	↓ SVR, ↓ BP, with reflexive ↑ HR, ↑ inotropy, ↑ CO	↓ AV nodal conduction but typically stable HR, ↓ SVR, ↓ CVR, ↓ MVO_2, ↑ CO
CNS	↓ Cerebral vascular resistance	↓ Cerebral vascular resistance with **nimodipine**	
GIT			↓ LOS tone
Interactions	Contraindicated with concurrent β-blocker use due to profound ↓ HR, ↓		Contraindicated with concurrent β-blocker use due to profound ↓

	inotropy		HR, ↓ inotropy

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
3. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.

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Direct Vasodilators

Direct vasodilators include:

- Ca^{2+} channel blockers (see Calcium Channel Blockers)
- Nitrates
  Increase production of NO:
  - NO activates guanylate cyclase, increasing cGMP
  - cGMP inhibits Ca^{2+} uptake into smooth muscle and enhances its sequestration into smooth endoplasmic reticulum
    The decrease in cytoplasmic $[Ca^{2+}]$ causes smooth muscle relaxation and vasodilation
- Hydralazine
  Multimodal mechanism of action, including:
  - Opens K^+ channels, hyperpolarising vascular smooth muscle
  - Decreases intracellular Ca^{2+} in vascular smooth muscle
  - Activation of guanylate cyclase

Property	Sodium Nitroprusside	GTN	Hydralazine
Class	Inorganic Nitrate	Organic Nitrate	Direct vasodilator
Uses	Afterload (with some preload) reduction	Afterload & preload reduction, angina	HTN
Presentation	Solution at $10mg.ml^{-1}$, must be protected from light	Spray, tablets, patch, IV solution which is absorbed into PVC - requires a polyethylene administration set	20mg ampoule or powder. Should not be reconstituted with dextrose.
Route of Administration	IV only	IV, topical, sublingual	PO, IV
Dosing	$0.5\text{-}6\mu g.kg^{-1}.min^{-1}$	$10\text{-}200\mu g.min^{-1}$	5-20mg IV
Absorption		<5% PO bioavailability	30% bioavailability due to high first pass metabolism
Metabolism	Prodrug. Reacts with Oxy-Hb in RBC to form 1x NO, 5x CN^-, and MetHb. MetHb reacts with CN to form cyanomethaemoglobin. CN is metabolised in the liver and kidney to form SCN, the majority of which is excreted in urine (though may be re-converted to CN). CN may also combine with hydroxocobalamin (vitamin B_{12}) to form cyanocobalamin, which is eliminated in urine.	Prodrug. Metabolised to NO and glycerol dinitrate (which is then also converted to NO) in the liver.	N-acetylated in gut and liver
Elimination	Renal elimination of SCN and cyanocobalamin. Impaired in renal failure which may worsen CN toxicity. $t_{1/2}$ for SCN is 2-7 days	$t_{1/2}$ 1-4mins. Urinary excretion	Dependent on acetylation rates
Resp	Inhibit hypoxic pulmonary vasoconstriction leading to ↑ shunt	Bronchodilation	
		Vasodilation predominantly of	Arteriolar vasodilation

CVS	↓ SVR > venodilation. ↓ SBP and ↓ preload, ↑ HR maintains CO, ↓ MVO_2	capacitance vessels, ↓ preload, ↓ VR, ↓ EDP, ↓ wall tension improving subendocardial blood flow, ↓MVO_2	with compensatory tachycardia and increased CO
CNS	↑ CBF following cerebral vasodilatation	↑ CBF following cerebral vasodilatation, which may cause headache	Increased CBF
Haematological	Methaemoglobinemia	Methanoglobinaemia	
Toxic Effects	**Three** mechanisms: hypotension, thiocyanate toxicity, CN toxicity.	Methaemoglobinaemia can occur with GTN GTN patches may **explode** if left on during DC cardioversion.	

Nitrate Toxicity

Nitrate toxicity can be related to:

- Cyanide
- Thiocyanate
- Methaemoglobinaemia

Cyanide Toxicity

Cyanide toxicity occurs only with SNP, as CN^- is produced as a byproduct of metabolism.

- **Kinetics**
  - Rapid cellular uptake
  - Small V_D
  - Hepatically metabolised to **thiocyanate**, using thiosulfate as a substrate
- **Mechanism**
  CN^- binds to cytochrome oxidase, preventing oxidative phosphorylation. This causes histotoxic hypoxia, and is characterised by:
  - Rapid loss of consciousness and seizures
  - Metabolic acidosis
  - Lactataemia
  - Arrhythmia
  - Increased MVO_2
  - Hypertension
    Due to tachyphylaxis to SNP.
- Risk of cyanide toxicity from SNP is related to:
  - Infusion rate
  - Infusion duration
- **Management**
  - Supportive care, including inotropes
  - Cyanide chelators
    Bind CN, removing it from the circulation. Include:
    - Dicobalt edetate
    - Hydroxycobalamin (Vitamin B_{12})
    - Sulfur donors

Provide additional sulfhydryl groups, allowing further hepatic metabolism of CN^- to SCN. Include:
    - **Thiosulfate**
  - Nitrites
    Converts Oxy-Hb to Met-Hb, which has a higher affinity for CN^- than cytochrome oxidase. Include:
    - Sodium nitrite
    - Amyl nitrite

Thiocyanate Toxicity

Thiocyante is produced with hepatic metabolism of CN^-. Toxicity occurs when thiocyanate accumulates, which occurs in:

- Long duration SNP infusions
  7-14 days.
- Patients with renal failure
  Reduced clearance, may occur in 3-6 days.
- Patients given thiosulfate for management of CN^- toxicity.

- **Effects**
  Multisystemic, including:
  - Rash
  - Abdominal pain
  - Weakness
  - CNS disturbance

- **Treatment**
  - Dialysis

Methaemoglobinaemia

Methaemoglobinaemia occurs when the Fe^{2+} (ferrous) ion in haemoglobin is oxidised to the Fe^{3+} (ferric) form, which is **unable** to **bind oxygen**.

- Due to the high concentration of oxygen in erythrocytes, methaemoglobin is continually being formed
- Several endogenous reduction systems exist to keep MetHb levels stable at ~1%
  - Predominantly cytochrome-b_5 reductase
  - NADPH-MHb reductase
    This reduces methaemoglobinaemia in the presence of a reducing agent, classically **methylene blue**.
  - Reduced glutathione
    More important in preventing oxidative stress in other cells than the RBC.
- Disease occurs due to the loss in oxygen-carrying capacity from the loss of effective haemoglobin
  - e.g. a 20% MetHb level gives a *theoretical* oxygen carrying capacity of 80% of the actual haemoglobin
    There is in fact a slight **left shift** of the **oxyhaemoglobin dissociation curve**, as oxygen binds more tightly to the partially-oxidised haemoglobin.

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1. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Angiotensin Converting Enzyme Inhibitors

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II by angiotensin converting enzyme (ACE) in the lungs, in turn reducing effects of angiotensin II. These effects include:

- Vasoconstriction
- Noradrenaline reuptake inhibition
- Thirst
- ADH release
- ACTH release
- Aldosterone release
- Reduces Kf, reducing GFR

Indications

- **Hypertension**
  - Particularly in insulin dependent diabetes with diabetic nephropathy
  - Less effective for this indication in the black population
  - Contribute to post-operative hypertension and may be withheld perioperatively
- **Cardiac failure**
  All grades.
- **MI with LV dysfunction**
  Improved prognosis.

Classification

Can be divided into three groups based on pharmacokinetics:

- Active drug with active metabolites
  Captopril.
- Prodrug
  Ramipril.
- Not metabolised and excreted unchanged in urine
  Lisinopril.

Common Features of ACE Inhibitors

Property	Drug
Resp	Bradykinin cough
CVS	↓ SVR and BP. Unaffected HR and baroreceptor response.
Endocrine	Hypoglycaemia in diabetics
Renal	With a normal renal perfusion pressure, natriuresis results. However, a fall in renal perfusion pressure may cause pre-renal failure (e.g. renal artery stenosis).
Haeme	Agranulocytosis, thrombocytopenia

Immune	Angioedema
Metabolic	↑ Renin release.
Interactions	↓ Aldosterone release, which ↑ the efficacy of spironolactone and may precipitate hyperkalaemia. Pharmacodynamic interaction with NSAIDs to drop renal perfusion pressure.

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Angiotensin Receptor Blockers

Angiotensin receptor antagonists are very similar to ACE inhibitors, except:

- Bradykinin does not accumulate as it is still broken down by ACE
  Therefore there is no cough and patient compliance is improved.
- The AT_1 receptor in cardiac tissue is more comprehensively blocked which *may* improve cardiac outcomes
- The AT_2 receptor is not blocked, which *may* also improve cardiac outcomes

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References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Potassium Channel Activators

Potassium channel activators stimulate ATP sensitive K^+ channels, causing an increase in intracellular cGMP and subsequent relaxation of smooth muscle in the:

- Heart
- Venous capacitance vessels
- Arterioles

Property	Nicorandil
Uses	HTN, angina, CHF
Route of Administration	PO
Dosing	10-30mg BD
Absorption	80% PO bioavailability
Distribution	Negligible protein binding
Metabolism	Hepatic denitration
Elimination	Renal elimination of active drug and metabolites
CVS	↓ Preload, ↓ afterload, ↓ BP, ↑ coronary flow
CNS	Headache, improves with ongoing use
Haeme	Inhibition of platelet aggregation

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Sodium Channel Blockers

Sodium channel blockers include:

- Class Ia:
  - **Procainamide**
  - Quinidine
  - Disopyramide
- Class Ib:
  - **Lignocaine**
  - Mexiletine (lignocaine analogue)
- Class Ic:
  - **Flecainide**

In general:

- IV preparations are given for VT
- Good PO bioavailability and low protein binding
- Metabolites are renally cleared

Property	Procainamide	Lignocaine	Flecainide
Class	Class Ia amide	Class Ib amide local anaesthetic	Class Ic amide local anaesthetic
Uses	SVT/VT	VT	SVT/VT
Presentation		Clear solution at 10-20mg.ml^{-1} (1-2%)	
Route of Administration	PO/IV	IV	PO/IV
Dosing	100mg IV load, followed by infusion at 2-6mg.ml^{-1}	Load at 1mg.kg^{-1} followed by infusion at 1-3mg.min^{-1}	2mg.kg^{-1} (up to 150mg) load over 10-30 minutes, followed by infusion at 1.5mg.kg^{-1}.hr^{-1}, aiming for levels of <0.9mg/ml
Absorption	75% bioavailability	IV only for arrhythmia	90% orally bioavailable
Distribution		33% unionised, 70% protein bound	50% protein bound
Metabolism	Hepatic to active metabolites via acetylation - slow acetylators at increased risk of side effects	Hepatic amidases to inactive metabolites	Hepatic to active metabolites
Mechanism of Action	Reduces the rate of rise of phase 0, raises the threshold potential, and prolongs the refractory period without prolonging the action potential	Reduces the rate of rise of phase 0 of the action potential. Repolarisation phase is shortened.	Reduces the rate of rise of phase 0 of the action potential. Repolarisation is unchanged.
CVS	↓ HR, ↓SVR, ↓BP, ↓CO, heart block, may ↑HR when used for SVT, ↑QT with risk of TDP	AV block, myocardial depression causing unresponsive ↓BP	Precipitate pre-existing conduction disorders, ↓ inotropy, ↑ pacing and defibrillation threshold
CNS		Circumoral tingling, dizziness, parasthesia, confusion, seizures, coma	Dizziness, parasthesia, headache

Immune	Lupoid syndrome in 20-30%, reduces antimicrobial effect of sulfonamides		
Interactions			Pharmacokinetic interactions with digoxin, propranolol, amiodarone

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.

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Beta-Blockers

β-blockers are competitive (often highly selective) antagonists of β-adrenoreceptors. They are sub-classified into into selective and non-selective agents:

- Selective (β_1 antagonism) (BEAM)
  - Bisoprolol
  - Esmolol
  - Atenolol
  - Metoprolol
- Non-selective (β_1 and β_2 antagonism)
  - Propranolol
  - Sotalol
  - Timolol
- Non-selective (β & α antagonism)
  - Carvedilol
  - Labetalol

Indications

- Cardio
  - Angina
  - Arhythmia
    - Rate-control in AF
    - Paroxysmal SVT
    - Sinus tachycardia from ↑ catecholamines
  - Cardiac Failure
  - Secondary prevention for MI

- Vascular
  - Hypertension (2nd line)
    Also useful for aggressive control of BP.
  - Hypotensive anaesthesia
  - Attenuate hypertensive response to laryngoscopy

- Non-CVS
  - Thyrotoxicosis
  - Glaucoma (topically)
  - Anxiety
  - Migraine prophylaxis

Common Features

Property	Action
Kinetics	Variability primarily due to lipid solubility. Poor lipid solubility confers poor gut absorption and minimises need for hepatic metabolism. Lipid soluble agents will have CNS effects and be excreted in breast milk.
Respiratory	Bronchospasm.

CVS	↓ Inotropy, ↓ HR, ↓ MVO_2, ↓ BP, ↑ SVR (β_2 effect), worsen arrhythmia.
CNS	Tiredness, nightmares, and sleep disturbance with lipid soluble agents. ↓ IOP.
Metabolic	↓ Insulin release and blunted hypoglycaemic response (β_2 effect).
Interactions	Contraindicated with cardioselective Ca^{2+} channel blockers. due to extreme ↓ HR & ↓ inotropy.

Comparison of Beta Blockers

Property	Esmolol	Metoprolol	Atenolol	Propranolol	Labeta
Class	Cardioselective	Cardioselective	Cardioselective	β non-selective	Non-selec β & selec α_1 Ratio of β antagonis 3:1 after I and 7:1 a IV administr
Uses	Short-term treatment of tachyarrhythmia and HTN	MI, HTN, migraine, thyrotoxicosis	HTN, angina, tachyarrhythmias, acute MI	HTN, Angina, dysrhythmia, essential tremor, anxiety HOCM, phaeochromocytoma, migraine, oesophageal varices	HTN, MI
Presentation	Clear, colourless solution	Clear, colourless solution, 50mg Tablet.	25/50/100mg tablets, syrup, colourless solution.	Tablets and solution at $1mg.ml^{-1}$	Tablets ar solution a $5mg.ml^{-1}$
Route of Administration	IV	PO/IV	PO/IV	PO/IV	PO/IV
Dosing	$50\text{-}200\mu g.kg^{-1}.min^{-1}$	IV: 1mg boluses PO: 12.5-100mg BD	PO: 50-100mg daily IV: 2.5mg IV up to 10mg	PO: 10-100mg BD/TDS IV: 1mg boluses titrated to response	PO: 100-800mg B IV: 10-20 IV bolus, followed 20-80mg Q30min u 300mg. Alternativ by infusio 1-2mg.mi
Absorption	IV only	50% bioavailability, improves with regular use	45% PO bioavailability	30% bioavailability	Highly variable bioavailal 10-80%
Distribution	60% protein bound	20% protein bound. Lipid soluble	5% protein bound	95% protein bound	50% prot bound
Metabolism	RBC esterases to an inactive metabolite and methyl alcohol. $t_{1/2}$ of 10 minutes	Hepatic with genetic variability in $t_{1/2}$ of active metabolites	Minimal metabolism - dose reduce in renal failure	Hepatic to active and inactive metabolites	Considera hepatic fi pass metabolis with inac metabolit
					Renal

Elimination			Renal elimination of active drug	Renal elimination of metabolites	eliminatio inactive metabolit
CVS	Venous irritant				↓ SVR, ↓ Does not to ↓ HR c CO when given acu
CNS					Orthostat dizziness

References

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Amiodarone

Amiodarone is an antiarrhythmic agent with a complex mechanism of action and many effects.

- K^+ channel blockade in cardiac myocytes, inhibiting the slow outward current and slowing repolarisation (Class III)
- β-blocker-like activity on SA and AV nodes, decreasing automaticity and slowing nodal conduction (Class II)
- Ca^{2+} channel blocker-like activity on L-type Ca^{2+} channels, decreasing the slow inward Ca^{2+} current, increasing depolarisation time and decreasing nodal conduction (Class IV)
- α-blocker-like activity, decreasing SVR

Property	Amiodarone
Class	Class III antiarrhythmic, though exhibits action from all 4 classes.
Uses	VT/VF, resistant arrhythmia, ALS.
Presentation	100/200mg tablets, IV: 150mg ampoule to be reconstituted in D5W.
Route of Administration	IV/PO.
Dosing	IV: Load with $5mg.kg^{-1}$ over 1/24, with a further $15mg.kg^{-1}$ over the following 24/24 PO: 200mg TDS for 1/52, 200mg BD for 1/52, 200mg OD thereafter.
Absorption	Poor PO absorption with bioavailability ~50%.
Distribution	Highly protein bound with very high V_D of ~$70L.kg^{-1}$s due to accumulation in fat and muscle.
Metabolism	Hepatic metabolism with inhibition of CYP3A4, to the active **desmethylamiodarone**.
Elimination	Very long $t_{1/2}$ of up to ~55 days. Biliary, skin, and lacrimal elimination, with < 5% of drug eliminated renally. Not removed by dialysis.
Resp	10% 3-year risk of pneumonitis, fibrosis, pleuritis.
CVS	↓ HR, ↓ BP, ↓ SVR, ↑ QT without risk of TDP. Irritant to peripheral veins.
CNS	Mild blurring of vision from corneal deposition, sleep disturbance, vivid dreams, peripheral neuropathy.
MSK	Photosensitivity, grey skin.
Endocrine	Hyperthyroidism (1%) and hypothyroidism (6%).
GIT	Nausea, vomiting, cirrhosis, hepatitis, and jaundice.
Other	Amiodarone has potential to cause a number of drug interactions due to its inhibition of CYP3A4 and its high protein binding. A selection include: Digoxin, statins, warfarin, phenytoin, and other antiarrhythmics. Contraindicated in **porphyria**.

A **mnemonic** for some of the rarer effects is **BITCH**:

- **B**lue skin
- **I**nterstitial lung disease
- **T**hyroid
- **C**orneal
- **H**epatic

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014. Peck and hill
2. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.

Last updated 2019-07-18

Sotalol

The D-isomer of sotalol is a **class III antiarrhythmic**, whilst the L-isomer also has **class II activity**.

Property	Action
Class	Class III antiarrhythmic
Uses	Tachyarrhythmia prophylaxis
Presentation	Solution at 10mg.ml^{-1} and tablets
Isomerism	Racemic mixture
Route of Administration	PO/IV
Dosing	PO: 40-160mg BD IV: 50-100mg over 20 minutes
Absorption	>90% bioavailability
Distribution	No protein binding
Metabolism	Not metabolised
Elimination	Excreted unchanged in urine
Resp	Bronchospasm
CVS	Torsades (< 2%) - more common with high doses, long QT, and electrolyte imbalances
CNS	Masking symptoms of hypoglycaemia
GU	Sexual dysfunction

References

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Last updated 2019-07-18

Digoxin

Digoxin is a cardiac glycoside used in the treat of atrial arrhythmias and in cardiac failure as a positive inotrope.

Digoxin has both a direct and indirect **mechanism of action**:

- Direct
  Inhibits cardiac Na^+/K^+ ATPase, causing:
  - Increasing intracellular $[Na^+]$, increasing activity of the Na^+/Ca^{2+} pump
  - Increased intracellular Ca^{2+} increases inotropy
  - Decreased K^+ results prolongs refractory period of the AV node and bundle of His
- Indirect
  Parasympathomimetic effects by increasing ACh release at cardiac muscarinic receptors.
  - Slows AV nodal conduction and ventricular response
    This improves coronary blood flow, increasing time for ventricular filling, and improving cardiac output.

Property	Action
Class	Cardiac Glycoside
Uses	Arrhythmia - particularly AF/Flutter, and CCF
Presentation	Tablets, elixir, clear colourless solution
Route of Administration	PO/IV
Dosing	PO: 62.5μg-250μg, IV: 250-500μg load
Absorption	>70% bioavailability though varies with formulation
Distribution	25% protein bound. V_D 5-11L.kg^{-1}, dependent on lean mass
Metabolism	Minimal hepatic metabolism
Elimination	Renal elimination of active metabolites $t_{1/2}$ 35 hours - increased in renal failure
CVS	↓ HR, ↑ inotropy, arrhythmias including; bigeminy, PVCs, 1st/2nd/3rd degree AV block, SVT, VT
CNS	Deranged red-green colour perception, visual disturbances, headache
Immune	Eosinophilia and rash
Metabolic	Gynaecomastia
Toxic Effects	Narrow TI. Severe arrhythmia with DC cardioversion

Interactions

Interaction	Drug
Increased level	Amiodarone, captopril, erythromycin, verapamil
Decreased level	Antacids, cholestyramine, phenytoin, metoclopramide

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Adenosine

Adenosine acts via A_1 adenosine receptors in the SA and AV node, which when stimulated open K^+ channels causing hyperpolarisation and a reduction in Ca^{2+} current, with subsequent blockade of AV nodal conduction.

Property	Action
Class	Naturally occurring purine nucleoside
Uses	SVT
Presentation	Colourless solution at $3mg.ml^{-1}$
Route of Administration	IV
Dosing	3mg/6mg/12mg in increasing doses
Metabolism	Rapidly deaminated in plasma. $t_{1/2}$ < 10s
Resp	Bronchospasm, ↑ RR and V_T
CVS	↓↓ AV nodal conduction, may cause AF/lutter
Toxic Effects	Contraindicated in sick-sinus syndrome, $2^{nd}/3^{rd}$ degree AV block

Interactions

Interaction	Drug
Increased effect	Dipyridamole
Decreased effect	Methylxanthines, such as aminophylline and caffeine

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.

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Magnesium

Mg^{2+} is a cation that is important for neurotransmission and neuromuscular excitability. Magnesium:

- Inhibits ACh release at the NMJ
- Acts a cofactor in multiple enzyme systems
- Is important in the production of:
  - ATP
  - DNA
  - RNA

Property	Action
Uses	HypoMg, arrhythmia, eclampsia, tocolysis, barium poisoning, asthma, tetanus, autonomic hyperreflexia
Presentation	2mmol.ml^{-1}, made up into 10mmol in 100ml for peripheral administration
Route of Administration	PO/IV
Dosing	IV: 10-20 mmol
Distribution	30% protein bound
Elimination	Significant urinary excretion, even when deficient
Resp	Bronchodilation
CVS	↓ SVR, hypotension, ↓HR
CNS	CNS depression, anticonvulsant
GU	↓ Uterine tone and contractility

Clinical Effects of Magnesium

[Plasma]	Effect
< 0.7 mmol.L^{-1}	Arrhythmia
4-6 mmol.L^{-1}	Nausea, **hyporeflexia**, speech impairment
6-10 mmol.L^{-1}	Weakness, respiratory depression, bradycardia
> 10 mmol.L^{-1}	Cardiac arrest

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1. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Atropine

Naturally occurring tertiary amine which competitively antagonises ACh at the muscarinic receptor, causing parasympatholytic effects.

Property	Atropine
Class	Naturally occurring tertiary amine. Muscarinic antagonist.
Uses	Bradycardia, organophosphate poisoning, antisialagogue, treatment of PDPH
Presentation	Clear, colourless solution at 600μg.ml^{-1}. Racemic mixture, with only the L-isomer active
Route of Administration	IV
Dosing	600μg-3mg
Distribution	50% protein bound, V_D 3L.kg^{-1}. Crosses BBB.
Metabolism	Extensive hepatic hydrolysis
Elimination	Renal elimination of metabolites and unchanged drug
Resp	Bronchodilation, ↓ secretions
CVS	↑ HR due to ↑ AV nodal conduction, peaks within 2-4 minutes and lasts 2-3 hours
CNS	Central anticholinergic syndrome, confusion, ↑ IOP, ↑ CSF secretion in choroid, cerebral vasoconstriction
MSK	Inhibits sweating
GIT	↓ LoS tone

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1. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Diuretics

> An understanding of the pharmacology of diuretics.

Diuretics are drugs that act on the kidney to increase urine production. They can be classified by their mechanism of action into:

- Thiazides
- Loop diuretics
- Potassium sparing
- Aldosterone antagonists
- Osmotic
- Carbonic Anhydrase inhibitors

Common Features of Diuretics

Property	Diuretics
Absorption	Typically poor bioavailability (exception: **acetazolamide**)
Distribution	Variable protein binding
Metabolism	Generally not metabolised. Key exceptions: Spironolactone is extensively metabolised with active metabolites, and a small amount of **frusemide** is metabolised to glucuronide.
Elimination	Renal elimination of unchanged drug
CVS	Reduced intra and extravascular volume
Renal	Any diuretic which inhibits sodium reabsorption can precipitate hypokalaemia (as a greater intra-luminal concentration of sodium results in exchange of sodium for potassium ions), hyponatraemia (as there is still a net loss of sodium), and alkalosis (from loss of hydrogen ions exchanged for sodium, or the overall raised strong ion difference).

Comparison of Diuretics

	Thiazides	Loop Diuretics	Potassium Sparing	Aldosterone antagonists	Osmotic
Example	Hydrochlorothiazide	Frusemide	Amiloride	Spironolactone	Mannitol
Site	Distal tubule	Loop of Henle	Distal tubule	Distal tubule	Glomerulus
Mechanism of action	Inhibit Na^+ and Cl^- reabsorption, and increase Ca^{2+} reabsorption in the DCT	Inhibit NKCC2, the $Na^+/K^+/2.Cl^-$ transport protein in the thick ascending limb, impeding the counter-current multiplier. This reduces the hypertonicity of the medulla, and subsequent water reabsorption in the collecting system.	Inhibits Na^+/K^+ exchange pump. Weak effect.	Competitive aldosterone antagonist. Aldosterone stimulates Na^+ reabsorption, which in turn stimulates K^+ secretion.	Filtered at the glomerulus and not reabsorbed, increasing filtrate osmolarity and increases water excretion.

Resp					
Cardiac	Antihypertensive due to reduced plasma volume and SVR	Arteriolar vasodilation, reducing SVR and preload			Increases intravascular volume, increasing preload. May increase CO or result in cardiac failure.
CNS					↓ ICP
Renal	Reduced renal blood flow and GFR	Increased renal blood flow and GFR			Increased renal blood flow
Metabolic	Hypokalaemic, hypochloraemic alkalosis. Hyperglycaemia.	Hypochloraemia, hyponatraemia, hypokalaemia, hypomagnesaemia. Occasional **hyper**uricaemia precipitating gout.	Hyperkalaemia.	Hyperkalaemia, hyponatraemia.	
Miscellaneous	Blood dyscrasias	Deafness, typically following large doses. More common in kidney impairment and with aminoglycoside use.		Gynaecomastia and menstrual irregularity due to anti-androgynism from aldosterone antagonism	

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Intravenous Fluids

Intravenous fluids can be classified into:

- **Crystalloids**
  Can pass freely through a semipermeable membrane. Can be further classified into:
  - ECF replacement solutions
    Have a [Na^+] similar to ECF, such that they are confined mostly to the ECF.
  - Maintenance solutions
    Designed to distribute throughout TBW.
  - Special solutions
    These solutions don't fit into the above two categories, and include:
    - Hypertonic saline
    - Mannitol
    - 8.4% Sodium Bicarbonate
- **Colloids**
  Substance evenly dispersed throughout another solution in which it is insoluble. Can be classified into:
  - Naturally occurring
    - Albumin
      Heat-treated human albumin.
      - Produced at low pH but not technically sterile
        Use within 3 hours of opening.
      - Contributes to plasma oncotic pressure
      - Contributes to drug and endogenous substance binding
  - Synthetic
    - Dextrans
      High molecular weight sugars synthesised from sucrose by bacteria.
      - Interfere with haemostasis due to vWF inhibition
      - Interfere with blood crossmatch
      - Risk of anaphylaxis
    - Gelatins
      High molecular weight proteins produced by collagen hydrolysis.
      - Greatest anaphylaxis risk
      - Do not interfere with clotting
    - Hydroxyl-ethyl starches
      - Risk of anaphylaxis
      - Risk of renal impairment
      - Accumulate in the reticuloendothelial system

Comparison of Crystalloids

Contents ($mmol.L^{-1}$)	0.9% NaCl	Hartmann's	Plasmalyte
Na^+	154	130	140
Cl^-	154	109	98
K^+		4	
Ca^{2+}		3	
$^{2+}$			

Mg^{2+}			1.5
Lactate		28	
Acetate			27
Gluconate			23
pH	5.0	6.5	5.5

References

http://www.anaesthesiamcq.com/FluidBook/fl7_2.php

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Propofol

Propofol (2-6 di-isopropylphenol) is a phenolic derivative with effects on many receptors including:

- $GABA_A$
  Potentiates the effect of GABA, prolonging Cl^- channel opening and hyperpolarising the cell.
- Glycine
- Nicotinic ACh
- D_2 receptors

Property	Action
Class	Phenolic derivative
Uses	Induction of anaesthesia, sedation, TIVA
Presentation	White oil-in-water emulsion at a **pH of 7-8.5** containing: - 10-20mg.ml^{-1} propofol - 10% Soybean oil (solubilising agent) - 1.2% Purified egg phosphatide (emulsifier) - 2.25% Glycerol (for tonicity) Bacteriostatic additives including: - Generics: Sodium metabisulfite - Diprivan: Disodium edetate (less allergenic) Risk of bacterial contamination limits shelf life. Energy content is 1.1kcal.ml^{-1}
pKa	11 - almost all is unionised (and active) at physiologic pH
Route of Administration	IV only
Dosing	Induction: 1-2.5mg.kg^{-1} Maintenance: 4-12mg/kg/hr. Target plasma concentration of 4-8µg.ml^{-1} to maintain general anaesthesia
Distribution	98% protein bound. Very high V_D at 4L.kg^{-1}. Rapid initial distribution: $t_{1/2}α$ (fast) 1-3 minutes, intermediate distribution $t_{1/2}α$ (slow) 30-70 minutes. $t_{1/2_{ke0}}$</sub> of **2.7** min.
Metabolism	Hepatic and extra-hepatic metabolism to inactive glucuronides and sulphates; $t_{1/2}β$ 2-12 hours. **Clearance** of **30-60ml.kg.min^{-1}**, unaffected by renal and hepatic disease. Context sensitive half-time peaks at **50 minutes** following a 9 hour infusion.
Elimination	Tri-exponential. Renal elimination of inactive metabolites.
Resp	Respiratory depression, apnoea. Strong suppression of laryngeal reflexes. ↓ Response to hypoxia and hypercapnea. Bronchodilation.
CVS	↓ Arterial and venous vasodilation (via stimulating NO release) causing ↓ SVR and ↓ VR, with ↓ BP. ↓ Inotropy via ↓ in SNS tone, ↓ MVO_2. Depresses baroreceptor reflex. Pain on injection due to lipid emulsion.
CNS	Hypnosis. Rapid LoC (within 1 arm-brain circulation time). ↓ CMRO2, CBF, and ICP. Anticonvulsant. ↓ IOP. Paradoxical excitatory effects seen in ~10% - dystonic movements of subcortical origin. EEG demonstrates non-specific seizure-like activity.
MSK	Pain on injection into small veins
Renal	Green urine
GIT	Anti-emetic. ↓ Hepatic Blood Flow
Metabolic	Fat overload syndrome, lipaemia following prolonged infusion. Inhibits mitochondrial function.
	Propofol infusion syndrome: Acidosis, bradycardia, and MODS following prolonged infusion (>24

	mitochondrial defects. Believed due to inhibition of mitochondrial function.

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1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. CICM July/September 2007 http://ceaccp.oxfordjournals.org/content/4/3/76.full.pdf
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Barbiturates

Thiopentone is a positive allosteric modulator at $GABA_A$ receptors (at a separate site to benzodiazepines) in the CNS. Barbiturates cause:

- Decreased rate of dissociation of GABA
  Increases the duration of channel opening, causing effective hyperpolarisation due to increased Cl^- conductance.
  - Clinical effects differ from benzodiazepines as benzodiazepines increase *frequency* of opening, whilst barbiturates increase *duration*
- Direct activation of the channel at higher doses

Property	Thiopentone
Class	Barbiturate
Uses	Induction of anaesthesia, status epilepticus, control of ICP refractory to other measures
Presentation	500mg of yellow powder with $NaCO_3$ for reconstitution as a 2.5% solution. Container uses nitrogen as a filler gas (to prevent HCO_3^{-1} formation when CO_2 combines with water during reconstitution, which ↓ pH and therefore water solubility). pH of 11 when reconstituted - bacteriostatic solution.
Isomerism	Tautomer. pKa of 7.6, such that 60% is unionised at pH 7.4 (i.e. water solubility decreases once injected).
Route of Administration	IV
Dosing	3-7mg.kg^{-1}. Consider 75mg boluses, assessing haemodynamic and neuronal effects.
Distribution	65-85% protein bound. High lipid solubility and CBF gives a rapid, reliable onset. Rapid offset due to redistribution, with a fast $t_{1/2}\alpha$ of 8 minutes. Prolonged elimination half life (11 hours) contributes to long CSHT. Increased unionised portion in acidosis. $t_{1/2}{}_{ke0}$ of 1.2 minutes.
Metabolism	Capacity dependent CYP450 metabolism - saturates at high doses (long CSHT with infusion). Metabolised to (active) **pentobarbital**, which also increases the duration of its clinical effects.
Elimination	Renal of metabolites, < 1% excreted unchanged
Resp	Respiratory depression, bronchospasm, laryngospasm
CVS	Vasodilation and venodilation (↓ MSFP), ↓ inotropy, with compensatory tachycardia (baroreceptor response preserved)
CNS	Hypnosis and anaesthesia within 40 seconds of injection, with reliable loss of lash reflex. Anticonvulsant. Dose-dependent flattening of the EEG (β α θ δ burst suppression isoelectric), causing progressive ↓ $CMRO_2$ (55% of maximal during burst suppression), ↓ CBF, and ↓ ICP. Resolution of induction dose in 5-10 minutes due to redistribution.
Endocrine	↓ RBF causing ↓ UO
GIT	Hepatic enzyme induction
Immune	Anaphylaxis ~1;20,000
Metabolic	May precipitate acute **porphyric crises** and is **contraindicated** in these patients
Other	Intraarterial injection causes precipitation as water solubility decreases at blood pH. Microembolisation and ischaemia result, which should be treated with intraarterial local anaesthesia, analgesia, anticoagulation, and sympathetic blockade of the limb. Tissue necrosis on extravasation.

References

1. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.
2. LITFL - Thiopentone
3. Hill, SA. Pharmacokinetics of drug infusions. Continuing Education in Anaesthesia. 2004.

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Ketamine

Ketamine is a phencyclidine derivative used for induction, sedation, analgesia, and as a bronchodilator in severe asthma.

Ketamine acts via:

- **Non-competitive antagonist** of **NMDA** and **glutamate** receptors in the CNS
- Reduces presynaptic glutamate release
- Sodium channel inhibition
  Local anaesthetic-like effect.
- Potential monoaminergic, muscarinic, and nicotinic antagonism

Property	Action
Class	Phencyclidine derivative
Uses	Induction of anaesthesia, sedation, analgesia, asthma
Presentation	Clear, colourless solution forming an acidic solution (pH 3.5-5.5)
Isomerism	Racemic mixture or the single S(+) enantiomer, which is 2-3x as potent as the R(-) enantiomer but has less bronchodilatory properties
Route of Administration	IV, IM, PO, PR, PN, via epidural (with preservative-free solution)
Dosing	Induction: 1-2mg.kg^{-1} IV, 5-10mg.kg^{-1} IM, Sedation: 0.2-0.5mg.kg^{-1} IV
Distribution	25% protein bound. $t_{1/2}\alpha$ 10-15 minutes
Metabolism	Hepatic metabolism to active norketamine by CYP450 and then to inactive metabolites, $t_{1/2}\beta$ 2-4 hours
Elimination	Renal elimination of inactive metabolites. Action of norketamine prolonged in renal failure.
Resp	Bronchodilation, tachypnea, relative preservation of laryngeal reflexes. Apnoea with rapid injection. Preserved central response to CO_2.
CVS	↑ Sympathetic outflow: ↑ HR, ↑ BP, ↑ SVR, ↑ MVO_2. Acts directly as a myocardial depressant - beware maximally stimulated patient. Depresses baroreceptor reflex.
CNS	Dissociation, analgesia, emergence phenomena (hallucinations, delirium) reduced by concurrent BDZ administration (increasing risk with higher doses and rapid administration). Produces dissociative anaesthesia within 90 seconds by dissociating thalamocortical and limbic systems on EEG. Purposeful movements unrelated to stimulus may occur even during surgical anaesthesia. ↑ IOP.
Renal	Cystitis with long-term, high-dose use
GIT	N/V

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Dexmedetomidine

Dexmedetomidine is a central α_2-agonist (α_2:α_1 activity 1600:1) used for its sedation and analgesic properties.

Property	Action
Class	Imidazole derivative
Pharmaceutics	D-stereoisomer of medetomidine (the L-stereoisomer is inactive)
Uses	Sedation without respiratory depression
Presentation	Clear colourless solution at 10µg.ml^{-1}
Route of Administration	IV only
Dosing	0.2-0.7µg.kg^{-1}.hr^{-1}
Distribution	95% protein bound
Metabolism	Hepatic to inactive metabolites
Elimination	Renal of metabolites, $t_{1/2}\beta$ of 2 hours
CVS	Initial transient ↑ SVR and BP due to α_1 effects, followed by ↓ MAP, ↓ HR. Rebound ↑ BP when abruptly ceased.
CNS	Sedation, anxiolysis at low dose (anxiogenic at high dose), amnesia. ↓ MAC. ↓ SNS outflow.

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Local Anaesthetic Agents

- Local anaesthetic drugs deliver a use-dependent, temporary blockade of neuronal transmission
- **Unionised** drug **passes through the cell membrane**, and then becomes **ionised intracellularly**
- The ionised drug is then able to bind to the ion channel, and prevent conduction of sodium and therefore generation of an action potential

- All local anaesthetics consist of:
  - A hydrophilic component
  - A lipophilic aromatic ring
  - An amide or ester link connecting the two

Common Features of Local Anaesthetics

Property	Action
Class	Amide (-NHCO-) or Ester (-COOH-)
Pharmaceutics	Amides are stable in solution, esters are unstable in solution. All are formulated as a hydrochloride salt to ensure water solubility.
pKa	All are weak bases, and have a pKa > 7.4
Onset	Onset is related to dose (Fick's Law) and pKa, with a **low pKa** giving a **faster onset** as there is more unionised drug present and therefore more drug able to cross the cell membrane. This is why local anaesthetics are poor at anaesthetising infected tissues, as the tissue pH is low resulting in a greater proportion of ionised drug, and less drug reaching the effect site.
Duration of Action	Duration of action is related to protein binding, with **greater protein binding** giving a **longer duration of action**
Potency	Potency is related to lipid solubility (**higher lipid solubility increases potency**) and vasodilator properties (**weaker vasodilators having greater potency**)
Absorption	Systemic absorption **varies with site of entry** (from highest absorption to lowest: IV, intercostal, caudal epidural, lumbar epidural, brachial plexus, subcutaneous), **dose**, and **presence of vasoconstrictors**
Distribution	Amides are extensively protein bound, esters are minimally bound
Metabolism	Amides are hepatically metabolised, esters are hydrolysed by plasma cholinesterases (giving a much shorter $t_{1/2}$)
CVS	Vasodilatation at low concentrations, vasoconstriction at high concentrations. Inhibition of cardiac Na^+ channels, inhibiting maximum rate of rise of phase 0 of the cardiac action potential. Negative inotropy proportional to potency.
CNS	Does-dependent CNS effects: circumoral tingling, visual disturbances, tinnitus, tremors, dizziness, slurred speech, convulsions, coma, apnoea. Potentiated by other CNS depressants and hypercarbia (due to ↑ CBF and ↓ seizure threshold).
Toxic Effects	Esters have a higher incidence of **allergy** due to their metabolite para-amino benzoic acid (PABA). Local anaesthetic toxicity is predominantly CNS and CVS.

Comparison of Local Anaesthetics

Property	Lignocaine	Bupivacaine	Ropivacaine	Cocaine

Class	Amide	Amide	Amide	Ester
Uses	Local/regional/epidural, ventricular dysrhythmia	Local/regional/epidural	Local/regional/epidural	Topical anaesthesia and vasoconstriction
Presentation	Clear, colourless solution at 0.5/1/2% with or without adrenaline. Spray. Ointment. 4% solution.	Clear, colourless solution at 0.25/0.5%	Clear, colourless solution	1-4% solution, Moffat's solution (8% cocaine, 1% $NaCO_3$, 1:2 000 adrenaline)
pKa	7.9	8.1	8.1	8.6
Route of Administration	SC, epidural, IV	SC, epidural	SC, epidural	Topical
Onset/Duration	Rapid onset, short duration	Intermediate onset, long duration	Intermediate onset, long duration	20-30 minutes
Maximum Dose	Analgesia: $4mg.kg^{-1}$ without adrenaline, $7mg.kg^{-1}$ with adrenaline	$2mg.kg^{-1}$	$3mg.kg^{-1}$	$3mg.kg^{-1}$
Distribution	70% protein bound	Highly protein bound	Lower lipid solubility reduces motor block compared to bupivacaine	Highly protein bound
Metabolism	Hepatic with some active metabolites	Hepatic to inactive metabolites	Hepatic to active metabolites	Plasma esterases, some hepatic metabolism (unlike other esters)
Elimination	Reduced in hepatic or cardiac failure			Elimination of active drug and inactive metabolites
CC/CNS ratio	7	3	5	
Other		Most toxic of LA agents as it takes longer to dissociate from the myocardial Na^+ channel. **Levobupivacaine** is less cardiotoxic the racemic mixture, possibly as it has more intrinsic vasoconstrictive properties.		May cause ↑ BP, ↑ HR, coronary vasoconstriction, myocardial depression, VF, ↑ temperature due to ↑ serotonin, dopamine, and noradrenaline reuptake

Lignocaine Toxicity

Serum concentration ($\mu g.ml^{-1}$)	Phase	Effect
2	Safe	Antiarrhythmic. May begin to have lightheadedness, circumoral tingling, numbness
5	Excitatory	Dysarthria
8	Excitatory	Visual changes

10	Excitatory	Seizures
12	Depressive	Loss of consciousness
20	Depressive	Respiratory depression
25	Depressive	CVS depression

Pharmaceutics of Topical Local Anaesthetics

Effect of topical local anaesthetics is governed by **Fick's Law**.

Characteristic	Effect
Pharmaceutic Factors	
Presentation	Aerosol improves speed of onset by moisturising skin
Concentration of active component	Increase speed of onset
Stability	
pH	↑ pH ensures more local anaesthetic is in the unionised form, ↑ absorption.
Additives	Affect pH and vasoconstrictor activity
Drug Factors	
Molecular weight	Small molecules will diffuse more easily
pKa	Affects ionisation and therefore lipid solubility
Lipid solubility	↑ lipid solubility improves speed of onset.
Potency	Determines amount of drug needed to produce an effect
Vasoconstrictor activity	Will affect both speed of onset and degree of systemic absorption
Patient Factors	
Site	Degree of vascularity of site
Skin	Skin thickness and area will affect onset

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Benzodiazepines

Benzodiazepines are double-ringed positive allosteric modulators of the GABA receptors in the CNS. They:

- Bind to the α/γ interface of the receptor, increasing affinity of the receptor for GABA
- This leads to **hyperpolarisation** of the **cell membranes** and decreased neuronal transmission
  The mechanism varies between receptors:
  - $GABA_A$ is a **ligand gated** post-synaptic Cl^- ion channel
    Activation **increases Cl^- conductance** via **increasing frequency** of channel opening.
  - $GABA_B$ is a pre- and post-synaptic **G-protein coupled** receptor
    Activation **increases K^+ conductance**.

Common Features of Benzodiazepines

Property	Action
Uses	Sedation, anxiolysis, hypnotic, anticonvulsants, amnestic, muscle relaxation
Absorption	
Distribution	Highly lipid soluble and protein bound, very low V_D
Metabolism	Generally active metabolites.
Elimination	Renal elimination of active and inactive metabolites.
Resp	↓ V_T, ↑RR, apnoea.
CVS	↓ SVR, ↓SBP, ↓ DBP, ↑HR. Typically stable CO.
CNS	Hypnosis, sedation, anterograde amnesia, anticonvulsant, ↓ CBF. ↓ MAC.
MSK	Skeletal muscle relaxation.
Metabolic	↓ Adrenergic stress response.

Comparison of Benzodiazepines

Property	Midazolam	Diazepam	Clonazepam
Physicochemical	pKa 6.5. Structure is dependent on surrounding pH - at a pH < 4 its ring structure opens and it becomes water soluble.	40% propylene glycol.	
Route of Administration	PO/IV/IM.	PO/IV/IM.	PO.
Absorption	50% PO bioavailability.	Good PO bioavailability.	
Distribution	V_D 1.5L.kg^{-1}, 95% protein bound.	95% protein bound.	
Metabolism	Partially metabolised to oxazepam and 1-α-hydroxy-midazolam. Clearance ~7ml.kg^{-1}.min^{-1}.	Hepatic to all active metabolites including oxazepam, temazepam, and des-methyl-diazepam (has $t_{1/2}\beta$ up to 100 hours).	Hepatic to inactive metabolites.
Elimination	$t_{1/2}\beta$ 2-4 hours, prolonged with cirrhosis, CHF, obesity and in the	$t_{1/2}\beta$ 20-45 hours.	

	elderly.	1/2

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Antidepressants

Symptoms and management of TCA overdose is covered under Tricyclic Antidepressant Overdose.

Antidepressant drugs include:

- Tricyclic Antidepressants (TCAs)
  Mechanism of action by multiple effects, including:
  - Competitively inhibit reuptake of NA and 5-HT
  - Muscarinic antagonism
    Leads to anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention).
  - H_1 and H_2 antagonism
  - α_1 antagonism
  - NMDA antagonism
- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Inhibit neural reuptake of 5-HT
  - Preferred over TCAs as:
    - Similar effectiveness
    - Better side effect profile
- Monoamine Oxidase Inhibitors (MAO-Is)
  - Inhibit monoamine oxidase on external mitochondrial membrane, increasing the level of amine neurotransmitters in the CNS and PNS
    Two enzymes exist:
    - MAO-A
      - Dominant enzyme in CNS
      - Acts on serotonin, noradrenaline, adrenaline
    - MAO-B
      - Dominant in GIT and platelets
      - Responsible for 75% of MAO activity
      - Preferential metabolism of non-polar amines
  - MAO-Is classified by their mechanism and selectivity
    - Non-selective, irreversible
      Bind covalently to the enzyme, permanently inactivating it.
      - May lead to hypertensive crisis when catecholamine levels increased
        - Tyramine in food
          Metabolised by MAO-B.
        - Indirectly acting **sympathomimetics**
          Absolutely contraindicated.
      - Risk of serotonin syndrome with serotonin reuptake inhibitors
      - Include:
        - Phenelzine
        - Isocarboxazid
        - Tranylcypromine
      - Enzyme levels will take 2-3 weeks to recover following cessation
    - MAO-A selective, reversible
      - Hypertensive crisis is less common
        - MAO-B unaffected - tyramine is metabolised
        - Short acting
          Enzyme levels normalise after 24 hours of cessation.
      - Include:

        - Moclobemide
    - MAO-B selective
        - Much lower risk of hypertensive crisis
        - Include:
            - Selegiline
- Discontinuation syndrome may occur if abruptly ceased

Property	Tricyclic Antidepressants	Selective Serotonin Reuptake Inhibitors	Monoamine Oxidase Inhibitors
Example	Amitriptyline	Fluoxetine	
Uses	Depression, treatment of chronic pain and trigeminal neuralgia	Depression, anxiety	Treatment resistant depression. Now largely superseded due to side-effect profile
Absorption	High PO bioavailability	High PO bioavailability	
Distribution	Highly lipid soluble with High V_D. Very highly protein bound - leads to interactions with warfarin, digoxin, and aspirin	Highly protein bound, high V_D	
Metabolism	Hepatic with active metabolites. Large interpatient variability	Hepatic with non-linear kinetics Venlafaxine does not affect CYP450 enzymes.	
Elimination		Unaffected by renal impairment	
Resp	Dry mouth		
CVS	Postural hypotension, ↑ HR. QT prolongation and widening QRS in overdose, with arrhythmia more likely when QRS exceeds 0.16s.	Less cardiotoxic than TCAs, may precipitate serotonin syndrome	
CNS	Sedation, blurred vision, lowered seizure threshold. Excitation, followed by seizures and depression in overdose.	Identical antidepressant effect to TCAs. Less sedation	
Renal	Urinary retention		
GU	Sexual dysfunction	Greater incidence of sexual dysfunction compared with TCAs	
GIT	Constipation	Greater incidence of N/V compared with TCAs	
Other	Multiple complex drug interactions, including arrhythmias and variable BP with sympathomimetics, central anticholinergic syndrome, serotonin syndrome, and seizures. ↑ Sensitivity to catecholamines - suggest avoiding: -Indirectly acting sympathomimetics -Ketamine -Surgical stress	Continue during perioperative period to avoid risk of discontinuation syndrome.	

Serotonin Syndrome

Serotonin syndrome is excessive serotonin in the CNS, typically as a consequence of drug interactions. The syndrome may be mild, moderate, or severe, and presents with some or all of:

- Altered mental state
    - Confusion
- Motor changes
    - Myoclonus
    - Hyperreflexia
    - Tremor
- Autonomic instability
    - Diaphoresis
    - Shivering
    - Fever

Serotonin syndrome is typically self-limiting and resolves with cessation of the drug.

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Antipsychotics

Antipsychotics are drugs used for the management of psychoses and thought disorders. They have a complicated mechanism of action with effects on multiple receptors:

- Central dopamine (typically D_2, but varies with agent) antagonism
  Responsible for the antipsychotic properties
- $5\text{-}HT_2$ antagonism
- Other receptors which are quantitatively less important:
  - H_1 antagonism
  - α_1 antagonism
  - Muscarinic ACh antagonism

Based on their affinity to various receptors, they are (loosely) classified as either:

- **Typical** or 1st generation antipsychotics
  Higher affinity for D_2 receptors (subsequently less blockade of $5\text{-}HT_2$), causing a greater effect on 'positive' symptoms' and a greater incidence of extrapyramidal side effects
- **Atypical** or 2nd generation, which typically have fewer motor effects
  Have greater effect on negative symptoms.

Common Features of Antipsychotics

Property	Drug
Uses	Behavioural emergencies, schizophrenia/psychosis
CVS	QT prolongation
CNS	Apathy, ↓ initiative, ↓ response to external stimuli, ↓ aggression. No loss of intellectual function.
Endocrine	↑ Prolactin (typical antipsychotics)
Haeme	Leukopenia and agranulocytosis (predominantly clozapine, but can be all)
Metabolic	Weight gain, diabetes, hypercholesterolaemia (all atypical > typical)
Other Toxicities	Neuroleptic malignant syndrome, EPSE

Neuroleptic Malignant Syndrome

Antipsychotic Malignant Syndrome is rare and presents similarly to MH, with a rapid rise in body temperature and confusion. It has a high mortality (up to 20%).

Extra-Pyramidal Side Effects

Motor disturbances from antipsychotic use are termed EPSEs, and are divided into two main types:

- **Acute Dystonic Reactions** are involuntary movements and parkinsonian symptoms. They are:
  - More common with typical agents
  - Decline with ongoing use
  - Reversible with cessation of the agent
- **Tardive dyskinesia** is similar to ADR, except:

- Involuntary movements are more pronounced and disabling
- It occurs with long term use (10-20 years)
- They are **irreversible**, and worsen when therapy is stopped

Comparison of Antipsychotics

Property	Haloperidol	Olanzapine	Clozapine
Class	Typical	Atypical	Atypical ("3rd gen")
Uses	Behavioural Emergencies	Behavioural Emergencies, Psychosis/Schizophrenia	Treatment resistant schizophrenia
Presentation	Tablets, syrup, clear solution for injection at $5mg.ml^{-1}$	Tablets, solution for injection	Yellow tablet
Route of Administration	PO/IM/IV	PO/IM	PO
Dosing	1-5mg IV, 2-30mg IM, 1-15mg PO	IM 5-10mg, PO 5-20mg	Must be prescribed by a psychiatrist
Absorption	50% PO bioavailability	60% PO bioavailability	Rapid absorption
Distribution	92% protein bound	93% protein bound, V_D ~$14L.kg^{-1}$	V_D $2L.kg^{-1}$
Metabolism	Hepatic to largely inactive metabolites	Hepatic to inactive metabolites	May obey **zero-order** kinetics at the upper limit of the dose range
Elimination	Renal of metabolites	Renal of inactive metabolites	Renal of active drug (~25%) and inactive metabolites
CVS	Hypotension		Myocarditis (potentially fatal)
CNS			Seizures
GIT	Antiemetic		Hepatitis
Haeme			Agranulocytosis, thromboembolic disease

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Anticonvulsants

In **general**, anticonvulsants are:

- Well absorbed orally
- Highly protein bound
- Hepatically metabolised by CYP450 enzymes, and induce their own metabolism (as well as that of other drugs)
- Renally eliminated
- Interact with each other

Property	Phenytoin	Sodium Valproate	Carbamazepine	Levetiracetam
Uses	GTCS, partial seizures, trigeminal neuralgia, ventricular arrhythmias	Partial seizures	Antiepileptic, trigeminal neuralgia	GTCS, partial seizures, myoclonic seizures, seizure prophylaxis
Presentation	Capsules, syrup, solution. IV formulation incompatible with dextrose.	Tablets, syrup, solution	Tablets, suppositories, syrup	Tablets, oral liquid, IV liquid
Route of Administration	PO, IV, IM	PO, IV	PO	PO, IV (over 15 minutes)
Dosing	15-20mg.kg^{-1} load, aiming plasma levels 10-20mcg.ml^{-1}	300-1250mg BD	50-800mg BD	Typically 1g loading, then 500mg BD increasing up to 1.5g BD. Dose adjusted in renal impairment.
Mechanism of Action	Stabilises Na^+ channels in their inactive state, inhibiting generation of further action potentials.	Stabilises Na^+ channels in their inactive state and GABAergic inhibition	Stabilises Na^+ channels in their inactive state and potentiates GABA	Unknown, but different to other antiepileptics and may be related to inhibition of N-type Ca^{2+} currents
Absorption	Slow PO absorption. PO bioavailability 90%	PO bioavailability 100%	95% PO bioavailability	Near 100% PO bioavailability
Distribution	Highly protein bound	Highly protein bound	Highly protein bound	Nil significant protein binding, V_D ~0.5L.kg^{-1}
Metabolism	Hepatic hydroxylation with highly individual variation in dosing. Obeys first-order kinetics in the therapeutic range, and **zero-order kinetics just above the therapeutic range**. Metabolised by **CYP450**. Induces warfarin, benzodiazepines, OCP metabolism. Inhibited by metronidazole, chloramphenicol, isoniazid. **Genetic polymorphism** results in	Hepatic to inactive and active metabolites	Hepatic	Hepatic hydrolysis to inactive metabolites

	reduced metabolism in 5-15% of patients.			
Elimination	Renal elimination of inactive metabolites and active drug	Renal elimination of metabolites and active drug	Renal elimination	Renal of active drug (major route) and metabolite (minor route)
CVS	↓ BP, heart block, and asystole with rapid administration, antiarrhythmic properties		Antiarrhythmic	
CNS	↑ Seizure threshold, paraesthesia, ataxia, nystagmus, slurred speech, tremor, vertigo.	↑ Seizure threshold	↑ Seizure threshold	↑ Seizure threshold, anxiolytic. Minimal ↓ in seizure threshold on cessation.
Renal			Water retention from ADH-like effects	Rarely precipitates AKI
GIT	Hepatotoxicity (idiosyncratic). Nausea and vomiting.		Hepatotoxicity.	
Haeme	Aplastic anaemia and other blood dyscrasias		Thrombocytopenia, leukopenia (requires regular testing)	Thrombocytopenia
Immune	Rash			SJS
Metabolic		Hyperammonaemia		
Other	Requires monitoring due to narrow therapeutic window and significant pharmacokinetic variation. Gum hyperplasia. Teratogenic. May precipitate porphyria.		Reduces efficacy of aminosteroids. Teratogenic.	

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GABA Analogues

Gabapentin and pregabalin:

- Are both **structural analogues** of GABA
- Have no direct action on the $GABA_A$ receptor
- **Act on the $\alpha_2\delta$ subunit of voltage gated Ca^{2+} channels** in the CNS, inhibiting neurotransmitter release
- May have some NMDA receptor activity

Comparison of GABA Analogues

Property	Gabapentin	Pregabalin
Uses	Focal seizures, neuropathic pain	Focal seizures, neuropathic pain, anxiety
Route of Administration	PO	
Dosing	100mg TDS, increasing up to 1200mg TDS	50mg BD/TDS, up to 600mg in divided doses (BD or TDS)
Absorption	PO bioavailability of 60%, decreases with increasing dose due to saturation of transporter	90% PO bioavailability, delayed by food but unaffected by dose
Distribution	Minimally protein bound	Minimally protein bound
Metabolism	Not metabolised	Not metabolised
Elimination	Renal elimination of active drug, $t_{1/2}\beta$ 6 hours	Renal elimination of active drug, $t_{1/2}\beta$ 6 hours
CNS	Drowsiness, ataxia, psychiatric symptoms	Confusion, psychiatric symptoms, drowsiness
GIT		N/V

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Inhalational Anaesthetic Agents

> Describe the effects of inhalational agents on the cardiovascular, respiratory and central nervous systems

> Describe the toxicity of inhalational agents

> Describe the comparative pharmacology of ~~nitrous oxide~~, halothane, enflurane, isoflurane, desflurane, sevoflurane, xenon and ether

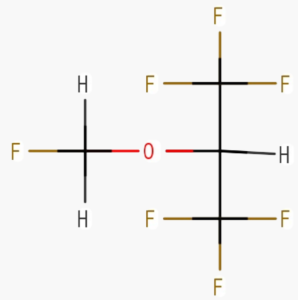
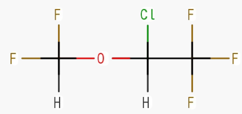
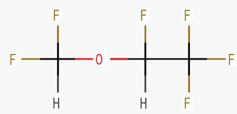
This section covers features and structures of inhalational anaesthetics. Structure-activity relationships are covered under inhalational anaesthetics.

Common Features of Inhalational Agents

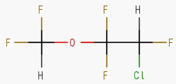
Property	Action
Metabolism	Hepatic CYP450 (CYP2E1) metabolises C-halogen bonds to release halogen ions (F^-, Cl^-, Br^-), which can be nephrotoxic and hepatotoxic. The C-F bond is minimally metabolised compared to the C-Cl, C-Br, and C-I bonds. All agents undergo hepatic oxidation, except for halothane which is reduced.
Resp	All halogenated agents ↓ V_T and ↑ RR, with an overall ↓ in MV and therefore cause $PaCO_2$ to ↑; and ↓ sensitivity of central respiratory centres to CO_2. Impairment of HPV may worsen V/Q matching and ↑ shunt.
CVS	↓ MAP (predominantly by ↓ in SVR due to NO release and Ca^{2+} channel blockade), ↓ inotropy due to Ca^{2+} channel blockade.
CNS	Hypnosis. ↓ $CMRO_2$. Above 1 MAC there is **uncoupling** of the CBF-$CMRO_2$ relationship, and CBF ↑ despite ↓ $CMRO_2$ due to cerebral vasodilation. ICP may mirror CBF changes. All except halothane have some analgesic effect. ↓ EEG frequency such that θ- and δ-wave dominate the EEG as depth ↑. May cause burst suppression.
MSK	Muscle relaxation via blockade of Ca^{2+} channels. Additional augmentation of the effects of NMBD due to skeletal muscle vasodilation. May precipitate MH.
Renal	Dose dependent ↓ in RBF, GFR, and UO secondary to ↓ in MAP and CO. Fluorinated ethers produce F^- ions when hepatically metabolised, which may produce high-output renal failure at serum concentrations **>50μmol/L**. This is probably only a concern with methoxyflurane (as it has significant (>70%) hepatic metabolism) when used at anaesthetic doses.
GIT	↓ Hepatic blood flow.
GU	Tocolysis.
Toxic Effects	Decreased fertility and increased risk of spontaneous abortion in operating theatre personnel.

Comparison of Common Inhalational Agents

Property	Sevoflurane	Isoflurane	Desflurane
Pharmaceutics	Minimally soluble, light stable, not flammable. Formulated with 300ppm of H_2O to prevent formation of HF acid by Lewis acids in glass.	Soluble in rubber, light stable, not flammable.	Light sensitive, flammable at 17%.

Structure			
Molecular Weight	200.1	184.5	168.0
Boiling point	58.5°C	48.5°C	23.5°C
SVP (mmHg) at 20°C	158	239	669
Blood:gas coefficient	0.7	1.4	0.42
Oil:gas coefficient	50	98	29
MAC	2	1.15	6.6
Metabolism	3-5% CYP2E1 metabolism to hexafluoroisopropanol and inorganic F^- (which may be nephrotoxic)	0.2% hepatic to nontoxic metabolites	
Resp	Bronchodilation, ↓ MV. Smallest ↓ in V_T and therefore smallest ↑ in $PaCO_2$	Bronchodilation, airway irritability. ↓ MV (greater than halothane) with ↑ in RR	Airway irritability manifest as coughing and breath-holding, ↑ secretions
CVS	↑ QT, ↓ SVR causing ↓ MAP without a reflex ↑ HR. Inotropy unchanged. Smallest ↓ in BP of any inhalational agent.	Reflex ↑ HR due to ↓ MAP from ↓ SVR. Small ↓ inotropy and CO, equivalent to sevoflurane but greater than desflurane. May cause **coronary steal**.	Minimal ↓ inotropy (least of all inhalational agents), but greater ↓ in SVR and BP than sevoflurane. ↑ in HR, with a bigger increase at >1.5 MAC. Large ↑ in SNS tone with rapid ↑ in desflurane concentration.
CNS	↑ Post-operative agitation in children compared to halothane. Smallest ↑ in CBF at > 1.1 MAC, with no increase in ICP up to 1.5 MAC. Cerebral autoregulation intact up to 1.5 MAC.	Best balance of ↓ $CMRO_2$ for ↑ in CBF.	
Toxic Effects	Sevoflurane interacts with soda lime to produce **Compound A** (as well as B through E, which are unimportant), which is nephrotoxic in rats (but not, it seems, in humans).	$-CHF_2$ group may react with dry soda lime to produce CO.	Desflurane has much greater greenhouse gas effects than sevoflurane or isoflurane.

Comparison of Uncommon Inhalational Agents

Property	Enflurane	Halothane	Xenon
Pharmaceutics	Structural isomer of isoflurane with different physical properties	Light unstable. Corrodes some metals and dissolves into rubber.	Not flammable. Very expensive to produce.
Structure			
Molecular Weight	184.5	197	131
Boiling point	56.5°C	50.2°C	-108°C
SVP (mmHg) at 20°C	175	243	-
Blood:gas coefficient	1.8	2.4	0.14
Oil:gas coefficient	98	224	1.9
MAC	1.7	0.75	71
Metabolism		~25% undergoes oxidative phosphorylation by CYP450 systems, producing **trifluoroacetic acid**, which binds to protein and can cause a T-cell mediated hepatitis, which can be fatal in ~1/10,000 anaesthetics.	Not metabolised.
Resp	Largest ↓ in V_T, therefore largest ↑ in $PaCO_2$	↑ In RR, ↓ in V_T with overall unchanged $PaCO_2$	↓ RR, ↑ in V_T such that MV is constant. 3x as dense and 1.5x as viscous as N_2O, which increases effective airway resistance. Does not appear to cause diffusion hypoxia.
CVS		Greatest ↓ in inotropy, HR, SVR, and MAP. Significant ↑ in catecholamine sensitivity.	More stable MAP, ↓ HR
CNS	Produces 3Hz "spike and wave" EEG pattern at high concentrations, resembling grand mal seizures	Greatest ↑ in CNS blood flow at > 1.1 MAC	Analgesic, ↑ PONV
MSK			Muscle relaxation when >60%. Does not trigger MH.
Renal	Direct nephrotoxicity, potentially related to fluoride (though this association is not present with other anaesthetic agents)		
GU	Least tocolytic effect		
Toxic effects	Produces F^- ions	Hepatic damage may be: - Reversible transaminitis - Fulminant hepatic necrosis, with a	

		mortality of 50-75%.

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Nitrous Oxide

> Describe the pharmacology of nitrous oxide

> Describe the comparative pharmacology of nitrous oxide, ~~halothane, enflurane, isoflurane, desflurane, sevoflurane, xenon and ether~~

Property	Nitrous Oxide
Pharmaceutics	Non-flammable but supports combustion. Produced by heating ammonium nitrate to 250°C. Potential contaminants include NH_3, N_2, NO_2, and HNO_3. **Stored as a liquid**, such that the gauge pressure is only accurate when all remaining N_2O is in the gaseous phase. The **filling ratio** is the mass of N_2O in the cylinder compared to the mass of water it could hold, and is **0.75** in temperate regions, and **0.67** in warmer regions.
Molecular Weight	44
Boiling point	-88°C
Critical Temperature/Pressure	36.5°C / 72 bar
SVP (at 20°C)	39,000 mmHg
Blood:gas coefficient	0.47
Oil:gas coefficient	1.4
MAC	105 (MAC awake 68)
Mechanism of Action	Several different mechanisms, including: - Stimulates dynorphin release (acts at KOP receptor) - Positive allosteric modulator at $GABA_A$ receptor - NMDA antagonist
Metabolism	< 0.01% hepatic reduction.
Resp	Diffusion hypoxia due to second gas effect. Small ↓ in V_T, ↑ in RR such that MV is unchanged.
CVS	↑ SNS tone, mild myocardial depression. ↑ PVR - beware in pulmonary hypertension.
CNS	Powerful analgesic when > 20%, via endorphin and enkephalin modulation, and on opioid receptors. ↑ CBF. Loss of consciousness common at 80%. 1.4x relative risk of PONV
GU	Not tocolytic - useful adjuvant in GA caesarian section to reduce volatile anaesthetic use
GIT	Expansion
Metabolic	↑ Homocysteine.
Toxic Effects	More soluble than N_2 means it will rapidly diffuse into air-filled cavities, increasing the volume of compliant cavities (PTHx, bowel), and increasing the pressure of non-compliant cavities (middle ear). Prolonged use (> 6 hours) **oxidates cobalt ion in vitamin B_{12}, preventing its action as a cofactor** for **methionine synthetase**, preventing DNA synthesis. This leads to: - Megaloblastic changes in bone marrow - Agranulocytosis - Peripheral neuropathy - Possible teratogenicity - avoid in early pregnancy Greenhouse gas.

Entonox

Entonox is a 50/50 mixture of nitrous oxide and oxygen, used as analgesia in labor and minor procedures.

Property	Entonox (50% O_2, 50% N_2O)
Pharmaceutics	The gases dissolve each other and behave differently than would be expected from their individual properties. This is the **Poynting effect**.
Critical Temperature/Pressure	*Pseudo*critical temperature of **-6°C**, below which it will separate into **liquid** 50% N_2O (with some dissolved O_2), and gaseous O_2. This is most likely to occur at 117 bar, and can lead to delivery of a hypoxic mixture. Delivery of a hypoxic mix is prevented by: - Storing cylinders horizontally (↑ area for diffusion) - Storing cylinders at temperatures > 5°C - Using a dip tube so that liquid 50% N_2O is used before the gaseous mixture

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Opioids

Common Features

Property	Effect
Uses	Analgesia, sedation, elimination of sympathetic response to laryngoscopy/surgical stress response
Resp	↓ CNS sensitivity to CO_2 causing respiratory depression (↓ RR > ↓ V_T) - ↑ reliance on hypoxic drive (therefore respiratory depression may be potentiated by high FiO_2)
CVS	↓ HR. May ↓ BP due to histamine release (less with synthetic agents). ↑ PVR
CNS	Sedation, euphoria. Nausea and vomiting due to CTZ stimulation. Meiosis due to stimulation of the Edinger-Westphal nucleus. ↓ MAC up to 90%
Renal	↓ RPF, ↑ ADH, ↑ ureteric and sphincter tone
MSK	Muscle rigidity, pruritus (especially with intrathecal administration)
Metabolic	↓ ACTH, prolactin, gonadotrophic hormone secretion. ↑ ADH secretion
GIT	↓ Peristalsis and GIT secretions with subsequent constipation
Immunological	Impaired: chemotaxis, lymphocyte proliferation, and antibody production

Comparison of Naturally Occurring Opioids

Property	Morphine
Receptor	MOP, KOP
Route of Administration	SC/IM/IV/Intrathecal
pKa	8.0, 23% unionised at physiologic pH.
Absorption	Low (relative) lipid solubility - slower onset and SC absorption. PO preparations absorbed in small bowel, bioavailability 30% - high first pass metabolism.
Distribution	~35% protein binding. V_D 3.5L.kg^{-1}
Clearance (ml.kg^{-1}.min^{-1})	15
Metabolism	Hepatic glucuronidation to 70% inactive morphine-3-glucuronide and 10% active morphine-6-glucuronide, which is 13x as potent as morphine. $t_{1/2}\beta$ of 160 minutes.
Elimination	Renal elimination of active metabolites - accumulation in renal failure
Time to Peak Effect (IV)	10-30 minutes
Duration (IV)	3-4 hours
Equianalgesic Dose (IV, to 10mg IV morphine)	10mg

Comparison of Semisynthetic Opioids

Property	Oxycodone	Buprenorphine
Receptor	MOP, KOP, DOP	Partial MOP agonist, KOP antagonist (antanalgesic effect)
Route of Administration	PO/IV	Topical
pKa	8.5, < 10% is unionised at physiologic pH.	
Absorption	PO bioavailability 60-80%	Significant 1st pass metabolism
Distribution	As lipid soluble as morphine, 45% protein bound, V_D 3L.kg^{-1}. More rapid onset than morphine despite higher pKa potentially due to active CNS uptake	
Clearance (ml.kg^{-1}.min^{-1})	13	
Metabolism	Hepatic demethylation to noroxycodone (80%, via CYP3A) and the more potent and active oxymorphone (20%, via CYP2D6). $t_{1/2}\beta$ 200 minutes.	Hepatic to active norbuprenorphine
Elimination	Renal elimination of active drug and metabolites	70% biliary, 30% renal elimination, $t_{1/2}\beta$ 40 hours
Time to Peak Effect (IV)	5 minutes	
Duration (IV)	4 hours	
Equianalgesic Dose (IV, to 10mg IV morphine)	10mg. Note 10mg PO oxycodone is ≈ 15mg PO morphine due to higher first pass metabolism of morphine	

Comparison of Synthetic Opioids

Property	Fentanyl	Alfentanil	Remifentanil
Receptor	MOP	MOP	MOP
Route of Administration	SC/IM/IV/Epidural/Intrathecal/Transdermal	IV	IV (contains glycine, so cannot be administered intrathecally)
pKa	8.4, < 10% unionised at pH 7.4	6.5, 90% unionised at pH 7.4 conferring rapid onset	7.3 means 58% unionised at physiologic pH.
Absorption	Rapid onset of action (< 30s, peak at 5min) due to lipid solubility (600x that of morphine).	90x more lipid soluble than morphine, but more rapid onset than fentanyl. This is due to: 1. Low pKa means a greater proportion is unionised at physiological pH. 2. Lower potency of alfentanil compared to fentanyl means a greater dose is required (Bowman's Principle)	20x more lipid soluble than morphine.

Distribution	600x as lipid soluble as morphine conferring a larger V_D (4L.kg^{-1}). 85% protein bound.	90x as lipid soluble as morphine, small V_D of 0.6L.kg^{-1}. 90% protein bound	20x as lipid soluble as morphine, very small V_D of 0.4L.kg^{-1}. 70% protein bound. CSHT is constant due to rapid metabolism.
Clearance (ml.kg^{-1}.min^{-1})	13	6	40
Metabolism	Significant first pass pulmonary endothelial uptake. Hepatic demethylation to inactive norfentanyl. $t_{1/2}\beta$ of 190 minutes, longer than morphine due to higher lipid solubility and V_D.	Shorter elimination $t_{1/2}\beta$ than fentanyl (100 minutes) despite lower clearance due to lower V_D. Prolonged with administration of midazolam due to CYP3A3/4 competition.	Rapid metabolism by plasma and tissue esterases - $t_{1/2}\beta$ 10 minutes
Elimination	Renal elimination of inactive metabolites	Renal elimination of metabolites	Renal of inactive metabolites
Time to Peak Effect (IV)	5 minutes	90 seconds	1-3 minutes
Duration (IV)	Variable depending on dose and distribution. With doses > 3μg.kg^{-1} tissues become saturated and the duration of action is significantly prolonged	5-10 minutes	Offset 5-10 minutes from ceasing infusion
Equianalgesic Dose (IV, to 10mg IV morphine)	150mcg	1mg	50mcg

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COX Inhibitors

Cyclo-oxygenase inhibitors are typically **used** to treat **mild to moderate pain**. Oral COX inhibitors typically have:

- **Rapid absorption**
- **High protein binding**
- **Low V_D**

Mechanism of Action

There are two(ish) **isoenzymes** of COX:

- **COX-1**
  Important for homeostatic function.
- **COX-2**
  Induced with tissue damage and contributes to inflammation. COX-2:
  - Exists in the vascular endothelium where it synthesises prostacyclin (which opposes the action of thromboxanes)
  - Inhibition may result in a relative abundance of thromboxane, causing platelet aggregation and vasoconstriction
- **COX-3**
  Variant of COX-1 which exists centrally and mediates the analgesic and antipyretic effects of paracetamol.

Effects occur due to:

- Decrease in endoperoxidases
  Inhibited by COX.
- Increase in other arachidonic-acid derived factors
  Due to the diversion of arachidonic acid down other pathways.

COX inhibition has different effects in different tissues:

- Prevents subsequent conversion of prostaglandins to thromboxane A_2 and PGI_2
- Peripherally, inhibition of prostaglandin synthesis is anti-inflammatory
- Centrally, it is anti-pyretic
- In the stomach, it decreases mucous production and leads to mucosal ulceration

- Aspirin (a non-specific COX inhibitor), prevents production of both thromboxane A_2 and PGI_2
  - As platelets **have no nucleus**, the COX inhibition remains for the entirety of the platelet lifespan
  - Endothelial cells will produce new COX within hours, and so its anti-inflammatory effects are temporary

Adverse Effects

- **Asthma/Bronchospasm**
  Secondary to increased leukotriene synthesis due to increased arachidonic acid levels. Occurs in 20% of asthmatics with NSAID use.

- **Platelet dysfunction**
  A consequence of COX-1 inhibition only, and may result in increased perioperative bleeding risk (though decreased AMI and CVA risk).

- **Thrombotic events**, including MI and CVA
  Risk is greater with **COX-2** inhibitors, due to **selective inhibition of prostacyclin**. with NNH for non-fatal MI being 500 patient-years, and NNH for fatal MI being 1000 patient-years.

- **Impaired GFR**
  Occurs as a consequence of uninhibited afferent arteriolar constriction. Worse with concurrent hypovolaemia, renal artery stenosis, or concurrent ACE-I use.
- **Gastric erosion**
  A consequence of impaired mucosal secretion through COX-1 inhibition. This can result in pain, anaemia, or fatal bleed. In general, risk of gastric erosion is (from highest to lowest risk):
  - Ketorolac
  - Diclofenac/naproxen
  - Ibuprofen (<1.2g/day)
  - COX-2 Inhibitors
- **Transaminitis** may occur following NSAID use

Comparison of COX Inhibitors

Characteristic	Aspirin	Diclofenac	Ketorolac	Ibuprofen	Celecoxib	I
Mechanism of Action	Irreversible inhibition of platelet thromboxane production. As platelets are anucleate, they are unable to regenerate thromboxane.	Non-selective COX inhibitor	Non-selective COX inhibition	Non-selective COX-inhibition	COX-2 inhibitor (30:1 in favour of COX-2)	CC inl (6: fav CC
Uses	Prevention of arterial thromboembolism, MI, CVA, migraine, analgesia, others (e.g. Still's disease)	Mild-to-moderate pain	Potent anti-analgesic, minimal anti-inflammatory properties	Mild-to-moderate pain	Analgesia, particular chronic arthritic pain	Ac inf pa
Distribution	85% protein bound. Weak acid with a pKa of 3, unionised in the stomach and ionised at physiological pH				97% protein bound	
Absorption	Gastric absorption (pKa 3) leads to rapid onset.					
Metabolism	Hepatic metabolism to salicyluric acid and glucuronides. May have zero-order elimination in overdose.			CYP to inactive metabolites	CYP2C9 to inactive metabolites	CY ina me
Elimination	Renal. Elimination may be increased with urinary alkalinisation.					
	Low-dose (100mg					

Dose	daily) selectively inhibits platelet COX, whilst preserving endothelial COX, resulting in decreased platelet aggregation whilst maintaining vasodilation. 300-900mg for analgesia/migraine.	50mg BD/TDS	15-30mg IM/IV Q6H	400-800mg TDS, or 10mg/kg	100-200mg BD	20
Route	PO	PO/PR/IM/IV	IM/IV (off-label in Australia)	PO/PR	PO	IV
Respiratory	Aspirin uncouples oxidative phosphorylation, increasing O_2 consumption and CO_2 production. It also may stimulate, and (at higher doses) depress the respiratory centre. In overdose, these are significant, and may result in a **mixed** respiratory and metabolic **acidosis**.					
CVS	MI and CVA risk reduction. Increased bleeding.	Risk of MI similar to COX-2 inhibitors. Local thrombus with IV injection.		Lower dose not associated with prothrombotic events.	Unclear effect on CVA and MI, but recommended to avoid use in IHD/CVD	Ur on M re to in
Metabolic	**Reye's syndrome** is mitochondrial damage, hepatic failure, and cerebral oedema (and encephalopathy) in children <12. Mortality 40%.					

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Tramadol

Tramadol is an analgesic agent with a complicated mechanism of action:

- Action at all opioid receptors, but particularly MOP, causing analgesia as well as nausea and vomiting
- Inhibits 5-HT reuptake which provides descending inhibitory analgesia
- Inhibits NA reuptake descending inhibitory analgesia
- NMDA receptor antagonist

Properties	Tramadol
Class	Cyclohexanol derivative. Racemic mixture of (+)Tramadol which has greater MOP and 5HT reuptake effects, and (-)Tramadol, which mediates NA reuptake inhibition
Uses	Analgesia
Presentation	Racemic mixture - each isomer has complementary effects. IV solution is clear at $50mg.ml^{-1}$
Route of Administration	PO/IV/Topical
Dosing	50-100mg QID. Potency $1/5^{th}$ that of morphine.
Absorption	Bioavailability 70%
Distribution	V_D $4L.kg^{-1}$
Metabolism	Hepatic to active and inactive metabolites
Excretion	Urinary of predominantly inactive metabolites, $t_{1/2}\beta$ 300 minutes
Respiratory	Minimal respiratory depression
CVS	Avoid concomitant MAO-I use given NA reuptake inhibition
CNS	Increased seizure risk in those with epilepsy or concurrent SSRI/SNRI/TCA use. Minimal addiction potential
GIT	N/V

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Paracetamol

Paracetamol an analgesic and antipyretic which is typically classed as an NSAID, though it is unique and important enough to get its own page. It has a number of mechanisms of action:

- **Non-selective COX inhibition**, including COX-3
  This confers some of the analgesic properties
- **Inhibition of central prostaglandin synthesis**
  This confers the antipyretic effect by inhibiting prostaglandin E synthesis in the anterior hypothalamus in response to pyrogens
- **Serotonergic inhibition**
  Provides some additional analgesic action
- **Cannabinoid inhibition**
  Provides some additional analgesic action via endocannabinoid reuptake inhibition.

Property	Effect
Class	NSAID, acetanilide derivative
Uses	Analgesia, antipyretic
Presentation	Tablets, capsules, syrup, clear colourless solution for IV administration
Route of Administration	PO/PR/IV
Dosing	10-15mg.kg^{-1} Q4H up to 90mg.kg^{-1}.day^{-1}
Onset	IV: 5 mins, peak at 40 mins PO/PR: 40 mins, peak at 1 hour
Absorption	Rapid absorption (via small bowel, therefore proportional to gastric emptying), variable bioavailability (up to 90%) - greater by PR route
Distribution	10% protein bound, small V_D: 0.5-1L.kg^{-1} (though larger than other NSAIDs)
Metabolism	Predominantly hepatic glucuronidation. However, 10% is metabolised to NAPQI by CYP2E1 which is hepatotoxic.
Elimination	Active secretion into renal tubules - consider dose reduction in renal impairment
Resp	May exacerbate analgesic asthma due to glutathione depletion
CNS	Excellent analgesia. Synergistic with other analgesics, resulting in agent-sparing effect and reduced side effects
Metabolic	Antipyretic
Haeme	Cytopaenias (rare)

Toxicity

- Paracetamol is partially metabolised to the toxic N-acetyl-p-amino-benzoquinone imine (**NAPQI**)
  - In normal circumstances this rapidly conjugated with glutathione
  - In toxicity, glutathione is exhausted
  - NAPQI then covalently binds to critical proteins in hepatocytes, causing centrilobular hepatic necrosis and cell death

- Toxic doses:
  - **>200mg.kg^{-1}** in a single ingestion
  - Repeated ingestion of >150mg.kg^{-1}.day^{-1} for two days
  - >100mg.kg^{-1}.day^{-1} for three days

- Risk factors for toxicity:
  - Glutathione deficiency
    - Extremes of age
    - Malnutrition
    - Hepatic dysfunction
  - Enzyme inducers:
    - Anti-epileptics
      - Carbamazepine
      - Phenytoin
      - Phenobarbitone
    - Rifampicin
    - ETOH
    - OCP

Features of Overdose

- Conscious
- Nausea, vomiting, and epigastric pain
- Haemolytic anaemia
- Distributive shock
- Hyperglycaemia
- Late (>48 hours) hepatic failure
- Later (3-5 days) coagulopathy
- Fulminant hepatic failure (3-7 days)

Treatment of Overdose

- Activated charcoal with tablet ingestion if seen within 1 hour of ingestion.

- Serum paracetamol level to determine requirement for NAC (N-acetylcysteine) based on the nomogram
  - IV NAC is used as it is a glutathione precursor, replenishing depleted glutathione and facilitating further conjugation of NAPQI

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Antimuscarinics (Cardiac)

Antimuscarinics used for bronchodilation are covered under Antimuscarinics (Respiratory), whilst atropine is covered separately.

Antimuscarinics are as competitive, reversible antagonists of ACh at the muscarinic receptor. They are divided into:

- Naturally occurring **tertiary amines**
  These can cross the blood-brain barrier, and have central effects.
  - Atropine
  - Hyoscine
- Synthetic **quaternary amines**
  Do not cross the blood-brain barrier.
  - Glycopyrrolate

Property	Glycopyrrolate	Hyoscine
Class	Quaternary amine. Muscarinic antagonist	Tertiary amine
Uses	Bradycardia, antisialagogue	Antisialagogue, motion sickness
Presentation	Clear, colourless solution at 200μg.ml^{-1}. Incompatible with diazepam and thiopentone.	Racemic, only L-isomer active
Route of Administration	IV/IM	PO, SC, IV/IM
Dosing	200-400μg	20-40mg IV slow push or IM
Absorption	Minimal PO absorption - not used via this route.	< 50% PO bioavailability
Distribution	Crosses placenta but not BBB, V_D 0.5L.kg^{-1}	V_D 2L.kg^{-1}
Metabolism	Minimal hepatic hydrolysis	Extensive metabolism by hepatic esterases
Elimination	Renal of 85% unchanged drug	Renal of metabolites
Resp	Bronchodilation, antisialagogue	Bronchodilation, greatest antisialagogue effect
CVS	Initial bradycardia due to partial agonist effect. Reverses vagal causes of bradycardia, may cause tachycardia in doses >200μg. HR peaks at 3-9 minutes following administration.	Least likely anticholinergic to cause tachycardia
CNS		Most likely anticholinergic to cause central anticholinergic syndrome
MSK	Anhydrosis	
GIT	Reduced oral and gastric secretions, and gastric motility	Reduced oral and gastric secretions, and gastric motility. Increases biliary peristalsis
GU	Difficult micturition	

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Anticholinesterases

Anticholinesterases antagonise AChE, decreasing the breakdown of ACh and therefore increasing its availability at the:

- Nicotinic receptor
  Increases muscle strength.
  - Reversal of non-depolarising neuromuscular blockade
- Muscarinic receptor
  Increases parasympathetic tone.

Anticholinesterases can be:

- Reversible
- Form a carbamylated enzyme complex
- Irreversible

Property	Neostigmine	Organophosphates
Class	Quaternary amine, forms carbamylated enzyme complex	Irreversible anticholinesterase
Uses	Reversal of non-depolarising NMB, myasthenia gravis, analgesia	Insecticides, pesticides, chemical weapons
Presentation	Clear, colourless, light stable solution at 2.5mg.ml^{-1}	
Route of Administration	PO, IV, intrathecal	Topical
Dosing	0.05mg.kg^{-1} for reversal, 15-30mg PO for MG	
Absorption	Low PO bioavailability	Rapid topical absorption due to high lipid solubility
Distribution	Does not cross BBB, V_D 0.7L.kg^{-1}	Crosses BBB
Metabolism	Majority by plasma esterases to quaternary alcohol, with some hepatic metabolism	Not metabolised
Elimination	55% unchanged in urine	$t_{1/2}\alpha$ of weeks
Duration	50 minutes	Until new AChE is synthesised
Resp	Bronchospasm, ↑ secretion	Bronchospasm, ↑ secretion
CVS	↓ HR (may be profound), ↓ CO	↓ HR, ↓ CO
CNS	N/V and analgesic when administered intrathecally, cerebral vasoconstriction	Central cholinergic syndrome
MSK	Reversal of NMB, ↑ fasciculations, ↑ sweating, may cause paralysis	Paralysis
GIT	↑ Peristalsis, ↑ LoS tone, N/V	↑ Peristalsis, ↑ LoS tone, N/V
Other	Muscarinic receptors affected at low dose, nicotinic receptors at high dose	May be reversed in initial stages (before organophosphate-AChE complex has 'aged') with pralidoxime

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Depolarising NMBs

Succinylcholine binds to the nicotinic ACh receptor causing depolarisation. It cannot be hydrolysed by acetylcholinesterase in the NMJ, and so remains bound to the receptor. This:

- Produces a sustained depolarisation which keeps voltage-gated sodium channels in their inactive state
- Prevents the post-junctional membrane from responding to further ACh release

Property	Succinylcholine
Class	Depolarising muscle relaxant.
Uses	Facilitate tracheal intubation.
Presentation	Colourless solution of pH 3, at 50mg.ml^{-1}. Structurally, it is two ACh groups joined at the acetyl groups.
Route of Administration	IV, IM.
Dosing	1-2mg.kg^{-1} IV, 3-4mg.kg^{-1} IM up to 150mg.
Onset and Duration	IV onset in 30s to 1 minute, lasting 2-3 minutes, with offset typically within 10 minutes. Offset occurs due to dissociation of drug out of NMJ into plasma, as a concentration gradient is established by drug breakdown in plasma. Prolonged duration in patients with **pseudocholinesterase deficiency**. IM onset in 2-3 minutes.
Distribution	30% protein bound. Nil distribution due to rapid metabolism - V_D 0.25L.kg^{-1}. Crosses placenta in very small amounts.
Metabolism	Rapid hydrolysis by plasma cholinesterases such that only **20%** of administered dose reaches the NMJ.
Elimination	Minimal renal elimination due to rapid metabolism.
Resp	Apnoea, and **suxamethonium apnoea**. May cause **masseter spasm**. ↑ Salivation due to muscarinic effects.
CVS	Arrhythmia due to SA node stimulation, as well as secondary to hyperkalaemia. Bradycardia (due to muscarinic effects with second/large doses, or in children).
CNS	↑ ICP (due to contraction), ↑ IOP (by 10mmHg - this is **significant**) such that it is contraindicated in globe perforation.
Metabolic	**Malignant Hyperthermia**.
MSK	Myalgias post depolarisation, particularly in young females. Prolonged blockade with pseudocholinesterase deficiency.
Renal and Electrolyte	Hyperkalaemia (K^+ ↑ by ~0.5mmol.L^{-1}) due to depolarisation causing K^+ efflux, ↑ in burns (>10%), paraplegia (first 6 months) and neuromuscular disorders including muscular dystrophy and myopathies (including **critical illness myopathy**).
GIT	Intragastric pressure ↑ by 10cmH$_2$O, matched by ↑ in LoS pressure.
Immunological	Anaphylaxis - highest risk of all NMBs at ~11/100,000

Adverse Effects

The adverse effects of suxamethonium can be remembered as **three major, three minor, and three pressures**:

- **Major**

    - Anaphylaxis
    - Suxamethonium Apnoea
    - Malignant hyperthermia
- **Minor**
    - Hyperkalaemia
    - Myalgias
    - Bradycardia
- **Pressure**
    - IOP
    - ICP
    - Intragastric pressure

Phase I and Phase II Blockade

Initial blockade is termed **Phase I**, which is a partial depolarising block. Sustained use of suxamethonium may causes a Phase II block which:

- Appears similar to a non-depolarising block
- May be due to:
    - Presynaptic inhibition of ACh synthesis and release
    - Desensitisation of the post-junctional receptor

Key differences include:

Property	Phase I Block	Phase II Block
Block Amplitude	Reduced	Reduced
Train-of-four ratio	>0.7	< 0.7
Post-tetanic potentiation	No	Yes
Effect of anticholinesterases	Block augmented	Block inhibited

Malignant Hyperthermia

- Rare autosomal dominant genetic condition
- Triggered by suxamethonium and volatile anaesthetic agents
- Mutation of the ryanodine receptor causes excessive amounts of calcium to leave the sarcoplasmic reticulum, causing continual muscle contraction
    - Results in greatly increased carbon dioxide, lactate, and heat production
    - Cell lysis with myoglobulinaemia and hyperkalaemia results

Suxamethonium Apnoea

- A deficiency of butylcholinesterase causes suxamethonium to not be metabolised
- May be congenital (genetic) or acquired (hepatic failure)
- Can be treated with fresh frozen plasma

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Non-Depolarising Neuromuscular Blockers

Non-depolarising NMBs are muscle relaxants used to:

- Facilitate laryngoscopy and tracheal intubation
- Control ICP
- Improve respiratory system compliance
- Improve patient safety on transportation

Mechanism of action is by competitive antagonism of ACh at the NMJ, preventing generation of end-plate potentials. Effective pharmacodynamic response requires >70% receptor occupation.

Common Features of Neuromuscular Blockers

Property	Action
Route of Administration	IV/IM
Distribution	Small V_D as they are polar and unable to cross lipid membranes
Elimination	Reduced urinary clearance which prolongs the mechanism of action of aminosteroids in renal failure
Resp	Apnoea
MSK	↑ Duration in hypothermia
Renal	↑ Duration in acidosis, ↑ duration in hypokalaemia, ↓ duration in hyperkalaemia, ↑ duration in hypermagnesaemia
Metabolic	Critical Illness Myopathy in patients with long-term relaxant use

The ED_{95} is:

- The dose of a neuromuscular blocking drug required to produce a 95% reduction in twitch height in 50% of the population
- A commonly-used therapeutic end-point for neuromuscular blocking drugs
  Typically, induction doses used are 2-5x the ED_{95}.

Comparison of Neuromuscular Blockers

Property	Rocuronium	Vecuronium	Pancuronium	Atracurium	Cisatracurium
Class	Aminosteroid	Aminosteroid	Bis-quaternary aminosteroid	Benzylisoquinolinium derivative	Benzylisoquinoliniu derivative
Presentation	Clear, colourless solution at 10 $mg.ml^{-1}$	10mg powder for reconstitution in water. Contains mannitol and NaOH.	Colourless solution at 2 $mg.ml^{-1}$, which must be stored at 4°C	Colourless solution at $10mg.ml^{-1}$, which should be stored at 4°C. Mixture of all ten extant diastereoisomers.	R-Cis, R'-Cis isomer of atracurium, which is 15% of atracurium by weight but provides 50% of its NMBD action. Colourless solution a $2\text{-}5mg.ml^{-1}$, which should be stored at 4°C

Intubating Dose	0.6-1.2 $mg.kg^{-1}$	0.1 $mg.kg^{-1}$	0.05-0.1 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	0.15-0.2$mg.kg^{-1}$
ED_{95}	0.3 $mg.kg^{-1}$	0.05 $mg.kg^{-1}$	0.07 $mg.kg^{-1}$	0.25 $mg.kg^{-1}$	0.05 $mg.kg^{-1}$
Onset	45-90s	90-120s	90-150s	90-120s	60-180s
Duration	~30 minutes with normal renal function, repeat doses may be more unpredictable	45-65 minutes	60-100 minutes	15-35 minutes	25-30 minutes
Metabolism	< 5% hepatic deacetylation to inactive metabolites	20% hepatic deacetylation with weakly active metabolites	20% hepatic deacetylation with weakly active metabolites	60% by ester hydrolysis, with remainder by Hofmann elimination. Metabolised to **laudanosine**, which causes seizures in high concentrations (relevant when administered by long infusion)	Hofmann elimination
Elimination	60% biliary, 40% urinary. Prolonged duration in hepatic and renal failure	70% biliary, 30% urinary	80% biliary, 20% urinary		
Resp				Slight risk of bronchospasm with rapid injection	Slight risk of bronchospasm with rapid injection
CVS	↑ HR at high doses	**No** ↑ HR	↑ HR and MAP due to muscarinic antagonism	Risk of ↓ BP with rapid injection	Risk of ↓ BP with rapid injection
Immune	Higher risk of anaphylaxis, ~6/100,000. Anaphylaxis risk associated with use of pholcodine in the previous 3 years.	Notably no anaphylaxis recorded in NAP 6		Anaphylaxis ~ 4/100,000.	
Other	Reversible with **sugammadex**	Reversible with **sugammadex**			

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Dantrolene

Dantrolene is a ryanodine (RYR1) receptor antagonist, which prevents release of Ca^{2+} from the sarcoplasmic reticulum, uncoupling the process of excitation-contraction.

Property	Dantrolene
Uses	MH, NMS, ecstasy intoxication, chronic muscle spasticity
Presentation	Vials of orange powder containing 20mg dantrolene and 3g mannitol, reconstituted with 60ml of H_2O to form an alkaline solution.
Dosing	2.5mg.kg^{-1} IV every 10-15 minutes, up to 10mg.kg^{-1}. Once resolved, continue giving 1mg.kg^{-1} every 4-6 hours for 24 hours.
Absorption	IV only, may cause skin necrosis if extravasates.
Distribution	85% protein bound
Metabolism	Hepatic metabolism to active 5-hydroxy-dantrolene
Elimination	Renal of metabolites, $t_{1/2}\beta$ of 12 hours
Resp	Respiratory failure due to skeletal muscle weakness
CVS	Volume overload due to large volume given with administration
MSK	Skeletal muscle relaxation
Renal	Diuresis
GIT	Hepatic failure

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3. ANZCA August/September 2011

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Sugammadex

Property	Sugammadex
Class	Gamma cyclodextrin.
Uses	Reversal of neuromuscular block induced by rocuronium and vecuronium.
Presentation	Clear colourless solution at $100mg.ml^{-1}$.
Pharmaceutics	Store below 30°C.
Route of Administration	IV only.
Dosing	$2mg.kg^{-1}$ if ToF > 2. $4mg.kg^{-1}$ if PTC > 2. $16mg.kg^{-1}$ for reversal following RSI dose.
Distribution	V_D of $11\text{-}14L.kg^{-1}$.
Metabolism	Not metabolised.
Elimination	Renal elimination of active drug and complex.
Mechanism of Action	Forms a complex with rocuronium and vecuronium, causing reversal of neuromuscular blockade.
CVS	Rarely may precipitate bradycardia - can result in cardiac arrest.
Immune	Anaphylaxis.
Other	Interacts with OCP - treat as missed pill Shortened duration of rocuronium and vecuronium when used within 24 hours of sugammadex administration. Onset is delayed up to 5 minutes, and duration shortened by 10-15 minutes. This period may be extended in renal failure.

References

1. Sugammadex Full Prescribing Information. FDA.

Last updated 2019-07-20

Anticoagulants

Property	Warfarin	Heparin	Enoxaparin
Uses	AF, DVT/PE, Prosthetic Valves	AF, DVT/PE, Extra-corporeal Circuit Anticoagulation	DVT Prophylaxis
Pharmaceutics	Marevan and coumadin may *potentially* have different bioavailabilities (it has not been assessed) and so should not be substituted	Mucopolysaccharide organic acid which occurs naturally in the liver and in mast cells, with a highly variable molecular weight (between 5,000 and 25,000 Da)	Smaller fragments of heparin (prepared from UFH), with a mean molecular weight of 5,000 Da
Mechanism of Action	Prevents the return of vitamin K to its reduced form, and therefore the gamma-carboxylation of vitamin-K dependent clotting factors (II, VII, IX, X), as well as Protein C and Protein S).	Potentiates the effect of ATIII, rapidly increasing its anti-IIa and anti-Xa effect (1:1 effect). In higher concentrations also inhibits IXa, XIa, XIIa, and platelet aggregation.	Potentiates the action of ATIII, increasing inhibition of Xa and IIa, but (unlike UFH) in a 4:1 ratio. More predictable effect on Xa standardises dosing and justifies lack of monitoring requirement.
Onset	8-12 hours. Peak at 72 hours due to the half-life of existing clotting factors, and the total body stores of vitamin K	Immediate IV onset	
Absorption	100% bioavailability	IV, SC	SC only
Distribution	99% protein bound	Low lipid solubility, highly protein bound	Does not bind to heparin-binding proteins
Metabolism	Complete hepatic metabolism. Significant pharmacokinetic interaction with enzyme inducers and inhibitors.	Hepatic interactions due to enzymatic induction (ETOH, amiodarone, salicylates, NSAIDs) and inhibition (OCP, barbiturates, carbamazepine)	Renal elimination of metabolites
Elimination	Faecal and renal elimination of metabolites, $t_{1/2}\beta$ of 40 hours	Renal of inactive metabolites	Renal of active drug and inactive metabolites
CVS	Microthrombi	Hypotension with rapid IV administration	
Metabolic	Less osteoporosis due to less protein (and therefore tissue) binding	Osteoporosis	
Renal		Inhibits aldosterone secretion	
GIT	N/V		
Haeme	Haemorrhage	Haemorrhage, HITTs	Haemorrhage, lower risk of HITTs than UFH. Less thrombocytopaenia.
Immune	Hypersensitivity reactions		

Reversal	- Waiting - Vitamin K - FFP - Prothrombinex	Reversed with protamine (1mg per 100U).	Incomplete reversal with protamine as only the anti-IIa effect is inhibited.
Other	Teratogenic. Complicated pharmacokinetics requiring monitoring using INR.	Requires monitoring with APTT or ATIII levels. Large interpatient variability due to variable amounts of ATIII. 1 unit is the amount of heparin required to prvent 1ml of blood clotting for 24 hours at 0°C	No monitoring required.

HITTs

Heparin-Induced Thrombotic Thrombocytopenia comes in two flavours:

- **Type I**:
    - Is non-immune mediated
    - Occurs within 4 days of anticoagulant doses
    - Is an isolated thrombocytopenia without clinical significance
- **Type II**:
    - Is immune mediated
    - Occurs within 4-14 days
    - Is associated with serious thrombosis and high mortality (typically from PE) and morbidity (from CVA and limb ischaemia)

Protamine

Protamine is:

- A basic cationic protein derived from salmon sperm which combines with the acidic anionic heparin to form a stable, inactive salt in solution
- Cleared more rapidly than heparin
  Rebound anticoagulation may occur.

Adverse effects from protamine include:

- Histamine release
    - Bronchospasm
    - Hypotension
- Pulmonary hypertension
  This can be profound and result in a dramatic increase in RV afterload and EDV, with a corresponding fall in LV preload (interventricular interdependence), leading to dramatic hypotension and arrest.
    - Mediated by thromboxanes
    - Due to **protamine-heparin complexes**, rather than protamine alone
      Administration of protamine in absence of heparin does not lead to pulmonary hypertension.
- Anticoagulation
  When given in excess.

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
3. ANZCA August/September 2011
4. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.

Last updated 2019-07-18

Direct Thrombin Inhibitors

Direct thrombin inhibitors prevent cleavage of fibrinogen to fibrin, and are therefore very effective anticoagulants.

Property	Dabigatran
Class	NOAC
Uses	VTE prophylaxis, AF
Presentation	75/110mg Capsules
Route of Administration	PO
Dosing	VTE: 220mg daily, AF: 150mg BD
Absorption	6.5% bioavailability
Distribution	35% protein bound
Metabolism	Prodrug - activated by plasma and hepatic esterases
Elimination	Renal elimination of active drug
Haeme	Haemorrhage
Immune	Allergy
Other	Significant interactions with amiodarone, quinidine, St. John's Wort, as well as other anticoagulant and antiplatelet agents. Dialysable. Potentially reversible with idarucizumab.

References

1. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Antifibrinolytics

Antifibrinolytics include aprotinin, aminocaproic acid, and **tranexamic acid**. All prevent the breakdown of fibrin (!) by various mechanisms. TXA competitively inhibits plasminogen activator, reducing rate of fibrinolysis.

Property	Tranexamic Acid (TXA)
Class	Antifibrinolytic
Uses	Trauma (within 3 hours), cardiac surgery, obstetric surgery, and menorrhagia
Presentation	Tablets, syrup, clear colourless solution for injection
Route of Administration	IV, PO
Dosing	1g slow IV, which may be followed by infusion of 1g over 8 hours
Absorption	50% bioavailability
Distribution	Low plasma protein binding, V_D 9-12 litres
Metabolism	Minimal hepatic metabolism
Elimination	Renal of active drug - dose reduce in renal impairment
GIT	Nausea, vomiting
Haematological	Reduces fibrinolysis, possible increase in DVT/PE
Immunological	Allergic dermatitis

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. LITFL - Tranexamic Acid

Last updated 2019-07-18

Antiplatelets

Note aspirin is included under COX inhibitors.

Classification of Antiplatelet Agents

Antiplatelet agents can be classified by which stage of platelet function they affect:

- Adhesion
  - vWF inhibitors
    e.g. Dextran 70.
- Activation
  - Prostacyclins
    e.g. Epoprostenol.
  - Phosphodiesterase inhibition
    e.g. Dipyridamole.
  - COX inhibitors
    Prevent thromboxane A2 production, e.g. aspirin.
- Aggregation
  - ADP receptor antagonists
    Prevent activation of GP IIb/IIIa receptors, e.g. clopidogrel.
  - GP IIb/IIIa receptor antagonists
    Prevent platelet aggregation via fibrin linkages between GP IIb/IIIa receptors, e.g. tirofiban.

Comparison of Common Antiplatelet Agents

Property	Clopidogrel	Dipyridamole	Tirofiban
Class	ADP antagonist	Phosphodiesterase inhibitor	GP IIb/IIa antagonists
Uses	PVD, STEMI, NSTEMI, stent prophylaxis	CVA	UA, NSTEMI
Route of Administration	PO only	PO/IV	IV only
Mechanism of Action	Irreversibly prevents ADP from binding to its receptor on the platelet, preventing activation of the IIb/IIIa receptor	Inhibits platelet adhesion to walls, potentiates prostacyclin activity and increases platelet cAMP, ↓ Ca^{2+} and inhibiting platelet aggregation and deformation. Also acts as a coronary vasodilator.	Reversible antagonism of IIb/IIIa receptor, preventing platelet aggregation
Dosing	300mg load, 75mg daily thereafter	200mg BD for CVA	Load 25 $mcg.kg^{-1}$, maintenance $15mcg.kg^{-1}$
Absorption	Rapid absorption and onset within 2 hours	Variable depending on oral intake	IV only. Onset within 10 minutes
Distribution	Highly protein-bound drug and metabolites	Highly protein bound	65% protein bound

Metabolism	**Prodrug**. Majority hydrolysed by esterases to inactive drug, with a small proportion hepatically metabolised by **CYP450** to active form. Prolonged duration of action due to irreversible ADP blockade rather than long elimination half-life.	Partial hepatic to inactive metabolites	Not metabolised.
Elimination	Urinary and faecal	Renal and faecal	Urinary as unchanged drug. Platelet aggregation returns to baseline within 4-8 hours
CVS		Vasodilatation may drop CPP in AS and recent MI	Coronary artery dissection
GIT	Mucosal irritation		
Haeme	Haemorrhage	Thrombocytopaenia and haemorrhage	Haemorrhage
Other	Many pharmacokinetic interactions, including genetic variability. Previously thought to kinetically interact with omeprazole - more recently disproved.		

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 6th Ed. Churchill Livingstone.

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Penicillins

- Penicillins are **bactericidal** antibiotics that prevent cell-wall synthesis by preventing cross-linking of peptidoglycans by replacing the natural substrate with their β-lactam ring
- Penicillins bind to penicillin binding proteins (**PBPs**) in the bacterial wall
- Penicillins only rarely achieve complete eradication of sensitive organisms without addition of a **synergistic antibiotic** (such as gentamicin)

Common Features

Property	Effect
Absorption	Typically well absorbed orally. IM dosing tend to cause localised pain and irritation.
Distribution	Typically have good tissue penetration. Only cross the blood-brain barrier and enter bone if it is inflamed. Typically low protein binding (exception is flucloxacillin, which is 95% protein bound).
Metabolism	Typically small proportion is hepatically metabolised.
Elimination	Majority (60-90%) is eliminated unchanged in urine predominantly by active tubular secretion, with renal clearance proportional to total renal plasma flow. A small quantity is secreted in bile.

Mechanisms of Resistance

- Alteration or protection of PBPs
  - Gram negative bacteria may have altered permeability of porins in their outer membrane, which protects the PDP
- Hydrolysis by **β-lactamase**-producing bacteria
  - **Clavulanic acid** and **tazobactam inhibit β-lactamase**, which can render otherwise resistant bacteria sensitive
  - Notably, flucloxacillin has a modified beta-lactam ring that is not sensitive to β-lactamases

Comparison of Penicillins

	Narrow spectrum, naturally occurring	Narrow spectrum, synthetic	Extended-spectrum	Antipseudomonal
Examples	**Benzylpenicillin**, phenoxymethylpenicillin	**Flucloxacillin**	**Ampicillin**, amoxacillin	**Piperacillin**, ticarcillin
Indications	Gram positives and anaerobes, particularly *streptococci* and meningococci. Also *listeria*, *Clostridia*, and *Treponema*.	Gram positive cocci, particularly *staphylococci* but also streptococci.	Gram positive, particularly *enterococci*. Some gram negative.	Gram positive, gram negative including pseudomonas.
Other bits	Highly bactericidal	Less active than benzylpenicillin on organisms sensitive to both.	Can penetrate some gram-negatives.	Gram negative cover.

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Barza M, Weinstein L. Pharmacokinetics of the penicillins in man. Clin Pharmacokinet. 1976;1(4):297-308.
3. Brunton L, Chabner BA, Knollman B. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th Ed. McGraw-Hill Education - Europe. 2011.
4. CICM July/September 2007

Last updated 2019-07-18

Glycopeptides

Non-β-lactam agents that inhibit cell wall synthesis. They are:

- Active against gram-positive anaerobes and aerobes
- Bacteriostatic against enterococci and streptococci
- Bacteriocidal against staphylococci

Property	Vancomycin
Uses	MRSA, C. difficile
Presentation	Powder for reconstitution
Route of Administration	PO, IV, Intrathecal
Dosing	Peak levels determined by dose, trough levels by dose and interval
Absorption	No oral bioavailability. Poor CSF penetration
Distribution	V_D 0.4-1 $L.kg^{-1}$. Poor CSF penetration even with inflamed meninges - higher levels are required for CNS penetration. ~50% protein bound.
Metabolism	Minimal hepatic metabolism
Elimination	90% secreted unchanged in urine - significantly prolonged in renal impairment
CVS	Phlebitis, red man syndrome (profound non-anaphylactic histamine release with rapid injection)
CNS	Ototoxicity
Renal	Nephrotoxicity, typically temporary and resolves on cessation
Haematological	Thrombocytopenia
Immunological	'Red man syndrome' due to histamine release with rapid injection, with accompanying ↑ HR ↓ BP. Neutropenia.
Other	Synergistic action with cephalosporins, aminoglycosides, and rifampicin

References

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2. Wellington ICU Drug Manual
3. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006 Jan 1;42 Suppl 1:S35-9.

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Aminoglycosides

Bactericidal antimicrobials that prevent protein synthesis by irreversible binding to the 30S ribosomal subunit, preventing mRNA transcription.

- As they are large, polar molecules, they must be actively transported into the cell
    - This occurs with an oxygen dependent transporter
      Therefore they are **not effective against anaerobes**.
- Transport is inhibited by increased Ca^{2+}, Mg^{2+}, low pH, and low O_2
- Aminoglycoside killing is dependent on the peak concentration over MIC
  Typically peak concentration must be 8-10x MIC.
    - Exposure to aminoglycosides causes bacteria to down-regulate aminoglycoside uptake, and therefore increases MIC
      This effect disappears after ~24 hours, and is one justification for daily dosing of aminoglycosides. Additional justifications include:
        - Allows larger single doses to be used, increasing bactericidal effect
        - Aminoglycosides exhibit a post-antibiotic effect
          Ongoing bactericidal activity even after concentration falls.

Property	Gentamicin
Uses/Spectrum	Gram negative including pseudomonas, limited gram positive (staph, limited strep), synergistic effects with β-lactams and vancomycin.
Route of Administration	IV only.
Dosing	$4\text{-}7mg.kg^{-1}$.
Distribution	70% protein bound. Very small V_D of $0.2L.kg^{-1}$, which may result in significant pharmacokinetic changes with oedema.
Metabolism	Not metabolised.
Elimination	Eliminated unchanged, elimination $t_{1/2}$ prolonged up to 70 hours in renal impairment.
CNS	Ototoxicity due to accumulation in perilymph, and is usually permanent. Increased risk with concomitant frusemide use.
MSK	Muscle weakness.
Renal	Nephrotoxicity due to accumulation in the renal cortex, typically reversible.
Toxic Effects	Narrow therapeutic index, requires monitoring and dose reduction in renal impairment.

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Stubbings W, Bostock J, Ingham E, Chopra I Mechanisms of the post-antibiotic effects induced by rifampicin and gentamicin in Escherichia coli. J Antimicrob Chemother. 2006 Aug;58(2):444-8.
3. Deranged Physiology - Kill Characteristics of Antibiotic Agents

Last updated 2017-08-12

Lincosamides

Inhibit protein synthesis by disrupting the 50S ribosomal subunit. May be bacteriostatic or bacteriocidal, depending on the concentration and the particular organism.

Property	Clindamycin
Spectrum of Activity	Gram positive cocci, anaerobes. Little action against gram negative aerobes. Also active against some protozoa, such as *P. falciparum*.
Route of Administration	PO/IV
Dosing	150-300mg Q6H
Absorption	90% PO bioavailability
Distribution	Excellent bony penetration
Metabolism	Hepatic to active and inactive metabolites
Elimination	Renal elimination of all metabolites
MSK	May cause neuromuscular blockade in overdose
GIT	Reasonable incidence of GIT upset, with fatal pseudomembranous colitis reported. Deranged LFTs
Immune	Atopy, eosinophilia, DRESS

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Lexicomp. Clindamycin (systemic): Drug Information. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2017.

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Metronidazole

Metronidazole interrupts cellular metabolism by **preferential reduction**, capturing electrons that would be usually transferred to other molecules. This leads to a build up of cytotoxic intermediate metabolic compounds and free radicals, that result in DNA breakage and subsequent cell death.

Property	Drug
Class	Nitroimidazole
Uses	Anaerobes and protozoa
Route of Administration	PO/IV
Dosing	500mg BD
Absorption	100% bioavailability
Distribution	Crosses BBB
Metabolism	Hepatic to active metabolites
Elimination	Renal of active metabolites
Metabolic	Significant rash, nausea, vomiting, headache, flushing
GIT	Nausea, vomiting, metallic taste
Immunological	Hypersensitivity reactions
Interactions	Disulfiram-like reaction with ETOH

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Lexicomp. Metronidazole (systemic): Drug information. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2017.

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Antifungals

Antimicrobial agents targeting eukaryotic and heterotrophic microbes. Can be divided by class into:

- Azoles
  Inhibit ergosterol synthesis. Subdivided into:
  - Triazoles
    - Fluconazole
    - Itraconazole
    - Voriconazole
    - Posaconazole
  - Imidazoles
    - Ketoconazole
- Echinocandins
  Inhibit glucan synthesis.
  - Caspofungin
  - Micafungin
  - Anidulafungin
- Polyenes
  Disrupt cell membrane.
  - Amphotericin B
  - Nystatin

Common Features

Mechanisms of Antifungal Resistance

Three broad mechanisms:

- Increased efflux
  Increased expression of transport proteins removing drug from cell.
- Alteration of target enzyme
  Changes to protein target prevent drug binding or inactivation.
  - Typically only requires changes in a few amino acids
- Alteration of drug metabolism
  Reduced enzyme activity prevents accumulation of toxic product.

Amphotericin resistance is rare *in vivo*, and is typically via different mechanisms:

- Decreased ergosterol content
- Altered sterol:phospholipid ratio

Comparison of Antifungals

Drug	Fluconazole	Voriconazole	Caspofungin	Amphotericin B
Class	Azole	AzoleEchinocandins	Polyenes	
			Candida (including azole resistant	

Spectrum of Activity	*Candida albicans* (most other species, especially *C. glabrata*and to a lesser extent *C. krusei* are **resistant**), as resistance rapidly develops), *cryptococcus*, *coccidioides*, *histoplasma*, *blastomyces*, and some *aspergillus* (resistance may also develop rapidly). At least as good as amphotericin in susceptible organisms.	As fluconazole, but broader spectrum of activity	*C. glabrata* and *C. krusei* and *Candida* biofilms), *aspergillus*. Notably **no** activity against *cryptococcus*, *fusarium*, and *trichosporon*. Additionally, echinocandins typically have no cross-resistance with other antifungals	Effective against many fungi, with **notable exceptions** being *Chromoblastomycosis*, *Aspergillus terreus*, *Candida lusitaniae*, *Scedosporium*, and some *Fusarium*.
Pharmaceutics	Poor water solubility	Poor water solubility	Poor water solubility	Four different formulations, most common is amphotericin B colloidal dispersion (ABCD)
Dosing	100-800mg OD, adjust in renal failure		Typically 70mg loading dose, followed by 50mg daily; dose reduced in hepatic impairment	Load with 0.25-0.5kg.kg^{-1}, followed by 0.25-1.5mg.day^{-1}, reduced in severe renal impairment
Route of Administration	IV or PO		IV only (high MW)	IV for systemic indications
Absorption	High PO bioavailability, PO absorption at low pH (interaction with antacids, vitamin supplements)		<5% PO bioavailability	
Distribution	Crosses BBB - good CSF penetration. Very low protein binding (~10%)	Not dialysable due to very high protein binding, V_D. Good tissue penetration.	Essentially no CSF penetration, 97% protein bound in serum	Rapid uptake by reticuloendothelial system. Binds to organic anion transporting peptides (important in hepatocyte drug binding), important in key drug interactions (such as tacrolimus)
Metabolism	Metabolised by and cause reversible inhibition of multiple hepatic CYP450 enzymes (including 3A4, 2C19, 2C9), leading to increased concentrations of many drugs/metabolites	As fluconazole	Extensive hydrolysis and N-acetylation to inactive metabolites	Minimal metabolism
Elimination	80% of fluconazole renally eliminated unchanged	Mostly cleared via liver.	Renal of metabolites	Renal and faecal elimination of unchanged drug
Mechanism of	Inhibit ergosterol synthesis		Prevent cell wall synthesis	Binds sterols, disrupting osmotic

Action	by inhibiting CYP450 enzyme	As fluconazole	by blocking production of beta-glucan	integrity of the cell membrane
CVS	HTN	Long QT	Histamine release	
CNS	Headache, visual disturbances	Hallucinations, psychosis		
Renal				AKI via afferent arteriolar constriction and direct tubular toxicity, hypokalaemia, renal tubular acidosis
GIT	Hepatotoxicity		Mild hepatotoxicity in up to ~15%	
Haeme				Thrombophlebitis, normocytic anaemia

References

1. Anderson JB. Evolution of antifungal-drug resistance: mechanisms and pathogen fitness. Nat Rev Microbiol. 2005 Jul;3(7):547-56.
2. Drew RH. Pharmacology of Amphotericin B. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2018.
3. Ashley ED, Perfect JR. Pharmacology of azoles. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2018.
4. Lewis RE. Pharmacology of echinocandins. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2018.
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Insulins

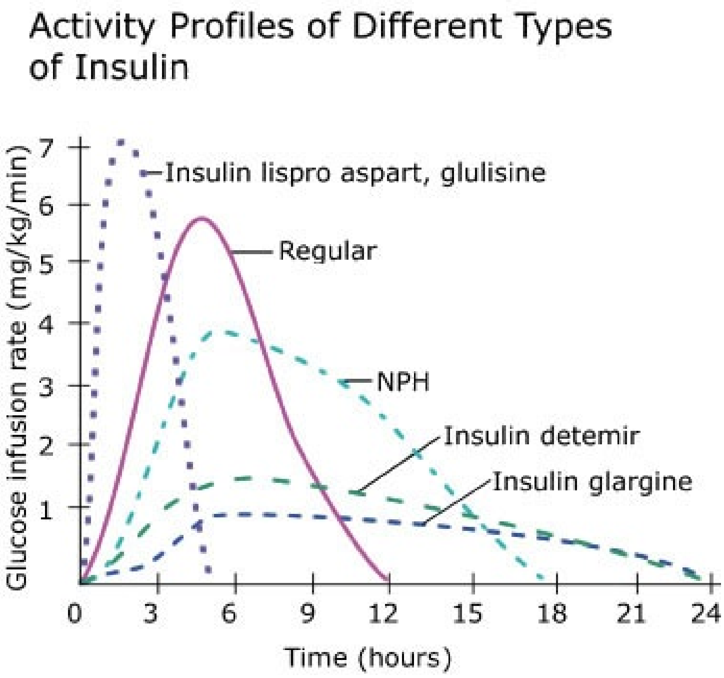
Insulins are synthetic polypeptide hormones. They:

- Have a similar mechanism of action and pharmacodynamics of endogenous insulin
- One unit of insulin is defined as the amount required to make a previously healthy 2kg rabbit hypoglycaemic

Types of Insulin

Different insulins are categorised by their time of **onset**, **peak**, and **duration**, and are classified as either:

- Fast acting
- Intermediate acting
- Long acting



Fast Acting

Fast acting insulins are used for controlling BSL spikes post meals, and for control of hyperglycaemia. Administered subcutaneously they have have an:

- Onset of 5-15 minutes
- Peak at 1-2 hours
- Last 4-6 hours.

Fast acting insulins include:

- Insulin Aspart (Novorapid)
- Insulin Lispro (Humalog)

Intermediate Acting

Intermediate acting insulins are used for control of BSL between meals as a pseudo-basal bolus. Administered subcutaneously they have an:

- Onset of 1-2 hours
- Peak at 4-6 hours
- Last >12 hours

Intermediate acting insulins include:

- NPH
- Protophane

Long Acting

Long acting insulins are used for creating a baseline insulin level. Administered subcutaneously they have an:

- Onset of 1-1.5 hours
- Peak at 5 hours
- Last 24 hours

Long-acting insulins include:

- Insulin glargine (Lantus)
- Insulin detemir (Levemir)

Pharmacokinetics of Exogenous Insulin Preparations

Property	Drug
Class	Synthetic polypeptide hormones
Uses	Diabetes, hyperglycaemia, hyperkalaemia, β-blocker toxicity, Ca^{2+}-blocker toxicity
Presentation	Clear colourless solution typically at 100 $IU.ml^{-1}$
Route of Administration	SC, IM, IV
Absorption	Variable, as described above. Insulin is complexed with different substances (e.g. protamine, zinc), which alter its rate of absorption
Distribution	Minimal protein binding and minimal redistribution out of ECF - V_D 0.075$L.kg^{-1}$
Metabolism	Glutathione insulin transhydrogenase. Metabolism is constant - duration of action is entirely due to different rates of subcutaneous absorption.
Elimination	Renal of inactive metabolites

References

1. Diabetes Education Online. Types of Insulin. UCSF. Accessed January 2016.
2. Graph of insulin activity profiles from: Diabetes Education Online. Types of Insulin. UCSF. Accessed January 2016.
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Last updated 2017-09-18

Oral Hypoglycaemics

Class	Biguanides	Sulfonylureas	Glitazones	Gliflozins
Example	Metformin	Gliclazide	Pioglitazone	Dapagliflozin
Uses	T2DM	T2DM	T2DM	T2DM
Mechanism of Action	Delay glucose absorption, increase peripheral insulin sensitivity, inhibit hepatic gluconeogenesis	Increase insulin secretion from pancreatic β-cells. May increase insulin sensitivity	Activates the intranuclear PPARγ receptor, affecting gene translation and increasing insulin sensitivity	Inhibits glucose reabsorption by the S-$GLUT_2$ co-transporter in the kidney, increasing glucose elimination in urine
Dosing	500mg-2g BD	40-160mg BD	15-30mg daily	5-10mg daily
Absorption	Bioavailability 60%	Bioavailability 80%	High bioavailability. Delayed onset and late peak effect given MoA	Bioavailability > 75%
Distribution	Minimally protein bound	Extensively bound to albumin by non-ionic forces, such that they do not tend to displace other highly protein bound drugs	Low V_D ($0.6L.kg^{-1}$)	
Metabolism	Not metabolised	Partial hepatic to inactive metabolites	Extensive hepatic phase I to inactive and active metabolites	Extensive hepatic to inactive metabolites
Elimination	Renal elimination of active drug	Renal elimination of active drug and inactive metabolites	Renal and GI elimination of active and inactive metabolites	Renal of inactive drug
CVS			May precipitate fluid retention	
Renal	Contraindicated in renal impairment due to increased risk of lactic acidosis			Contraindicated in renal impairment (< $60ml.min^{-1}$) as it has no benefit
MSK		Photosensitivity		
Metabolic		↑ Appetite, weight gain. Hypoglycaemia		Weight loss, reduced insulin requirements

		in fasting.		
Renal				Increased UTI and thrush risk
GIT	Nausea, Diarrhoea	Cholestasis		
Toxic	Severe lactic acidosis secondary to inhibition of oxidative glucose metabolism, especially in renal failure and alcoholics	Cross placenta, causing foetal hypoglycaemia.		May lead to **euglycaemic diabetic ketoacidosis** due to blunted insulin production in the face of stress hormones. Consider in patients with DKA symptoms (drowsiness, abdominal pain, nausea/vomiting), elevated ketones, and metabolic acidosis in the setting of a normal BSL.

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Last updated 2019-07-18

Oxytocics

Oxytocics are agents which increase the force of uterine contraction.

Property	Oxytocin	Ergometrine	$PGF_{2\alpha}$ (Dinoprost)	Carboprost
Class	Endogenous (typically synthetic version used) posterior pituitary hormone	Ergot alkaloid	Prostaglandin	
Uses	Augmentation of labour, increase uterine tone (PPH)	PPH	Severe PPH	Severe PPH
Presentation	Clear liquid at 5-10 $U.ml^{-1}$			Clear liquid at $250\mu g.ml^{-1}$, up to 8 doses (2mg)
Route of Administration	IV	IV, IM	Intramyometrial injection, IM	Intramyometrial, IM
Dosing	$1.5\text{-}12mU.min^{-1}$	250μg IM (IV in emergency via slow push)		500μg IM
Metabolism	Oxytocinases in liver and kidney			
Mechanism of Action	Oxytocin GPCR in the uterus, increase Ca^{2+} influx. Structurally similar to ADH.	Acts on α and $5HT_2$ receptors on uterine and vascular smooth muscle		
Resp		Bronchospasm (may be severe)	Bronchospasm (severe if IV so this route is contraindicated)	Bronchospasm, APO due to ↑ PVR with subsequent hypoxia
CVS	↑ HR, ↓ BP following boluses	↑ SVR, ↑ BP (may cause, ↓ HR) coronary vasoconstriction	↑ SVR, ↑ BP	↑ SVR, ↑ BP (usually transient)
CNS	Headache, nausea, vomiting	Headache, nausea	Nausea, vomiting	Headache
Renal	↓ UO due to ADH-like effects with prolonged infusions			
GU	↑ Uterine tone (↑ frequency at low dose, tetanic contraction at high dose), foetal distress, lactation	↑ Uterine contraction frequency and tone	↑ Uterine contraction frequency and tone	↑ Uterine contraction frequency and tone, contraindicated in pelvic inflammatory disease
Other	May be metabolised by oxytocinases in blood products if co-administered on the same line	Contraindicated in pre-eclampsia due to HTN	Deprecated by carboprost, increased body temperature	

References

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.
3. Smith S, Scarth E, Sasada M. Drugs in Anaesthesia and Intensive Care. 4th Ed. Oxford University Press. 2011.
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Tocolytics

Tocolytics are agents which decrease uterine tone. Tocolytics include:

- β_2-agonists
- Ca^{2+}-channel antagonists
- COX Inhibitors
- $MgSO_4$
- Nitrates
- Volatile anaesthetic agents

All tocolytics are discussed in more detail elsewhere - this covers just the mechanism of action of their uterine effects.

Drug	β_2-agonists	Ca^{2+}-channel antagonists	COX Inhibitors
Example	Salbutamol, Terbutaline	Nifedipine	Indomethacin
Mechanism of Action	Activate GPCR, ↑ cAMP, which activates protein kinase A and leads to inhibition of myosin light chain kinase and relaxation	Block L-type Ca^{2+} channels, causing relaxation	Inhibit prostaglandin synthesis, which are vital for uterine contraction

References

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Acid Suppression

Property	Non-Particulate Antacids	Particulate Antacids	Proton Pump Inhibitors	H_2 receptor antagonists
Example	Sodium citrate	Aluminium Hydroxide/Calcium carbonate	Omeprazole	Ranitidine
Uses	Aspiration prophylaxis	Aspiration prophylaxis	Aspiration prophylaxis, GORD, peptic ulceration	Aspiration prophylaxis, GORD, peptic ulceration
Absorption	Rapid absorption due to high water solubility	Lower water solubility results in slower absorption and onset but no risk of alkalosis	Absorbed in small bowel, high PO bioavailability	50% PO bioavailability
Distribution			Low V_D of 0.3 $L.kg^{-1}$	15% protein bound
Metabolism			Prodrug, activated within parietal cell. CYP450 metabolised, inhibits CYP2C19 (reducing, among other things, the antiplatelet effect of clopidogrel)	Partial hepatic by CYP450
Elimination			Renal of metabolites and active drug	Renal of metabolites and active drug
Mechanism of Action	Base reacts with gastric acid to produce salt and water	Base reacts with gastric acid to produce salt and water	Irreversible antagonism of the parietal H^+/K^+ ATPase	Competitive antagonism of the (Gs) H_2 receptor, which ↓ cAMP production, ↓ intracellular Ca^{2+}, and ↓ activity of the H^+/K^+ ATPase
Resp	Lower risk of pneumonitis if aspirated	Greater risk of pneumonitis if aspirated	Potentially increased severity of pneumonia if aspiration occurs (risk with micro-aspiration in long-term intubated patients)	Pneumonitis/pneumonia as per PPI
CVS				↓ HR, ↓ BP, and arrhythmogenic with rapid IV administration
Renal	Potential metabolic alkalosis	No risk of alkalosis	Interstitial nephritis	
GIT	↑ Gastric pH	↑ Gastric pH	↑ Gastric pH (pH ↑ by ~1), ↓ volume of secretions	
Other	Taste bad			

References

1. Petkov V. Essential Pharmacology For The ANZCA Primary Examination. Vesselin Petkov. 2012.
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Antiemetics

Antiemetic drugs can be classified by their mechanism of action:

- Serotonin antagonists
    - Ondansetron
- Corticosteroids
    - Dexamethasone
      Has additional effects on postsurgical pain and fatigue.
- Dopamine antagonists
    - Phenothiazines
        - Chlorpromazine
        - Prochlorperazine
    - Butyrophenones
        - Droperidol
    - Benzamides
        - Metoclopramide
- Anticholinergics
    - Hyoscine
    - Atropine
- Antihistamines
    - Cyclizine
- NK_1 antagonists
    - Aprepitant
- Others
    - Benzodiazepines
    - Cannabinoids
    - Propofol

Comparison of Antiemetic Drugs

Property	Ondansetron	Droperidol	Metoclopramide	Cyclizine
Class	Serotonin antagonist	Benzamide dopamine antagonist	Dopamine antagonist	Piperazine derivative/H_1 antagonist
Uses	Nausea. Ineffective for vomiting due to motion sickness or dopamine agonism	Antiemetic, sedation, behavioural control	Prokinetic, antiemetic	Antiemetic (including motion sickness and radiation sickness)
Presentation	Tablet, wafer, clear solution for injection at $4mg.ml^{-1}$	Clear solution in brown glass, incompatible with thiopentone and methohexital	Clear solution in plastic	50mg tablets or $50mg.ml^{-1}$ light-sensitive solution
Route of Administration	PO/SL/IV	IV	IV/PO	PO/IV/IM
Dosing	4-8mg TDS Give on induction for	IV Give at end of surgery for	25-50mg IV (note 10mg has no antiemetic properties	$1mg.kg^{-1}$ up to 150mg per day

	PONV	PONV		
Absorption	PO bioavailability 60%		PO bioavailability 30-90%	PO bioavailability 80%
Distribution	75% protein bound	90% protein bound, V_D 2L.kg^{-1}	Minimal protein binding, V_D ~3L.kg^{-1}	
Metabolism	Hepatic to inactive metabolites. Dose reduction in hepatic impairment. $t_{1/2}$ 3/24.	Extensive hepatic metabolism	Hepatic metabolism	Hepatic to inactive metabolites
Elimination	Renal elimination of inactive metabolites	Renal and hepatic of drug and metabolites	Renal of 20% unchanged drug and remainder as metabolites	Renal of metabolites
Mechanism of Action	Central and peripheral antagonism of 5-HT_3 receptors, reducing input to the vomiting centre	Central D_2 blockade and post-synaptic GABA antagonism	Antiemetic activity via central D_2 antagonism, prokinetic activity via muscarinic agonism, peripheral D_2 antagonism	Competitive H_1 antagonist and anticholinergic at M_1, M_2, M_3 receptors
CVS	Bradycardia with rapid IV administration, QT prolongation	QT prolongation, hypotension secondary to α antagonism	↑/↓ HR, ↑/↓ BP	↑ HR and ↓ BP due to α antagonism
CNS	Headache	Sedation (neurolepsis), extrapyramidal symptoms in ~1%	Extrapyramidal symptoms, neuroleptic malignant syndrome	Sedation
GIT	Constipation	Antiemetic	Antiemetic, prokinetic	Increased LoS tone
Endocrine			Hyperprolactinaemia	

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1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 4th Ed. Cambridge University Press. 2014.
2. Sébastien Pierre, MD, Rachel Whelan. Nausea and Vomiting After Surgery. Contin Educ Anaesth Crit Care Pain 2013; 13 (1): 28-32. doi: 10.1093/bjaceaccp/mks046
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Intravenous Contrast

Intravenous contrast may be divided into:

- **X-ray Contrast**
  These agents are all based on a tri-iodinated benzene ring, which absorbs x-ray radiation. Alterations to this ring alter toxicity, lipophilicity, and elimination.
    - Agents are classified by these structural differences into:
        - Ionic
          Ionic substances are strong acids and are water soluble due to ionisation. They are further divided into:
            - Monomers
              Typically high molecular weight.
            - Dimers
        - Non-Ionic
          Water soluble due to hydrophilic side chains. Lower molecular weight than ionic contrast agents.
            - Monomer
              Agent of choice for angiography.
                - Easy to inject
                - Water soluble at physiologic pH
            - Dimer
              Harder to inject than monomers due to higher viscosity. Typically used for urography.
    - All are renally eliminated, and may be retained in renal dysfunction
- **Gadolinium Contrast**
  Gd^{3+}, due to its seven unpaired electrons, is paramagnetic and will alters the magnetic field of an MRI machine.
    - Free gadolinium is nephrotoxic and must be chelated
    - This increases its solubility and allows it to be renally eliminated
    - Gadolinium also attenuates x-rays, but is not used as x-ray contrast as doses required would be toxic

Adverse Reactions

Adverse reactions to low-osmolarity agents are uncommon (3%), with severe reactions being very rare (0.04%) and fatal reactions being extremely rare (1:170,000).

General Adverse Reactions

Adverse reactions include:

- Chemotoxicity
    - Platelet inhibition
    - Increased vagal tone
        - Negative inotropy
        - Negative chronotropy
- Ionic toxicity
    - Cellular membrane dysfunction
      May worsen myasthenia gravis.
- Osmotoxicity
    - Pain
    - Emesis
    - Increased PAP

    - Decreased PVR
- Hypersensitivity reaction
  Typically occur within 20 minutes of injection.

Risk factors include:

- Asthma or atopy
- Critically ill
- Cardiac disease
- Renal disease

Contrast Nephropathy

Defined as an increase in creatinine by 25% above baseline within three days of IV contrast administration.

- It is theorised that osmotic stress and direct tubular toxic effects lead to renal tubular injury, and may cause acute tubular necrosis
- Typically is benign, with creatinine returning to baseline within 10-14 days
- Significant uncertainty as to whether contrast media do cause acute kidney injury
  IF this risk is present, it is probably only relevant in patients who have:
    - Impaired renal function
    - Arterial contrast
- Rehydration and volume correction are effective in preventing a rise in creatinine

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References

1. Dickinson MC, Kam PC. Intravascular iodinated contrast media and the anaesthetist. Anaesthesia. 2008 Jun;63(6):626-34.
2. The Royal Australian and New Zealand College of Radiologists. Iodinated Contrast Media Guideline. Sydney: RANZCR; 2016.

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Definitions

This appendix is a list of key definitions that are common to many topics.

A

- **Absolute Humidity**
  Mass of water vapour in a given volume of air. Measured in $mg.L^{-1}$.
- **Absorption**
  The rate at which a drug leaves its site of administration and the extent to which this occurs.
- **Accuracy**
  The ability of a measuring device to match the actual value of the quantity being measured.
- **Acid**
  A proton donor.
- **Acidaemia**
  Arterial blood pH < 7.35.
- **Acidosis**
  A process which leads to an excess of hydrogen ions, and *may* lead to acidaemia if there is inadequate compensation. Can be subdivided into:
  - **Respiratory acidosis**: $PaCO_2 > 45$
  - **Metabolic acidosis**: $HCO_3^- < 22$
- **Activity**
  The *effective* concentration of a substance in a reacting system.
- **Acute Pain**
  Defined as pain of:
  - Recent onset
  - Limited probable duration
  - Identifiable causal and temporal relationship to injury or disease
- **Adiabatic**
  A process that occurs without transfer of heat or matter. For example, gases heat up when compressed (greater than the energy used to compress them), and cool when allowed to expand (adiabatic cooling).
- **Affinity**
  Ability of a drug to bind to a receptor.
- **Afterload**
  Sum of forces, both elastic and kinetic, opposing ventricular ejection.
- **Aging**
  Naturally occurring, physiological decline in the structure and functional reserve of all organ systems.
- **Agonist**
  Drug which produces a maximal response at receptor site.
- **Alkalaemia**
  Arterial blood pH > 7.45.

- **Alkalosis**
  A process which leads to a deficit of hydrogen ions, and *may* lead to alkalaemia if there is inadequate compensation. Can be subdivided into:
    - **Respiratory alkalosis**: $PaCO_2$ < 35
    - **Metabolic alkalosis**: HCO_3^- > 26
- **Allodynia**
  Pain caused by a previously non-painful stimulus.
- **Allosteric Modulator**
  Substance which binds a receptor distant to the ligand-binding site, and modifies (positively or negatively) the effect of the ligand. Has no activity in absence of a ligand.
- **Anaesthesia**
  Without sensation.
- **Analogue Signal**
  Where the output of the transducer varies with the input signal.
- **Anion**
  Negatively charged ion.
- **Anode**
  The electrode which conventional current flows into.
- **Anrep effect**
  Method of myocardial autoregulation in which an increase in afterload causes an increase in contractility.
- **Antagonist**
  Drug which produces no response at the receptor, but prevents other ligands binding.
- **Autoregulation**
  Ability of an organ to maintain homeostasis in the presence of dynamic physiological conditions.
- **Azeotrope**
  A mixture of two substances that cannot be separated by fractional distillation, as each component shares same boiling point. This is typically temperature dependent.

B

- **Base**
  Proton acceptor.
- **Base Excess**
  Amount of acid that must be added to a solution to lower its pH to 7.4, at 37°C and with a $PaCO_2$ of 40mmHg.
- **Bathmotropy**
  Degree of myocardial excitability. Used with either positive or negative bathmotropy.
- **Bell-Magendie Law**
  The principle that in the spinal cord the dorsal roots are sensory and the ventral roots are motor.
- **Bias**
  The systematic distortion of the estimated intervention effect away from the “truth”, caused by inadequacies in the design, conduct, or analysis of a trial.

- **Black-body radiation**
  Electromagnetic radiation given off by all bodies at greater than 0°K. Wavelength of radiation emitted depends on the temperature of the body.
- **Bohr Effect**
  An increase in $[H^+]$ or $PaCO_2$ decreases Hb affinity for O2.
- **Boiling Point**
  The temperature at which the vapour pressure of a liquid equals the environmental pressure surrounding the liquid.
  - Therefore boiling point decreases as environmental pressure falls, as there is less external pressure keeping molecules in their liquid state
  - Boiling differs from evaporation as molecules anywhere in the liquid may enter the gaseous phase, whilst evaporation occurs only at the surface
- **Bowditch Effect**
  Increase in contractility seen with an increase in HR. Also known as the Treppe effect.
- **Boyle's Law**
  Pressure of a gas is inversely proportional to volume.
- **Buffer**
  Solution containing a weak acid and its conjugate base and will resist a change in pH when a stronger acid of base is added.

C

- **Calibration**
  A process of checking a monitoring device for linearity of correlation between actual and measured values over a given measurement range.
- **Capacitance**
  Ability of a system to store electrical charge. Measured in Farads.
- **Central Blood Volume**
  Volume of blood in heart and lungs.
- **Central Sensitisation**
  Increased responsiveness of nociceptive neurons in the central nervous system (i.e., post-synaptic) to their normal or subthreshold afferent input.
- **Chemotaxis**
  Movement of cells along a gradient of increasing concentration of an attracting molecule.
- **Chronic Pain**
  Pain that:
  - Persists beyond the time of tissue healing
  - Frequently has no clearly identifiable cause
- **Clearance**
  Volume of plasma completely cleared of a substance per unit time.
- **Coronary Blood Flow**
  At rest is **~5%** of CO, or 225 $ml.min^{-1}$, and may increase **3-4x** during exercise.
- **Colloid**
  Substance evenly dispersed throughout another solution in which it is insoluble.
- **Colligative Properties**

The properties of a solution that depend on the ratio of solute to solvent, and not on the type of molecules present. These include:
  - Vapour pressure
  - Boiling point
  - Freezing point
  - Osmotic pressure

- **Compliance**
  Distensibility of a system. Expressed as the change in volume for a given change in pressure.

- **Concentration Effect**
  Describes the disproportionately rapid rise in Fi/FA ratio of nitrous oxide, as its rapid diffusion across the alveolar membrane increases the concentration of alveolar gas, and also augments respiration by drawing in dead space gas.

- **Context-Sensitive Half-Time**
  Time taken for plasma drug concentration to fall to 50% of its starting value after cessation of a drug infusion aimed to maintain a constant plasma concentration. Varies with the context, or duration, of drug infusion.

- **Contractility**
  Factors affecting myocardial performance, independent of preload and afterload.

- **Critical Length**
  The length of axon which must be blocked in order to prevent action potential transmission. It is dependent on myelination and fibre diameter.

- **Critical Point**
  The point on a phase diagram where the liquid and gas phases of a substance have the same density, and are therefore indistinguishable.
  - This point is where a substance is at both its critical temperature and critical pressure

- **Critical Pressure**
  Pressure required to liquefy a vapour at its critical temperature.

- **Critical Temperature**
  Temperature above which a substance cannot be liquified, irrespective of how much pressure is applied.

- **Critical Volume**
  The volume occupied by a given amount of substance at its critical point.

D

- **Dalton**
  Unit of mass equal to 1/12th of the mass of Carbon-12.

- **Dalton's Law**
  The partial pressure of a gas in a mixture is equal to the pressure that gas would exert if it occupied the volume alone.

- **Dead Space**
  Inspired gas not participating in gas exchange. Includes:
  - Apparatus dead space
    Gas in the ventilator or breathing circuit.
  - Anatomical dead space
    Gas in the conducting zone of the lung.
  - Alveolar dead space
    Alveolar gas not participating in gas exchange. Also known as West Zone 1.

  - Physiological dead space
    Sum of alveolar and anatomical dead space.

- **Density**
  Mass per unit of volume.

- **Dependence**
  When a characteristic withdrawal syndrome occurs when a drug is withdrawn, or an antagonist administered.

- **Diffusion**
  Passive movement of a substance down an activity gradient by Brownian motion.

- **Diffusion Hypoxia**
  Fall in alveolar PAO_2 due to dilution of alveolar gas by N_2O diffusing from blood to alveoli.

- **Digestion**
  Process of breaking down macromolecules into readily absorbed compounds.

- **Doppler Effect**
  Alteration in frequency of a signal due to a relative difference in velocity between the emitter and observer. Detected frequencies will be:
  - Higher if the emitter is moving toward the observer
  - Lower if the emitter is moving away from the observer

- **Down regulation**
  Decrease in receptor number due to chronic agonist exposure.

- **Drift**
  A fixed deviation from the true value at all points in the measured range.

- **Drug**
  Substance administered to cause a change in a physiological system.

- **Duplicate Publication**
  Where the same set of results are published in multiple journals. Academically unethical, and will cause a systematic bias in a meta-analyses as the same set of patients are included twice.

- **Dyne**
  Force required to accelerate 1g by $1cm.sec^{-2}$.

E

- **Efficacy**
  Maximal effect produced by a drug. Analogous to intrinsic activity.

- **Electrocardiogram**
  Graphical recording of the vector sum of cardiac electrical activity, as measured by electrodes on the skin.

- **Emulsion**
  A fine dispersion of minute droplets of one liquid in another in which it is not soluble or miscible.

- **Enzyme**
  Biological catalyst.

- **Eutectic**
  A mixture of substances with the lowest possible melting point than any other mixture of the same substances (and lower than that of either substance).

- **Excitability**
  How rapidly an excitable cell depolarises. Given by the gradient of phase 0 of the action potential, and is dependent on the function of voltage-gated sodium channels.
- **Exponential Function**
  Mathematical function where the rate of change is proportional to the current value.
- **External Validity**
  How well findings from one setting can be applied to another.

F

- **Fahraeus-Lindqvist effect**
  Decrease in apparent viscosity that occurs when a suspension (e.g. blood) flows through a tube of smaller diameter.
- **Fasting**
  Metabolic state achieved after complete digestion and absorption of a meal prior to the onset of starvation.
- **Fick Principle**
  Blood flow to an organ equals the uptake of a tracer substance by that organ, divided by the arterio-venous concentration difference.
- **Flow**
  Quantity of fluid passing a point per unit time.
- **Fourier Analysis**
  Deconstruction of a complex waveform by separating it into its constituent sine waves. The slowest component is known as the **fundamental frequency**.
- **Free radical**
  Extremely reactive molecular constituent carrying an unpaired electron.
- **Freezing point**
  Temperature at which molecular movement begins.
- **Functional Residual Capacity**
  Volume of gas in the lungs at the end of a normal tidal expiration, when the recoil pressure of the lungs equals the expansile pressure of the chest wall.

G

- **Galvanometer**
  Device to measure electrical current, usually via deflection of a wire in a magnetic field.
- **Gas**
  Substance above its critical temperature.
- **General anaesthesia**
  Drug induced, controlled, and reversible production of unconsciousness.
- **Gibbs-Donnan Effect**
  Describes the tendency of diffusable ions to distribute themselves such that the ratios of the concentrations are equal when they are in the presence of non-diffusable ions.
- **Grahams Law**
  The speed of diffusion of a gas through a membrane is inversely proportional to the square root of the molecular weight.

H

- **Haldane effect**
  Deoxygenated blood forms carbamino compounds and buffers H^+ better than oxygenated blood.
- **Half-Life**
  Time taken for drug concentration (typically in plasma) to fall by half.
- **Heat**
  Kinetic energy content of a body, as measured in joules.
- **Henry's Law**
  Amount of gas dissolved in a substance is directly proportional to the partial pressure of gas at the gas-liquid interface.
- **Heterometric autoregulation**
  Change in ventricular function based on myocardial fibre length. Also known as **Starling's Law**.
- **Homeometric autoregulation**
  Mechanisms which alter myocardial performance independent of fibre length.
- **Hormone**
  Chemical messenger secreted by a **ductless gland** and has action on a distant target cell.
- **Hyperalgesia**
  Greater than normal amount of pain from a noxious stimulus. May be:
  - Primary
    Occurring in the region of tissue damage, e.g. in an inflamed area around a wound.
  - Secondary
    Extending beyond the region of tissue damage.
- **Hypoxaemia**
  When PaO_2 is less than 60mmHg.
- **Hypoxia**
  The point at which inadequate oxygenation of tissues results in anaerobic metabolism.
- **Hysteresis**
  When the future state of a system depends not only on its current state, but on the states preceding it.

I

- **Ideal Gas**
  A gas which will obey the ideal gas law. An ideal gas must have:
  - Negligible intermolecular attraction
  - A small molecular volume compared to the space between the molecules
- **Idiosyncrasy**
  An effect of a drug affecting only a small number of patients, typically due to the action of a particular metabolite.
- **Inductance**
  Property of a conductor by which a change in current induces an electromotive force in the conductor and any nearby conductors.
- **Inotrope**
  Drug which alters myocardial contractility.

- **Intrinsic Activity**
  Maximal effect produced by a drug. Analogous to efficacy.
- **Impedance**
  Resistance to alternating current.
- **Internal Validity**
  Where a causal relationship between variables has been properly demonstrated, i.e. a lack of bias.
- **Irritability**
  How easily an excitable cell can be stimulated. Given by how close the resting membrane potential is to threshold potential.
- **Isomer**
  Compound with the same chemical formula, but different chemical structure or arrangement of atoms.
- **Isotherm**
  Line of constant temperature drawn on a pressure-volume graph for a gas, which describes the relationship between pressure, temperature, and volume for a particular gas.

J

- **Joule**
  Energy transfered to an object when it is acted on by 1N for 1m.

L

- **Laminar Flow**
  Flow occurring smoothly and without turbulence.
- **Local Anaesthetic**
  Drug which reversibly prevents the conduction of the nerve impulse in the region to which it is applied, without affecting consciousness.

M

- **MAC**
  The minimal alveolar concentration (measured in % of 1 atm) at steady state which prevents a movement response to a standard surgical stimulus (midline incision) in 50% of a population.
- **Manometer**
  Device which measures gas pressure.
- **Mean Systemic Filling Pressure**
  The pressure measured anywhere in the systemic circulation when all flow of blood is stopped.
- **Mixed Venous Blood**
  Blood from the IVC, SVC and coronary sinus, which has been mixed by the pumping action of the RV and is typically sampled from the pulmonary artery.
- **Mole**
  Amount of a substance which contains as many representative particles as there are atoms in 12g of carbon-12.
- **Molality**
  Number of moles of solute per kg of solvent.

- **Molarity**
  Number of moles of solute per L of solvent. Varies with:
    - Temperature
    - Solvent density
    - Solute volume

N

- **Natural Frequency**
  Frequency at which a system will oscillate at if disturbed and left alone.
- **Nausea**
  Unpleasant subjective sensation associated with urge to vomit.
- **Neuropathic Pain**
  Pain caused by a lesion or disease of the somatosensory nervous system.
- **Nociception**
  Neural process of encoding a noxious stimulus.

O

- **Odds Ratio**
  Estimate of risk, where the OR is the ratio of odds of an outcome in those treated vs. those not treated. OR = 1 suggests no effect, ≤1 suggests reduced risk >1 suggests increased risk.
- **Ohm**
  Resistance which will allow one ampere of current to flow per volt of potential difference.
- **Opiate**
  Naturally occurring substance with morphine-like properties.
- **Oncotic Pressure**
  Proportion of osmotic pressure due to colloid.
- **Opioid**
  Describes any substance with activity at opioid receptors, and which can be reversed by naloxone.
- **Osmosis**
  Movement of a solvent across a semipermeable membrane to an area of greater solute concentration.
- **Osmotic Pressure**
  Pressure that must be applied to a solution to prevent the movement of a solvent from entering a solution with higher osmolality.
- **Oxygen Flux**
  Volume of oxygen delivered to the tissues per minute.

P

- **p50**
  The partial pressure at which an oxygen-carrying protein is 50% saturated.

- **Pain**
  Unpleasant sensory and emotional experience associated with actual or potential tissue damage, or expressed in terms of such damage.

- **Partition Coefficient**
  Describe the relative affinity of an agent for two phases. It is defined as the ratio of the concentration of agent in each phase, when both phases are of equal volume and the partial pressures are in equilibrium at STP.

- **Pasteur Point**
  PO_2 at which oxidative phosphorylation ceases.

- **PEEP**
  Supra-atmospheric airway pressure at the end of expiration.

- **pH**
  The power of hydrogen. Describes the activity of hydrogen ions in a solution, and is expressed as
  $pH = -log_{10}[H^+]$.

- **Preload**
  Load imposed on a muscle before contraction, and measured as the average myocardial fibre length at the onset of systole. May be approximated clinically using EDV.

- **Precision**
  The ability of a measurement device to provide reproducible results upon repeated measurement.

- **Pseudo-critical temperature**
  Temperature at which a gas mixture will separate into its constituent components.

R

- **Radiation**
  Transfer of energy via electromagnetic radiation.

- **Receptor**
  Component of a cell which binds to a ligand and results in a change in function.

- **Reduction**
  Reaction which results in a gain of an electron.

- **Reflex**
  Unconscious, predictable response to a stimulus.

- **Regurgitation**
  Passive passage of gastric contents into the mouth.

- **Relative Humidity**
  Ratio of mass of water vapour in a given volume of air, to the mass required to saturate that volume at that temperature. Expressed as a percentage.

- **Respiratory Exchange Ratio**
  Ratio of CO_2 produced to O_2 consumed at any given point.

- **Respiratory Quotient**
  Ratio of CO_2 produced to O_2 consumed at steady-state.

- **Reynolds Number**
  Dimensionless index which predicts the likelihood of turbulent flow.

S

- **Saturated Vapour**
  Vapour which is in equilibrium with its own liquid state, i.e. there are as many molecules entering the vapour phase as there there are those condensing into the liquid phase.
  - A saturated vapour contains the least amount of energy possible without condensing
- **Saturated Vapour Pressure**
  Pressure exerted by a vapour which is in equilibrium with its liquid state. Increases with temperature, since as the kinetic energy (heat) content of molecules increase, more of them enter the vapour phase.
- **Second Gas Effect**
  Disproportionately rapid rise in FA/Fi ratio seen when an anaesthetic agent is co-administered with nitrous oxide.
- **Seebeck effect**
  The generation of a potential difference at the junction of two dissimilar metals, with its value dependent on the temperature of the junction.
- **Shivering**
  Involuntary, oscillatory, muscular activity that augments metabolic heat production.
- **Shunt**
  Blood entering the left side of the circulation without being oxygenated via passage through the lungs.
- **Specific Gravity**
  Density of a liquid, in mass per unit volume.
- **Specific Heat Capacity**
  Amount of heat energy required to raise the temperature of 1kg of a substance by 1°K without a change in state.
- **Standard Base Excess**
  The base excess calculated for an Hb of 5g.L^{-1}, and which gives a better representation of ECF pH.
- **Surface Tension**
  Describes the tendency of a fluid to minimise its surface area.
- **Suspension**
  Particles of any phase dispersed in a liquid.
- **Synergism**
  When two drugs interact to produce a greater effect than would be expected.

T

- **Temperature**
  Ability of a body to transfer heat energy to another body, as measured in degrees.
- **Thirst**
  Conscious sensation of the physiological urge to drink.
- **Time constant**
  Time it would take for an exponential function to complete if the initial rate of change continued. A process is:
  - 63% complete at 1T
  - 86.5% complete at 2T
  - 95% complete at 3%

- **Tonicity**
  Effective osmolality of a solution. Given by the osmolality, minus the concentration of freely diffusable osmoles (in plasma, these are urea and glucose).
- **Tonometer**
  Device which measures pressure of liquid.
- **Transducer**
  Device which changes a signal from one energy form to another.
- **Treppe Effect**
  Increase in contractility with an increase in HR. Also known as the Bowditch effect.
- **Turbulent Flow**
  Irregular movement in radial, axial, and circumferential axes.

V

- **Valsalva Manoeuvre**
  Forced expiration against a closed glottis.
- **Vapour**
  Substance in a gaseous phase below its critical temperature.
- **Vapour pressure**
  Pressure experted by a vapour.
- **Venous admixture**
  Amount of mixed venous blood that must be added to pulmonary end-capillary blood to give the observed arterial oxygen **content**.
- **Viscosity**
  Describes the tendency of a fluid to resist flow.
- **Volt**
  Potential difference which dissipates 1W of energy per 1A of current.
- **Volume of Distribution**
  Apparent volume into which a drug is distributed to produce the identified plasma concentration.

Last updated 2019-07-20

Key Graphs

Graphs:

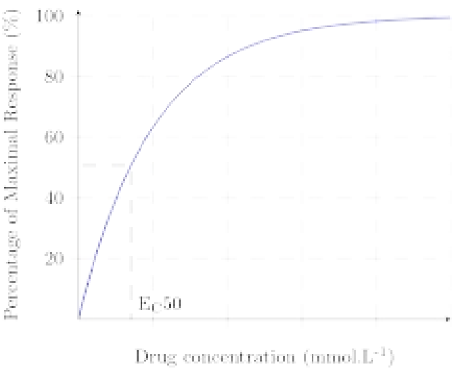
- Help you to convey knowledge and understanding efficiently in the written
- Are often a feature of the viva as they allow examiners to assess depth of understanding
    - You will be asked to demonstrate how they change under different physiological states

It is easy to get distracted by the curve, and forget the basics (especially in the written). To avoid this, approach them in the same way each time:

- **Axis**
  First draw the axis.
    - If the axis is continuous (e.g. PaO_2), ensure you place an arrow at the far end
    - If the axis ends at a fixed point (e.g. SpO_2), ensure you place a bar at the end to signify it does not continue indefinitely
- **Labels**
  Label each axis with what it is representing.
- **Units**
  Give each label **appropriate units**.
    - In the viva, you can just say this out loud as you're drawing the axes
- **Curve**
  Draw the curve.
- **Special Points**
  Identify the key points of the curve and label these points. These include:
    - Intercepts
    - Inflection points
    - Important values
      e.g. The mixed venous point.

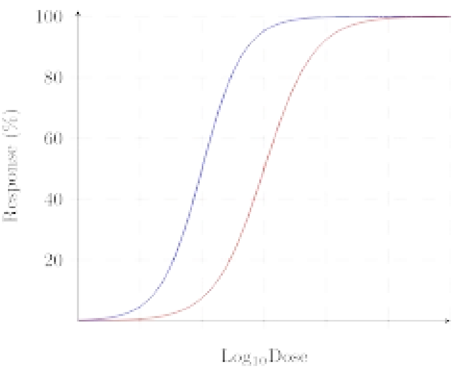
Pharmacology

Dose-Response:



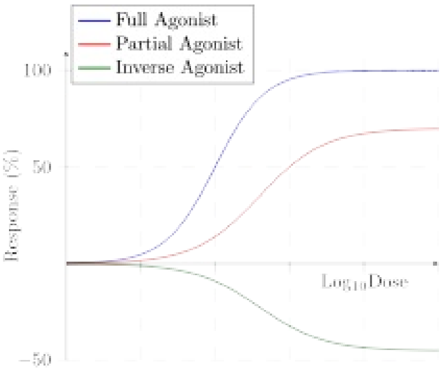
- Dose response curve is a wash-in exponential
- Difficult to compare different drugs using this curve

Log$_{Dose}$-Response:



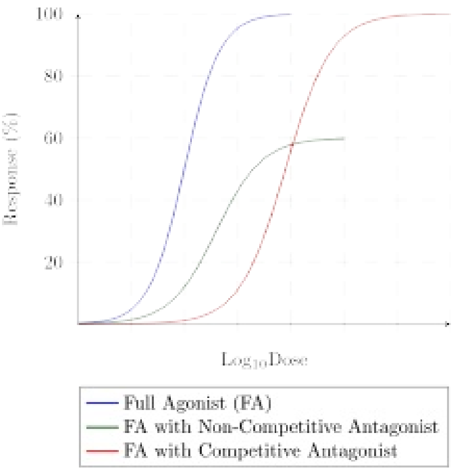
- Log-transform of dose allows different drugs to be compared
- Both red and blue drugs are full agonists (as they both reach 100% response), however the blue drug is more potent as it has a lower E$_D$50

Agonists:



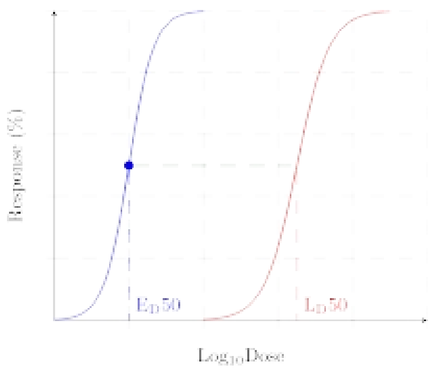
- Partial agonists do not reach 100% response
- Inverse agonists have a negative response

Antagonists:



- Non-competitive antagonists prevent maximal response being reached
- Competitive agonists right shift the curve, as they can be overcome with increasing dose of agonist

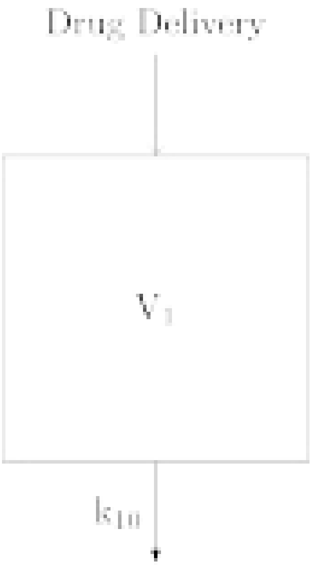
Therapeutic Index:



- Can be calculated from the ratio of the LD_{50} and ED_{50}

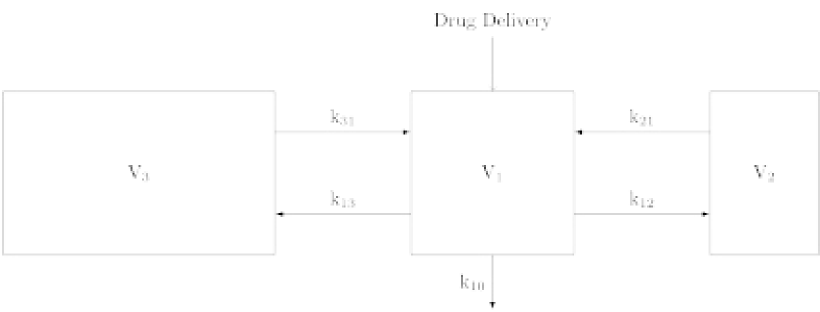
Models

The One-Compartment Model:



- Drug is added to and removed from the single central compartment
  There is no distribution possible.
- V_1 is equal to the volume of distribution
- k_{10} is the rate constant for elimination

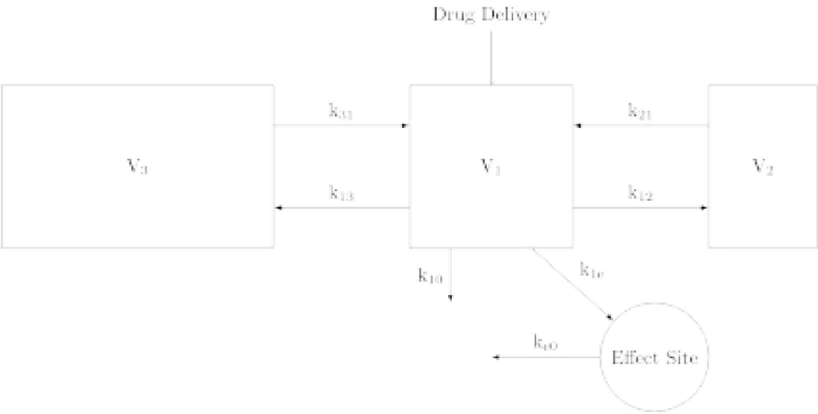
Three-Compartment Model:



- Drug is added to and removed from the central compartment
- Drug will also distribute to (and redistribute from) the peripheral compartments
- Plasma concentration will depend on:
  - Rate of drug delivery
  - Rate of drug distribution and redistribution

- Rate of drug elimination

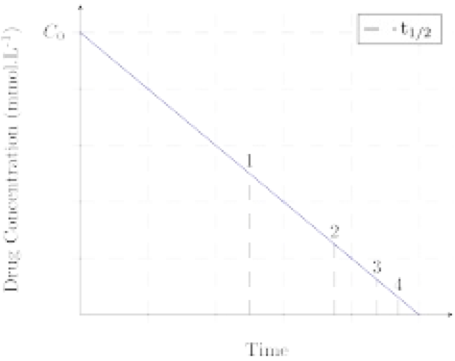
Effect-Site:



- Drug distributes to the effect site from the central compartment
- Effect site has no volume, but does have rate constants
- $t_{1/2}$ke0 is generally drawn with drug being eliminated from the effect site, however in reality this does not occur as drug should only be eliminated from the central compartment

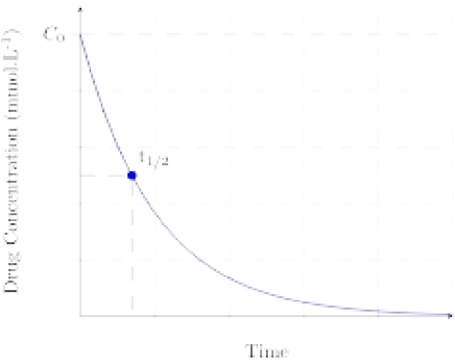
Pharmacokinetics

Zero-order kinetics:



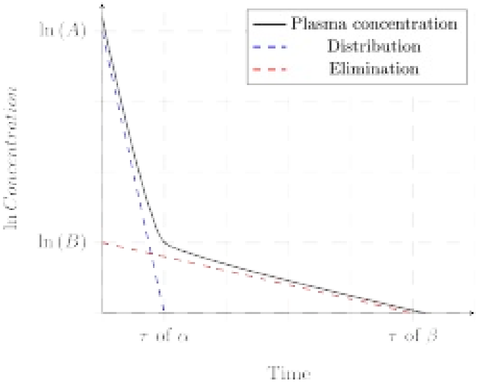
- A constant amount of drug is eliminated per unit time
- Half-life is not a constant value
  Half-life progressively shortens, as the time taken to go from 50% to 25% is half the time it took to go from 100% to 50%.

First-Order Kinetics:



- A constant proportion of drug is eliminated per unit time
- Half-life is a constant value

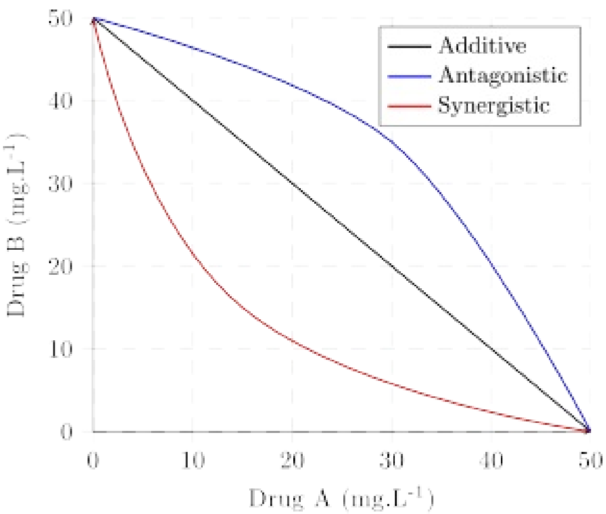
Biexponential elimination:



- Note that concentration has been log-transformed
- This describes the elimination of drug from a two compartment model

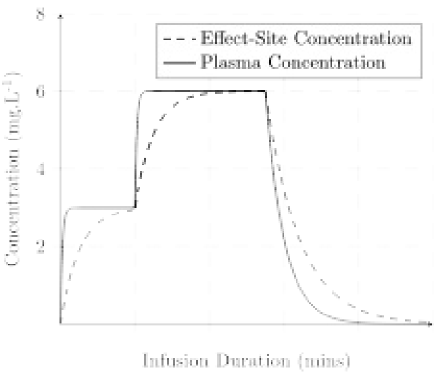
Pharmacodynamics

Isobologram:



- Plots lines of equal activity versus concentration of two drugs

Plasma-Site Targeting:



TCI graphs are easy to draw if you remember that:

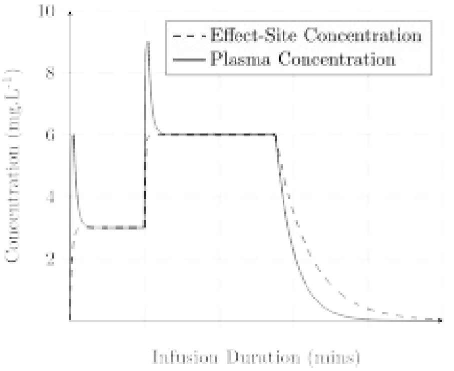
- The pump aims to achieve the targeted concentration:
  - As rapidly as possible
  - Without overshoot

- Effect site concentrations fall slower than plasma site concentrations Drug can only redistribute back to plasma when effect site concentration is greater than plasma concentration.

Therefore in plasma site targeting:

- Plasma concentration rises rapidly with initial bolus dose
- Does not overshoot
- Effect site concentration rises more slowly
  - Exponential wash in curve as the concentration gradient between plasma and effect site falls over time

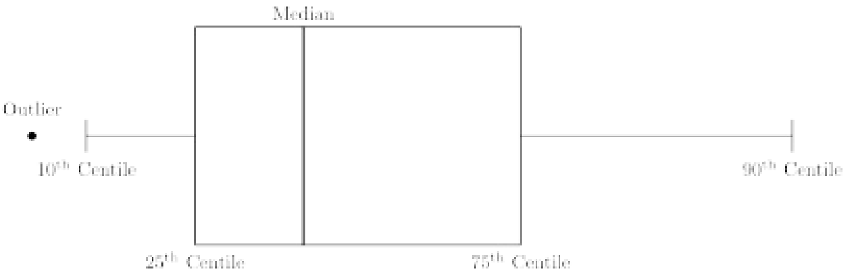
Effect-Site Targeting:



- Plasma concentration overshoots effect-site target and then declines rapidly
- Effect site concentration rises rapidly, and is achieved more quickly compared with plasma-site targeted model

Statistics

Boxplot:

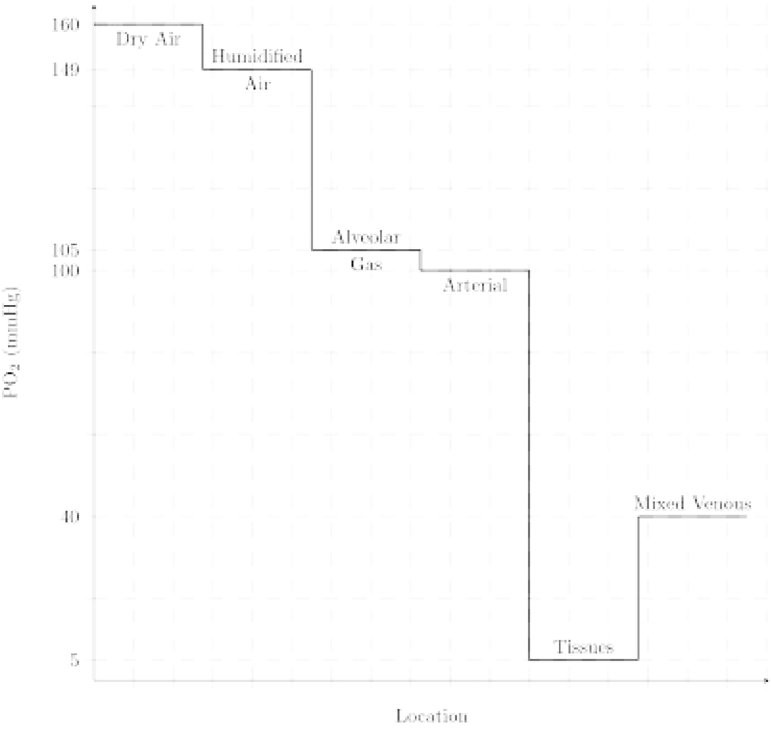


- Box is defined by the 25th and 75th centiles
- Line in the middle of the box is the median ("50th centile")
- "Whiskers" either side of the box define the 10th and 90th centiles
  - These may also refer to the 5th and 95th centiles
- Results outside of whiskers are defined as outliers, and are represented by single dots

Respiratory

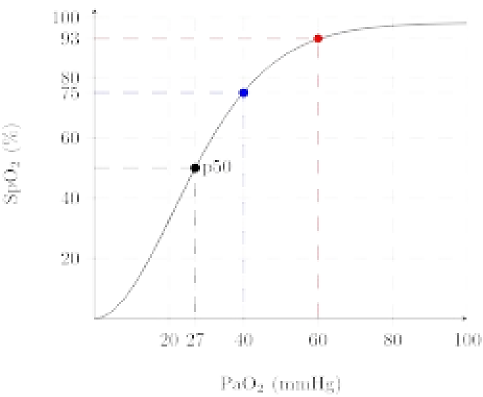
Oxygen

Oxygen Cascade:



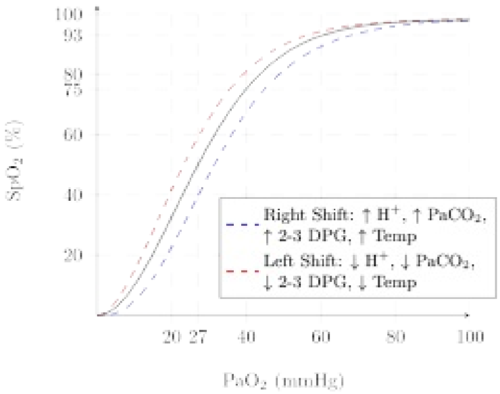
- Graph of location versus oxygen partial pressure
- Atmospheric (dry) air has a PO_2 of 160mmHg
- Tracheal (humidified) gas has a PO_2 of 149mmHg
  Reduced due to saturated vapour pressure of water.
- Alveolar gas has a PO_2 of 105mmHg
  Reduced to the presence of CO_2, as per the alveolar gas equation.
- Arterial blood has a PO_2 of ~100mmHg
  Reduced to the Alveolar-arterial oxygen gradient.
- Tissues have a PO_2 of ~5mmHg
- Mixed venous blood has a PO_2 of ~40mmHg
  Greater than tissue PO_2 as not all oxygen in blood diffuses into or is consumed by tissues.

Oxyhaemoglobin Dissociation Curve:



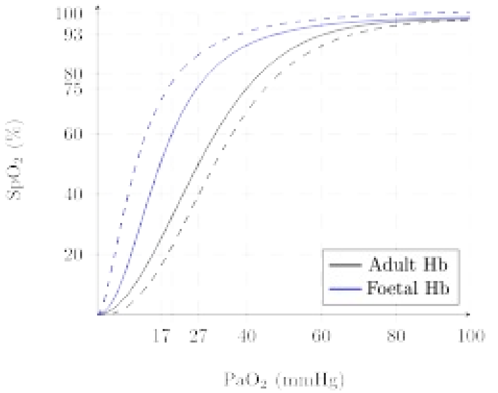
- Graph of PaO_2 versus oxygen saturation
- Note that $PaO2_2$ is continuous, and so an arrow should be drawn at the tip of the x-axis, whilst saturation is finite and so the y-axis should be capped at 100%
- The curve is a sigmoid shape
- Key points:
  - At 10mmHg, saturation is 10%

- The p50 is at 27mmHg
- The mixed venous point is at 40mmHg, where haemoglobin is 75% saturated
  Note that due to the Haldane effect, the mixed venous point does not technically exist on the arterial curve. This is a small point and is ignored in most graphs (including this one), but may be worth stating if you're feeling confident in the viva.
- The "ICU point" (the upper inflection) is at 60mmHg where haemoglobin is 93% saturated
- The arterial point is 97% saturated at 100mmHg



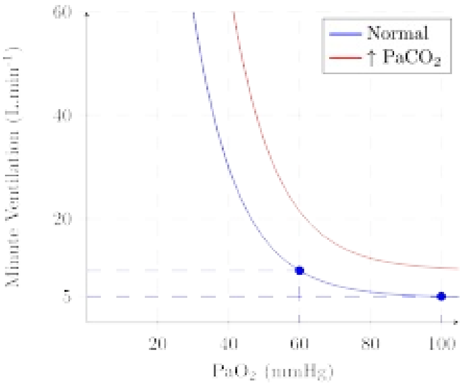
- The curve may be right-shifted by:
  - Increased H^+
  - Increased $PaCO_2$
  - Increased temperature
  - Increased 2-3 DPG
- These shifts are defined by a movement of the p50

Double-Bohr Effect:



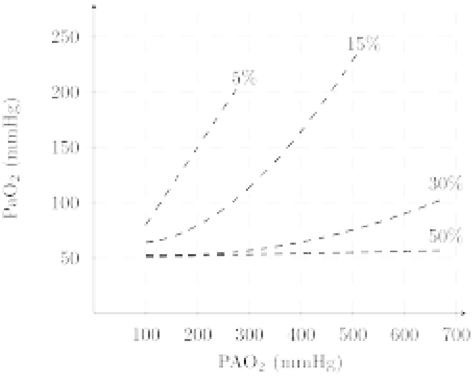
- The double Bohr effect can easily become confusing, especially when you are under pressure and only allowed one colour (as in the written exam)
  Here is a straightforward method which minimises the confusion:
  1. Draw an adult curve with a p50 of 27mmHg
  2. Draw a foetal curve with a p50 of 17mmHg
  3. Draw a right-shifted adult curve
  4. Draw a left-shifted foetal curve

PaO_2 and Minute Ventilation:



- Exponential curve
- Minute ventilation doubles as PaO_2 decreases from 100mmHg to 60mmHg
- Inflection point is ~50-60mmHg
  Below this there is a large increase in ventilation.
- Hypercapnea leads to a greater minute ventilation for any given PaO_2

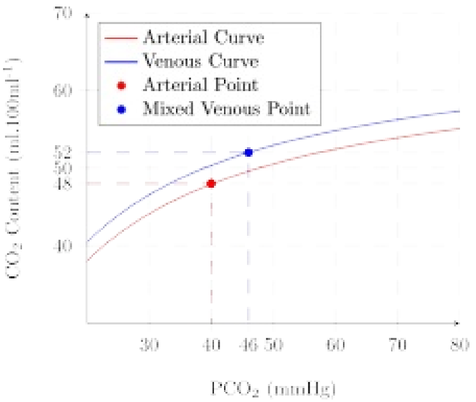
Isoshunt Diagram:



- Plots the relationship between PAO_2 versus PaO_2 for different (fixed) shunt fractions
- These are known as isoshunt lines
- Key isoshunt lines are:
  - At 50% shunt, PaO2 is essentially independent of PAO2
  - At 30% shunt, PaO2 will not increase above 100mmHg on 100% oxygen at atmospheric pressure

Carbon Dioxide

Carbon Dioxide Dissociation Curve:



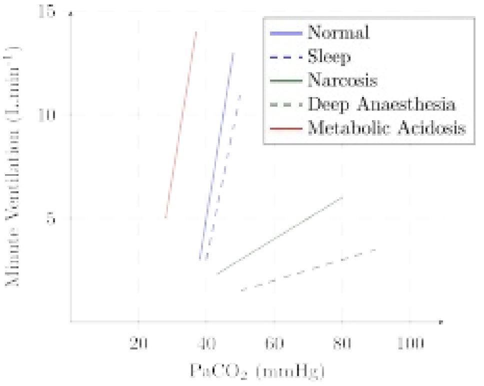
- Graph of carbon dioxide content versus partial pressure
- Key points on this curve:

-1

- Arterial CO_2 content is 48mls.100ml^{-1} of blood at 40mmHg
- Mixed venous CO_2 content is 52.mls.100ml^{-1} of blood at 46mmHg

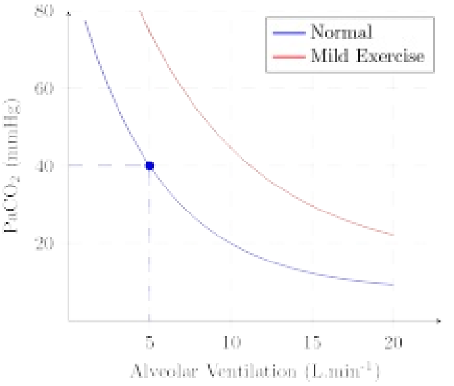
- Note that the mixed venous curve is up-shifted due to the Haldane effect
  Remember that 50% of the difference in CO_2 content is due to the Haldane effect. Therefore:
  - The mixed venous curve should be drawn such that CO_2 content is 50mls.100ml^{-1} at 40mmHg
  - The arterial curve should be drawn such that CO_2 content is 50mls.100ml^{-1} at 46mmHg

$PaCO_2$ and Minute Ventilation:



- Graphs the change in minute ventilation for **primary change in $PaCO_2$**
- Remember that minute ventilation increases by ~3L.min^{-1} for every 1mmHg increase in $PaCO_2$
  From this, the relationship to other states can be derived:
  - Minute ventilation is reduced during sleep, but the central response to CO_2 is only minimally affected
  - The central response to CO_2 is heavily affected during anaesthesia
  - Minute ventilation is increased for any given $PaCO_2$ in the setting of acidosis

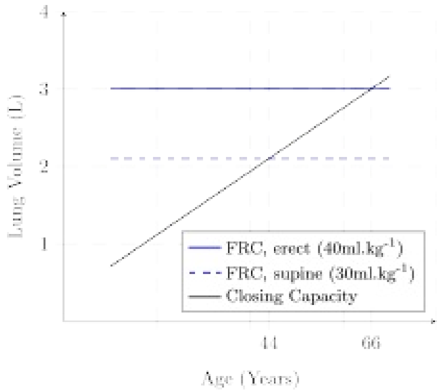
Alveolar Ventilation and $PaCO_2$:



- Graphs the change in $PaCO_2$ for a **primary change in minute ventilation**
- Exponential curve as $PaCO_2$ is inversely proportional to minute ventilation
- Minute ventilation is increased for any given $PaCO_2$ during exercise

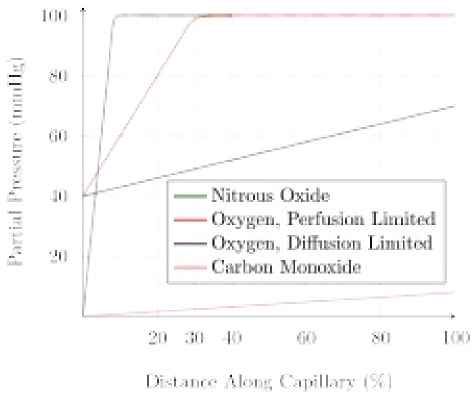
Anatomical and Physiological Interactions

Closing Capacity and Age:



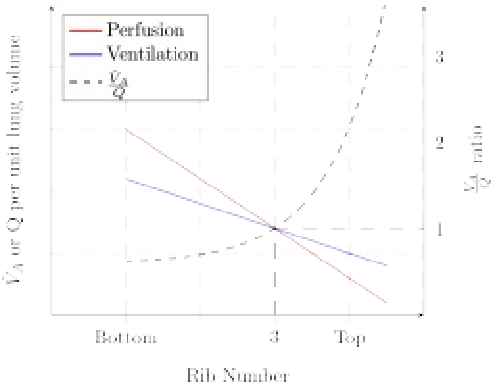
- Note that although FRC increases slightly with age, this is not generally shown on this graph
- Closing capacity increases with increasing age
  Key intersections are:
  - Greater than FRC when supine at 44 years of age
  - Greater than FRC when erect at 66 years of age

Diffusion and Perfusion Limitation:



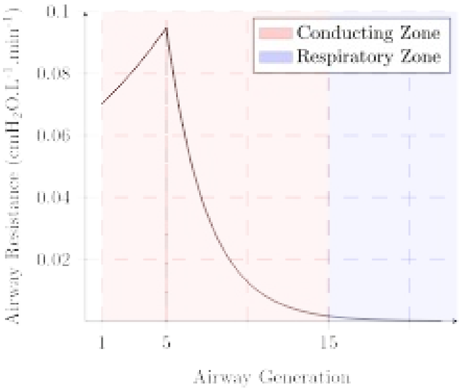
- Classically drawn as partial pressure versus distance along the capillary
  Time along capillary may also be used, however note that total transit time will change with cardiac output.
- Note that at the beginning of the capillary, oxygen partial pressure will be equal to that of mixed venous blood
  - In perfusion limitation, PaO_2 will equal PAO_2 before the end of the capillary
  - In diffusion limitation, partial pressures will not be equal at the end of the capillary
  - In normal circumstances, PaO_2 equals PAO_2 at ~1/3[2] of the distance along the capillary
    If time is being graphed on the x-axis, then this will occur at ~0.25s, as total capillary transit time is ~0.75s.
- Nitrous oxide rapidly diffuses into blood and is and not typically present in mixed venous blood, so this curve begins at the origin and PaN_2O will rapidly reach PAN_2O (in this instance 100mmHg)
- Carbon monoxide binds avidly to haemoglobin and so PaCO increases slowly, resulting in diffusion limitation

Regional Ventilation and Perfusion:



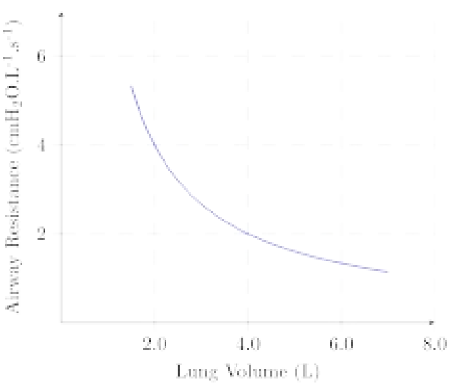
- Graph of alveolar ventilation and alveolar blood flow versus rib number in the **erect** person
- Basal alveolar have greater perfusion and ventilation than apical alveoli
- Note the perfusion gradient is steeper than the ventilation gradient
- Note that the V/Q ratio is:
    - ~1 at the 3rd rib
    - ~3.3 at the apex
    - ~0.63 at the base

Airway Resistance and Airway Generation:



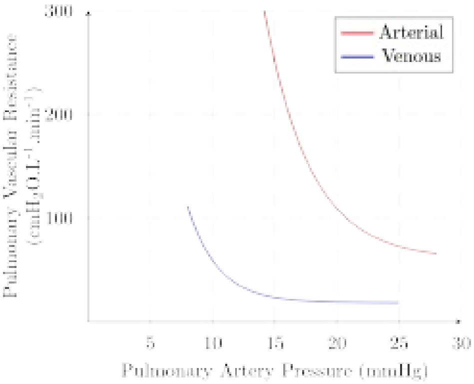
- Graph of airway resistance versus airway generation
- Airway generations are from 1 to 23, and so this graph should not extend outside these values
- Airway resistance is maximal at the 5th generation
  This has the lowest total cross-sectional area.
- Airway resistance is negligible in the respiratory zone, which exists after the 15th generation

Airway Resistance and Lung Volume:



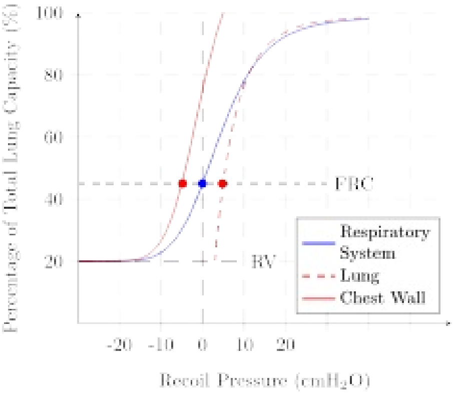
- Airway resistance decreases as lung volume increases as radial tension distends airways, increasing their cross-sectional area and lowering airway resistance

Pulmonary Vascular Resistance and Pulmonary Artery Pressure:



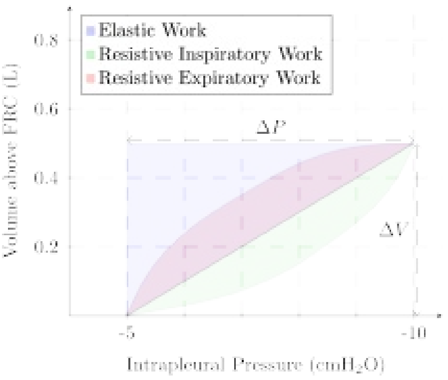
- Pulmonary vascular resistance decreases as pulmonary artery pressure increases
- Arterial pressure has a greater effect on PVR than venous pressure

Lung and Chest Wall Volume and Pressure Relationships:



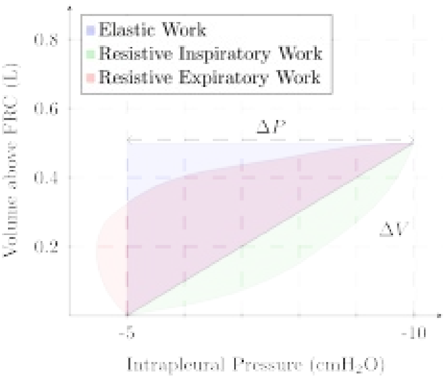
- Graph of lung volume versus **recoil pressure**
  - Expressing lung volume as a percentage of total lung capacity may make it easier to remember the key points on this graph
  - Note that recoil pressure is the pressure generated **between the lung and the chest wall** when they are distended, it is not intrapleural pressure
- This graph is complex and it is easy to draw incorrectly
  This is an approach to make it as easy as possible:
  1. Draw a sigmoid graph for the pressure-volume relationship of the respiratory system as a whole
     - As recoil pressure is 0 at FRC this will be the y-intercept
     - The graph will asymptote at residual volume, as volume (by definition) cannot become lower than this volume
  2. Draw a steep run-away exponential for the pressure-volume relationship of the chest wall
     - Recoil pressure should be ~-5cmH_2O at FRC
     - Recoil pressure should be 0cmH_2O at ~75% of TLC
     - Recoil pressure should not exceed ~5cmH_2O at TLC
  3. Draw a steep wash-in exponential for the pressure-volume relationship of the lung
     - Remember lung volume cannot fall below residual volume
     - Recoil pressure should be ~5cmH_2O at FRC
       This should be equal and opposite to the recoil pressure for the chest wall, as the sum of these must be 0 at FRC.
     - Note that this curve should slightly exceed the curve for the respiratory system as recoil pressure increases

Work of Breathing:



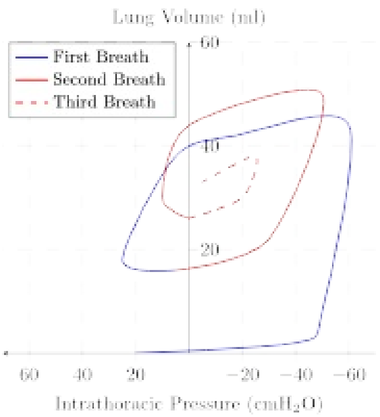
- Graph of lung volume (above FRC) versus intrapleural pressure
  Note that intrapleural pressure becomes more negative along the x-axis.
- The area under different sections of this curve give the work of breathing
  - Elastic inspiratory work of breathing is given the blue triangle
  - Resistive work of expiration is given by the red area
    Note that as this is entirely contained within the area of elastic inspiratory work, expiration is passive and does not require additional energy expenditure.
  - Resistive work of inspiration is given by the green area

Work of Breathing - Active Expiration:



- When resistive expiratory work exceeds elastic inspiratory work, active expiration must occur
- In this graph, active expiration is given by the red area not contained with the blue triangle

Neonatal First Breath:

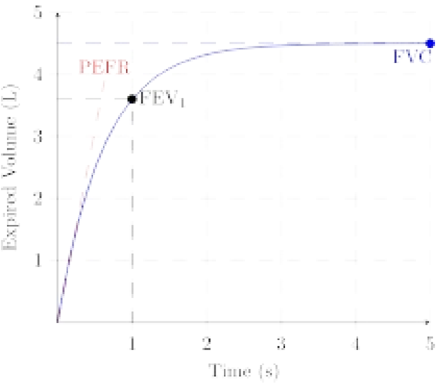


- This graph describes the pressure-volume changes of the neonate as it takes its first breaths and establishes FRC
- This graph is easy to draw provided you remember that:
  - Prior to the first breath, lung volume is 0
  - As the lung initially has very poor compliance, the intrapleural pressure must become very negative more lung volume

        increases substantially
    - At the end of each breath, intrathoracic pressure is close to 0
    - With each subsequent breath:
        - Lung compliance improves
          Therefore the magnitude of pressure swings is reduced.
        - FRC increases
          Lung volume at end-inspiration is increased.

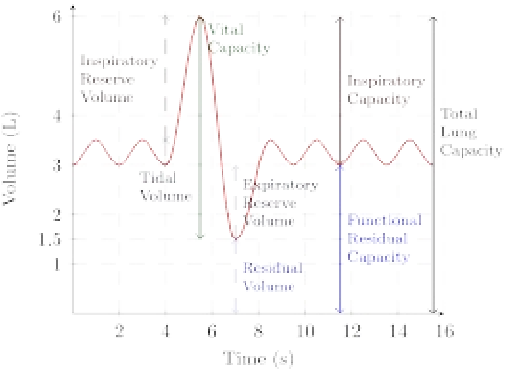
Spirometry

Forced Vital Capacity:



- Graph of expired volume (vital capacity) over time
- ~80% of total volume is expired within the first second (FEV_1)
- Total FVC is 4.5L in the 70kg Guyton Man
- The gradient of initial expiration is the peak expiratory flow rate

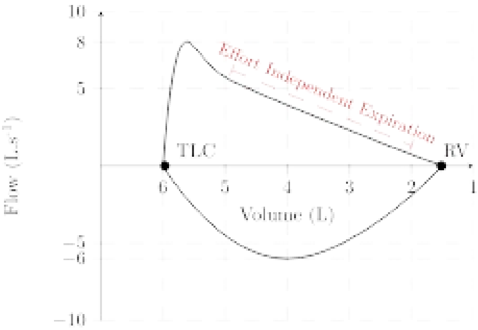
Spirometry:



- Graph of lung volume over time
- Includes a normal tidal breath and a vital capacity breath

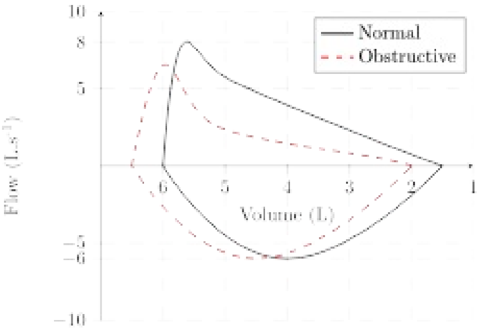
Flow-Volume Loops

Normal loop:



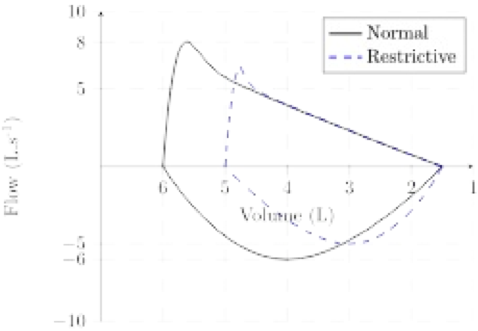
- Peak expiratory flow is ~8L.s^{-1}
- Peak inspiratory flow is ~6L.s^{-1}
- Effort independent expiration occurs during expiration

Obstructive Disease:



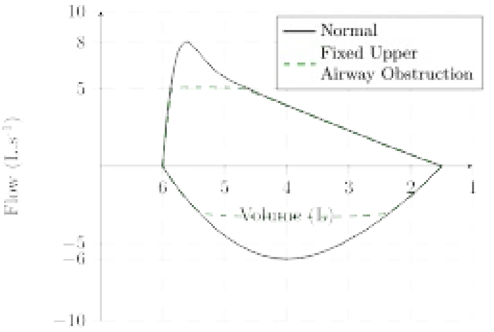
- Residual volume and total lung capacity are increased due to gas trapping
- Peak expiratory flow is reduced
- There is scalloping of the effort-independent portion of the curve
  Also known as a concave curve.

Restrictive Disease:



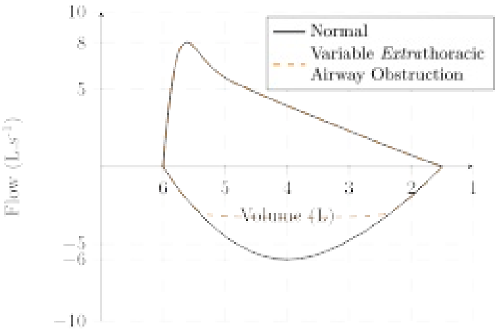
- Total lung capacity is reduced
- Residual volume is normal
- Peak expiratory flow *may* be reduced (as seen here)
  However the FEV_1:FVC ratio will be normal in purely restrictive lung disease.
- Effort-independent expiration is linear and will join with the normal curve

Fixed Upper Airway Obstruction:



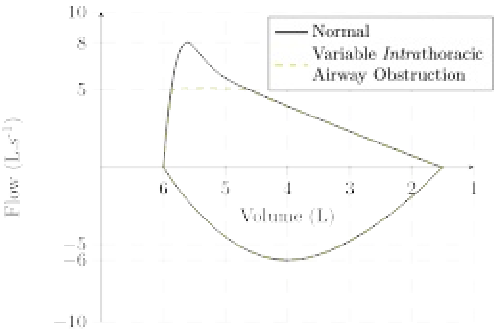
- Obstruction that does not change calibre throughout the respiratory cycle
- Peak expiratory and inspiratory flow rates are limited

Extrathoracic Obstruction



- Obstruction worsens during inspiration as it is 'pulled in' by negative intrathoracic pressure

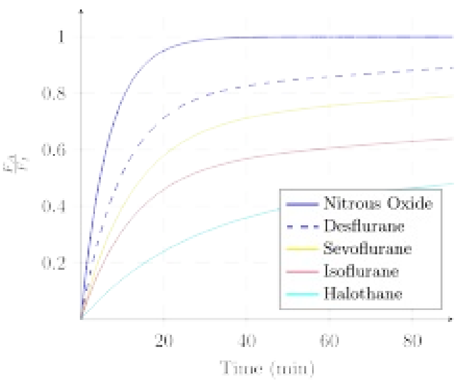
Intrathoracic Obstruction



- Obstruction worsens during expiration as it is compressed by dynamic airways compression

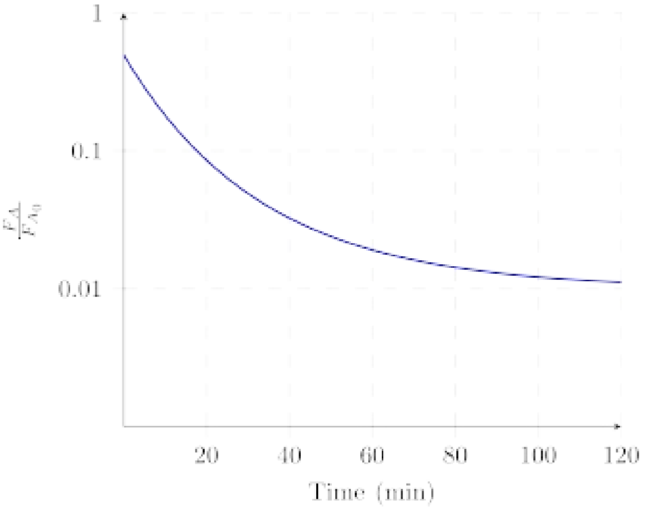
Anaesthetic Agents

F_A/F_I:



- Graph of the alveolar over inspired agent fraction versus time for various volatile agents
- Indicates the relative speed of onset of different agents
- Uptake of agent is proportional to solubility in blood, and therefore is in order of their blood:gas coefficients
    - The exception is nitrous oxide, which has a faster rate of rise than desflurane despite its greater blood:gas coefficient due to the concentration effect

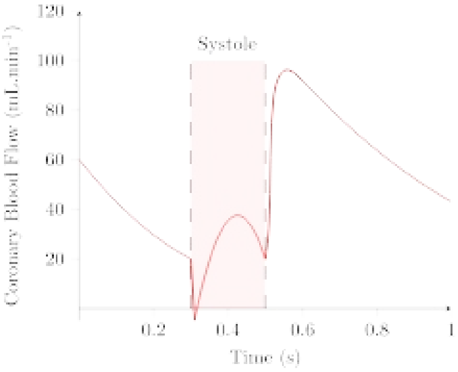
F_A/F_{A0}:



- Graph of alveolar agent fraction versus time for a volatile agent
- Note the logarithmic scale on the y-axis
- Exponential washout curve
- Function of two separate washout curves
    - Rapid washout with removal of agent from circuit and FRC
    - Slow washout due to diffusion of agent from tissues into blood, and then alveolus

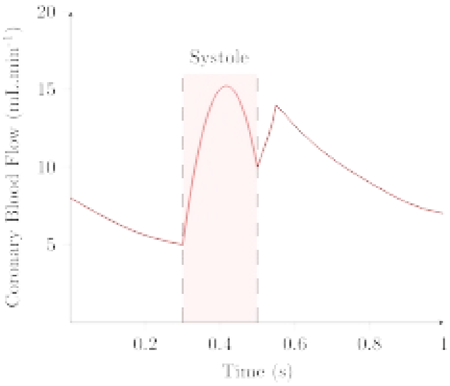
Cardiovascular

Left Ventricular Coronary Blood Flow:



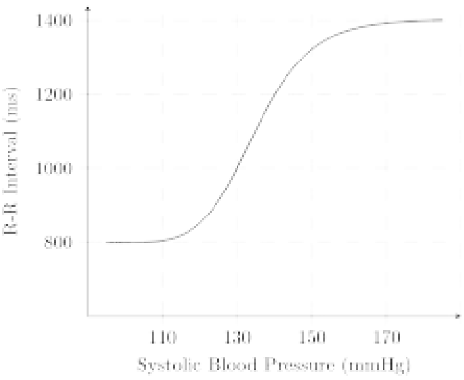
- Graph of blood flow to the left *ventricle* over time
  Systole should be clearly identified.
- Left ventricular flow occurs predominantly in diastole
  Peak flow is ~115ml.min^{-1}.
- There is a brief period of flow reversal during isovolumetric contraction

Right Ventricular Coronary Blood Flow:



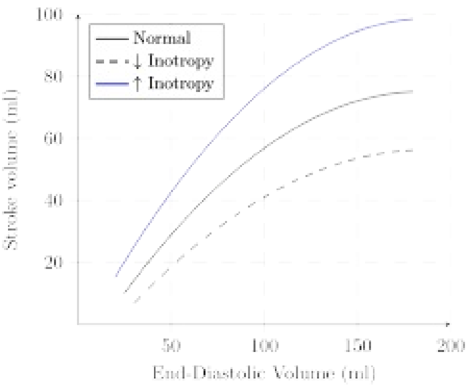
- Graph of blood flow to the right *ventricle* over time
- Right ventricular flow occurs throughout the cardiac cycle
  This is because aortic root pressure exceeds cavity pressure throughout the cardiac cycle.
- Peak flow is ~15ml.min^{-1}

Baroreceptor Response:



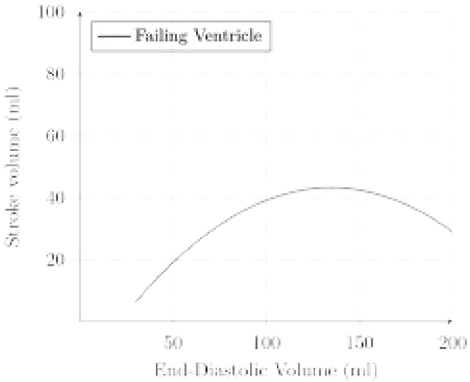
- Graph of heart rate versus systolic blood pressure
  Note that the RR interval is inversely proportional to heart rate.
- Heart rate responses asymptote at extremes of blood pressure

Starling Curve:



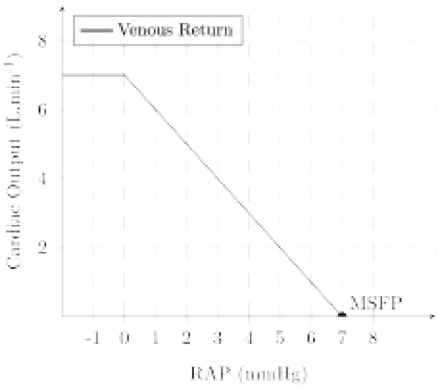
- Typically drawn as a graph of stroke volume (or cardiac output, assuming a constant heart rate) versus preload (typically estimated as end-diastolic volume, but may also be end-diastolic pressure)
- Graph does not cross the origin as EDV is never 0ml

Starling Curve - Failing:



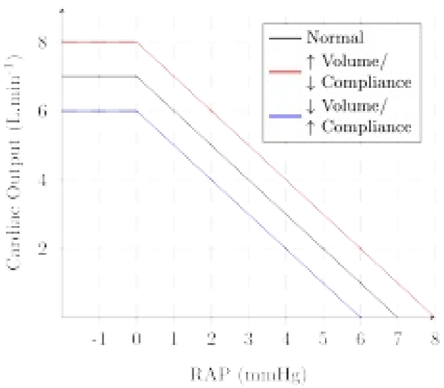
- Myocardium that has been overloaded by high end-diastolic volumes may lead to a decrease in tension generated by the myocardium

Venous Return:



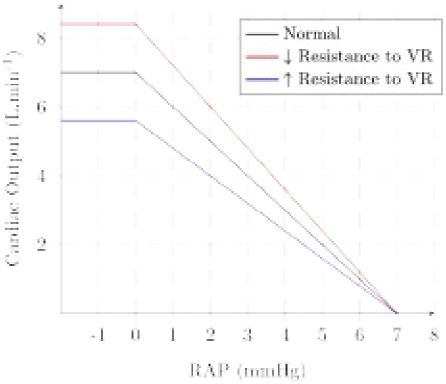
- Graph of venous return versus right atrial pressure
- The x-intercept is the point of no flow within the circulation (as VR = CO), and therefore is the mean systemic filling pressure
- The curve flattens when RAP becomes negative, as external tissues act as a Starling resistor and prevent further increases in flow

Venous Return - Compliance and Volume:



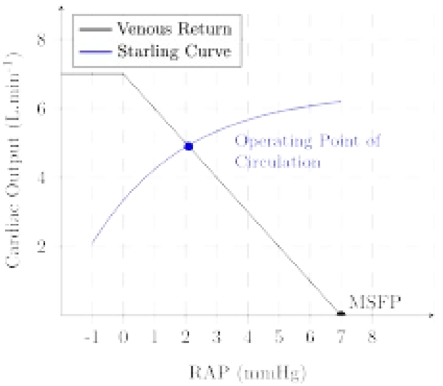
- Decreasing venous compliance or increasing circulating volume results in an increase in mean systemic filling pressure (as for any given compliance, pressure must increase if volume increases) and an increase in venous return for any given right atrial pressure
- The opposite occurs with a decrease in circulating volume or an increase in venous compliance

Venous Return - Resistance to Venous Return:



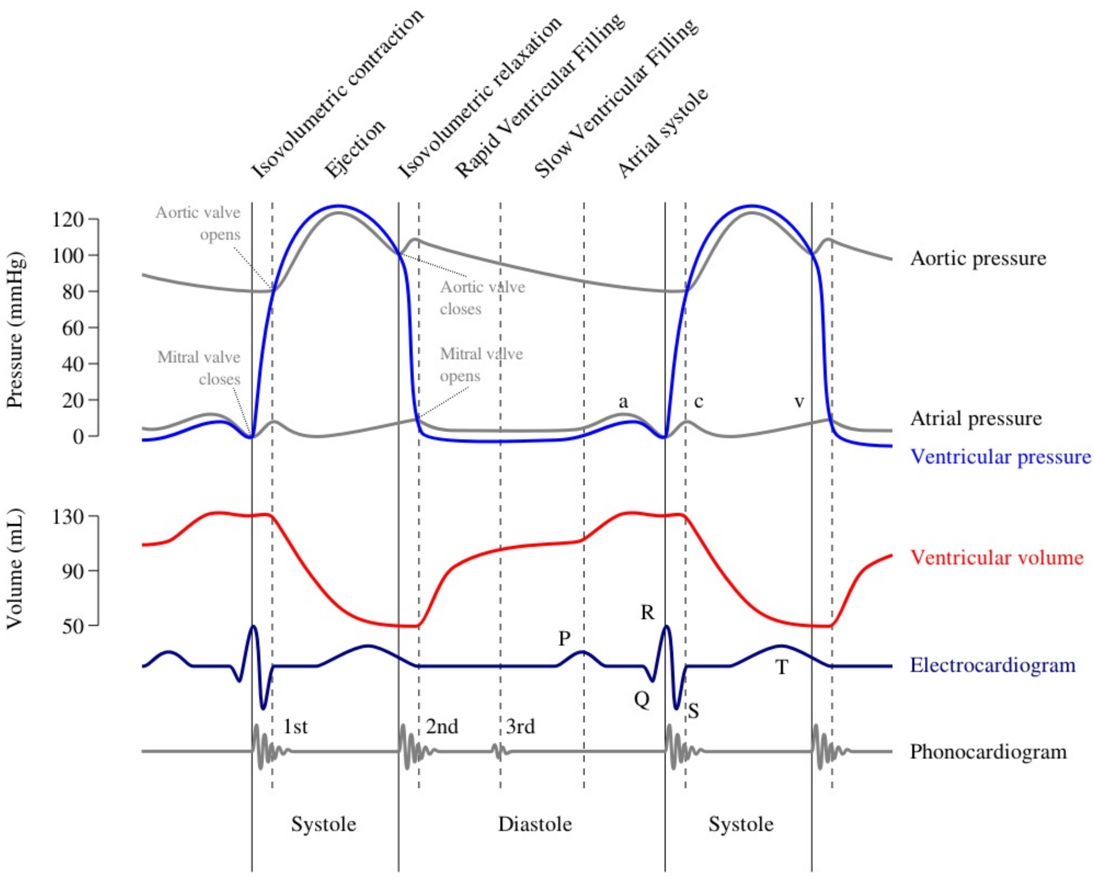
- Altering resistance to venous return (e.g. during pregnancy, or laparoscopic surgery) will alter venous return without changing mean systemic filling pressure

Circulatory Function Curve:



- Plotting the venous return curve and the Starling curve on the same axes generates this graph
  - This is only valid at steady state, i.e. when CO = VR
- Note that as steady-state exists when CO=VR, the intercept of these two curves is the operating point of the circulation

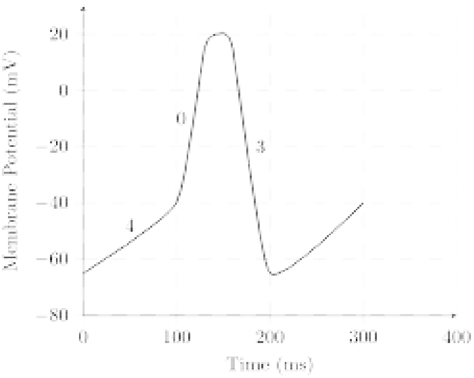
Wiggers Diagram:



- Wiggers diagram is a graphical representation of the events during each phase of the cardiac cycle
- Key points to note:
    - Aortic diastolic pressure occurs just prior to aortic valve opening
      A common mistake is to label diastolic pressure at the dicrotic notch.
    - Ventricular pressure exceeds aortic pressure during ejection
    - Aortic pressure will slightly exceed ventricular pressure during the last part of ejection
      This is due to the inertia of ejected blood causing ongoing forward flow despite the pressure gradient.
    - The dicrotic notch occurs on the aortic pressure curve
      A common mistake is to draw this on the ventricular curve.
    - CVP *slightly* exceeds ventricular pressure during ventricular filling
    - The C wave occurs during isovolumetric contraction
    - The V wave begins prior to the T wave, but peaks after the T wave has finished
    - Electrical events slightly proceed ventricular mechanical events

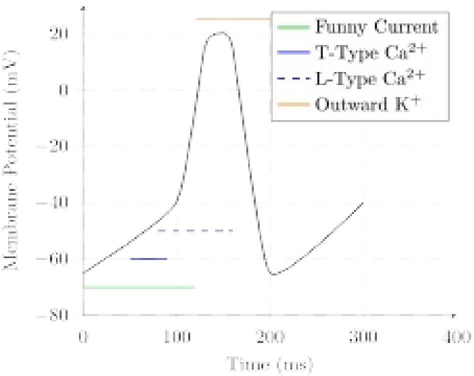
Action Potentials

Pacemaker Potential:



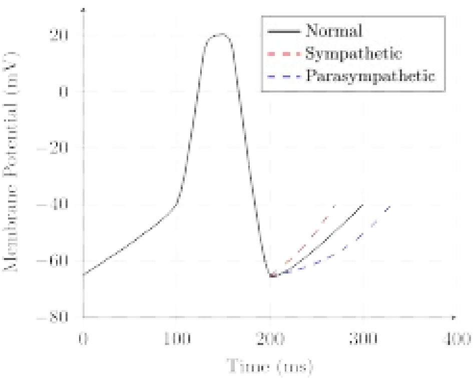
- The pacemaker potential has only three phases, and notably no 'resting phase'
  This is due to the funny current.
- Maximal diastolic potential is -65mV
- Peak membrane potential is ~20mV

Pacemaker Potential - Ion Flux:



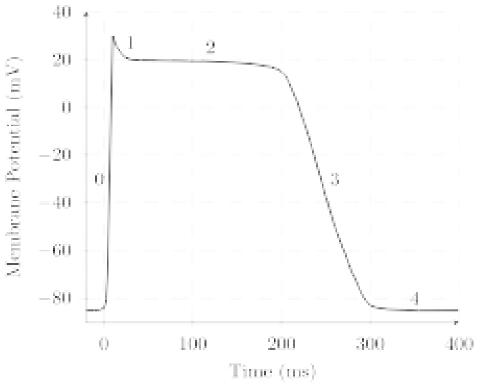
- Demonstrates the timing of electrolyte passage across the cell membrane
- Funny current occurs throughout phase 4 and the early part of phase 0
- T-type calcium current begins in late phase 4 and terminates prior to the onset of phase 0
- L-type calcium current overlaps with the T-type current and continues throughout phase 3
- Outward rectifying potassium current begins during phase 3 and continues during phase 4, restoring membrane potential

Pacemaker Potential - Autonomic Tone:



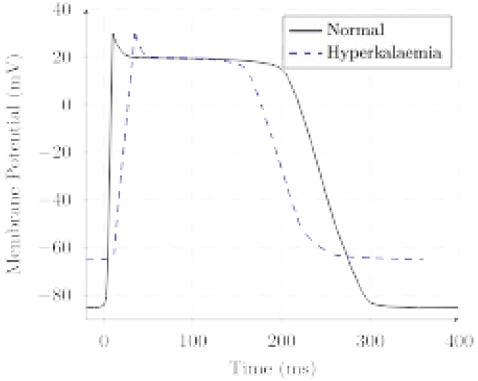
- Alteration to autonomic tone alters the slope of the funny-current
  (Some sources also note a change to maximal diastolic potential, although this is not shown here).

Ventricular Action Potential:



- The ventricular action potential consists of 5 phases
  - 0: Rapid depolarisation
  - 1: Partial repolarisation
    Due to initial efflux of potassium without proportional calcium influx.
  - 2: Plateau
    Outward potassium current is matched by inward calcium current.
  - 3: Repolarisation
    Note that the absolute refractory period ends when resting membrane potential falls below -50mV, which typically occurs at ~250ms.
  - 4: Resting membrane potential
    Note that:
    - Resting Membrane Potential is typically ~-85mV
    - The relative refractory period ends when the membrane potential is at its resting state

Ventricular Action Potential - Hyperkalaemia:

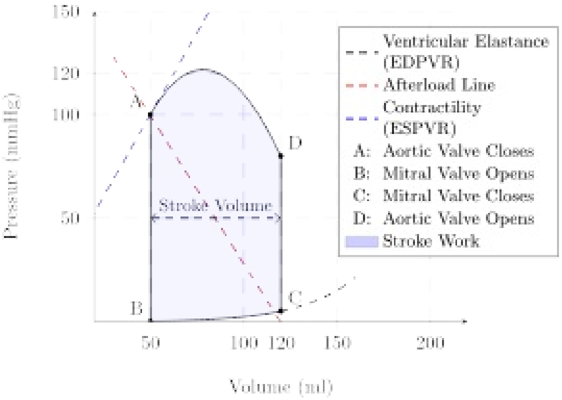


- In hyperkalaemia:
  - The ventricle is more *irritable* as resting membrane potential is less negative, bringing it closer to threshold potential
  - The duration of the action potential is shorter, increasing the chance for a re-entrant arrhythmia

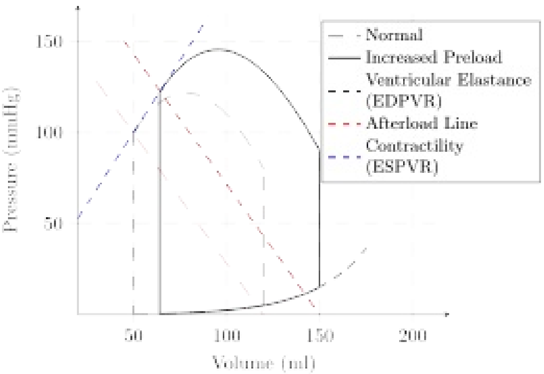
Basic Pressure-Volume Loops

Pressure-volume loops are covered in detail under pressure-volume relationships.

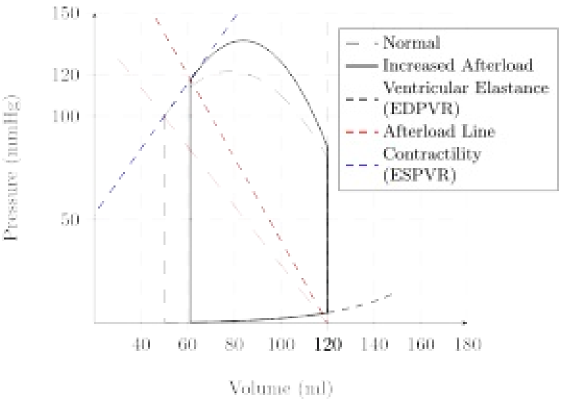
Left Ventricular P-V Loop:



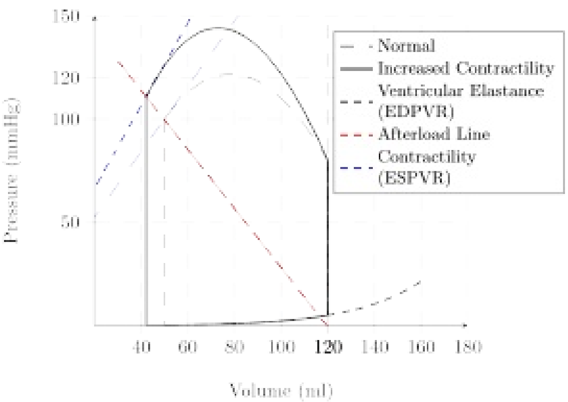
Left Ventricular P-V Loop - Increased Preload:



Left Ventricular P-V Loop - Increased Afterload:



Left Ventricular P-V Loop - Increased Contractility:



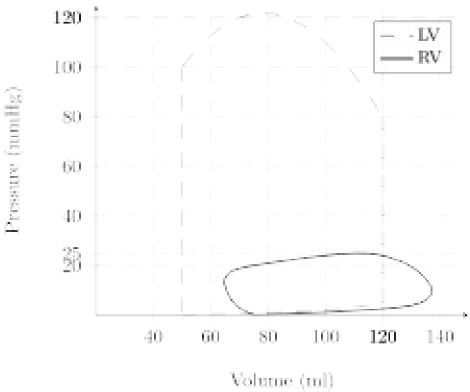
Advanced-Pressure Volume Loops

When drawing changes to more left-field pressure-volume loops which you may not have seen before approach them in the following way:

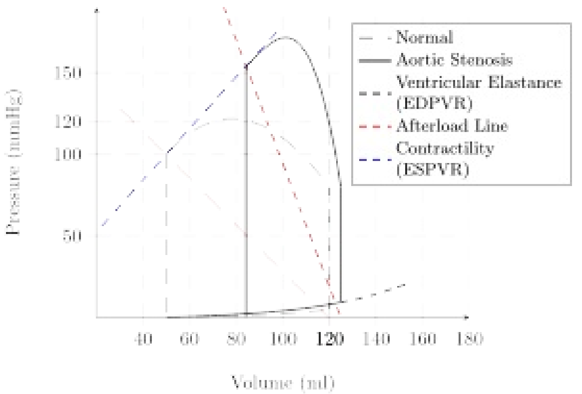
- How is preload changed?
- How is afterload changed?
- How is contractility changed?
- How are isovolumetric contraction and isovolumetric relaxation changed?

Advanced pressure-volume loops are covered in detail under pressure-volume relationships.

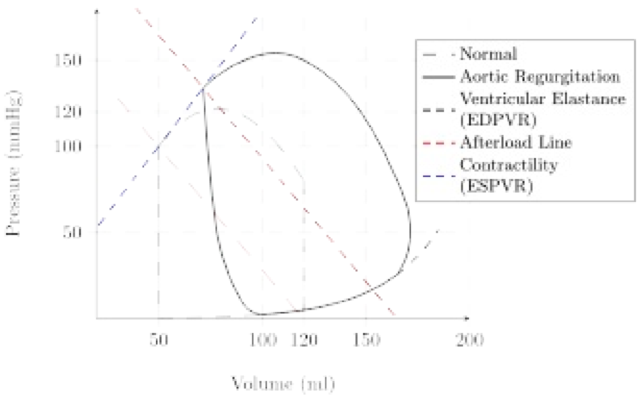
Right Ventricular P-V Loop:



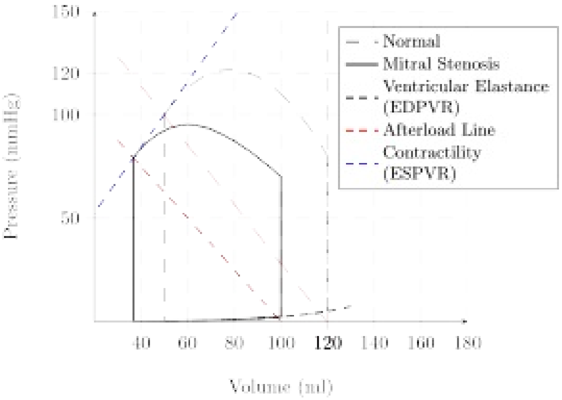
Left Ventricular P-V Loop - Aortic Stenosis:



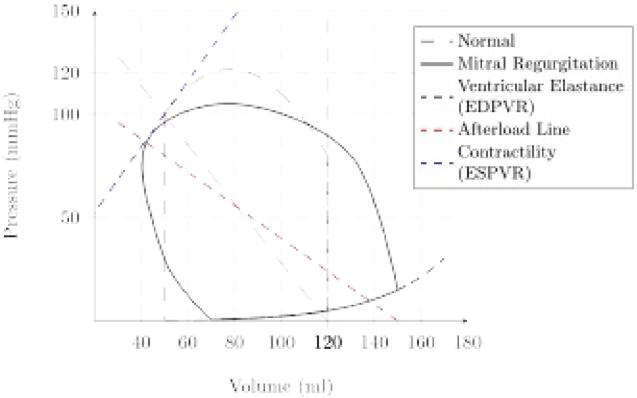
Left Ventricular P-V Loop - Aortic Regurgitation:



Left Ventricular P-V Loop - Mitral Stenosis:

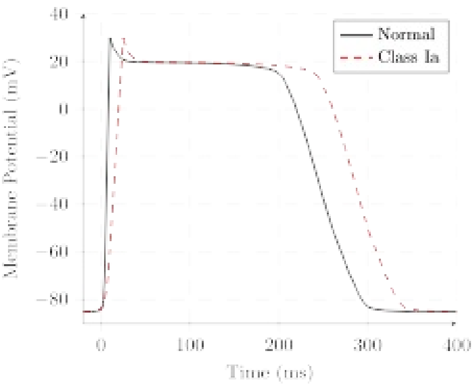


Left Ventricular P-V Loop - Mitral Regurgitation:



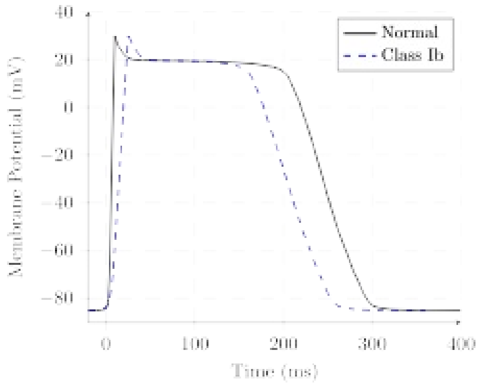
Antiarrhythmics

Ventricular Action Potential - Class Ia:



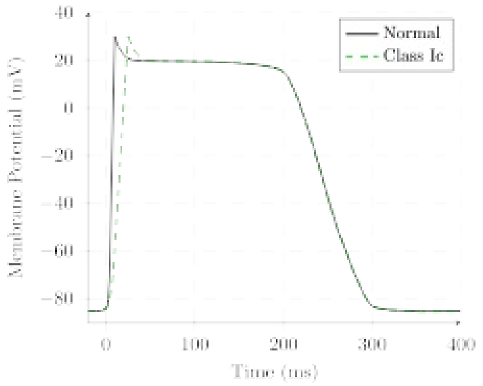
- Prolong the rate of rise of phase 0
- Lengthen the myocardial action potential

Ventricular Action Potential - Class Ib:



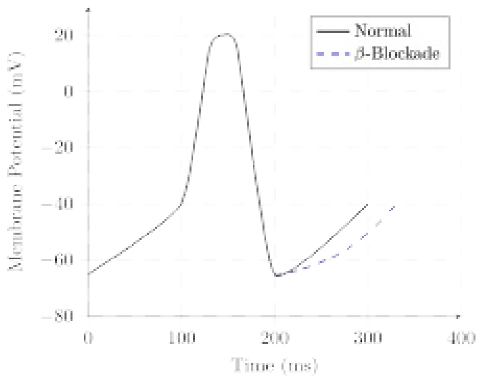
- Prolong the rate of rise of phase 0
- Shorten the myocardial action potential

Ventricular Action Potential - Class Ic:



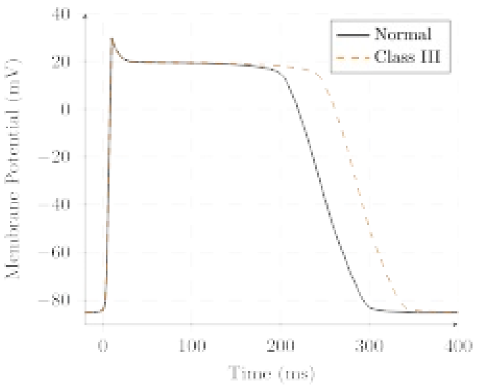
- Prolong the rate of rise of phase 0
- Do not alter the length of the myocardial action potential

Pacemaker Potential - Class II (Beta-Blockade):



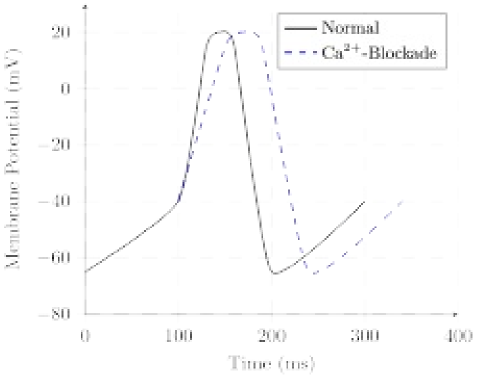
- Sympatholytic effect reduces the magnitude of the funny current

Ventricular Action Potential - Class III:



- Prolong duration of phase 3 of the myocardial action potential
  This prolongs the refractory period and reduces the chance of a re-entry circuit occurring, and therefore reduces tachyarrhythmias but may increase the risk of *torsade de pointes* due to an increased risk of after depolarisations.

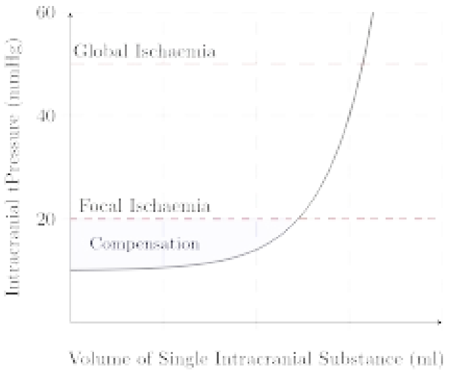
Pacemaker Potential - Class IV (Calcium Channel Blockade):



- In the pacemaker cell, reduce the magnitude of T-type and L-type calcium currents, reducing the rate of rise of phase 0 of the pacemaker action potential

CNS

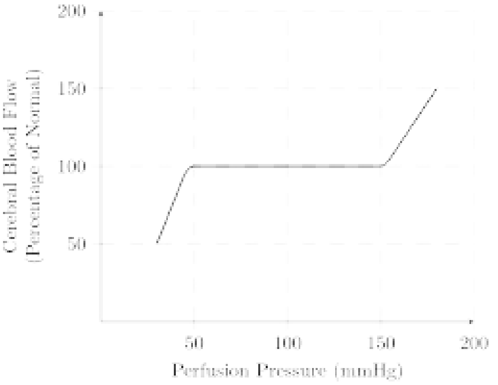
Monroe-Kellie Doctrine:



- Graphs the intracranial pressure versus the volume of a component (blood, brain, or CSF) in the cranial vault
  Note that overall volume is *not* correct, as this is unchanged - if overall volume increased the pressure would reduce (e.g. such as a decompressive craniectomy).
- Note the initial period of compensation, which occurs due to displacement of CSF to the spinal subarachnoid, decreased cerebral blood volume, and a decrease in CSF volume.
- Once compensatory responses are exhausted ICP will increase rapidly due to the poor elastance of the cranial vault

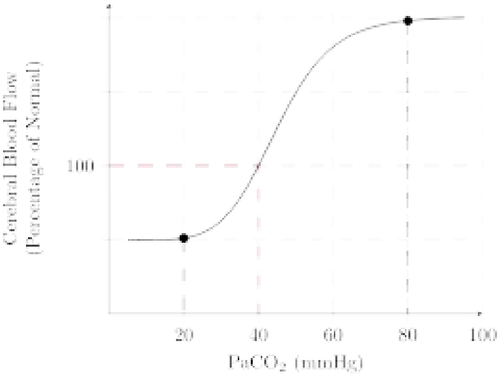
- Focal ischaemia occurs when ICP exceeds 20mmHg
- Global cerebral ischaemia occurs when ICP exceeds 50mmhg

Cerebral Blood Flow and Cerebral Perfusion Pressure:



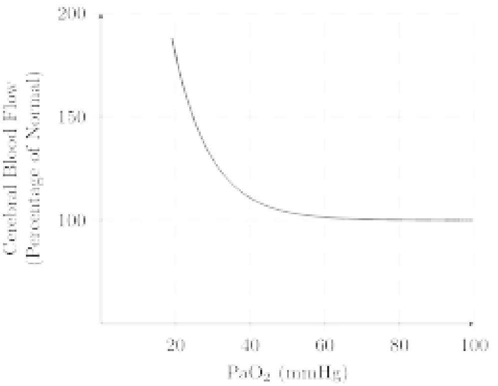
- Cerebral blood flow is autoregulated for a CPP of 50-150mmHg
  (Note that this classic relationship is probably incorrect, and that CBF is probably only autoregulated across a narrow range of blood pressures).

Cerebral Blood Flow and $PaCO_2$:



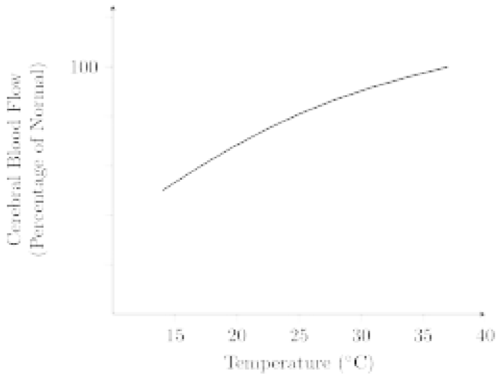
- CBF increases by ~3% for every 1mmHg increase in CO_2
- Below a $PaCO_2$ of 20mmHg, CBF cannot decrease further as the reduced flow results in tissue hypoxia, and metabolic autoregulatory responses
- Above a $PaCO_2$ of 80mmHg, CBF cannot increase further as vessels are maximally dilated

Cerebral Blood Flow and PaO_2:



- Above a PaO_2 of 60mmHg, CBF is essentially independent of PaO_2
- Below a PaO_2 of 60mmHg, CBF increases rapidly

Cerebral Blood Flow and Temperature:

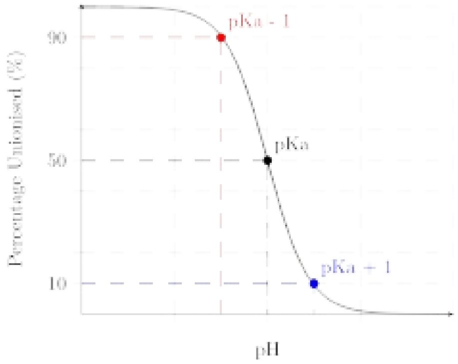


- Cerebral metabolic rate falls by ~6% per °C decrease in temperature
- This results in a concomitant reduction in CBF

  This is an *almost* linear response.

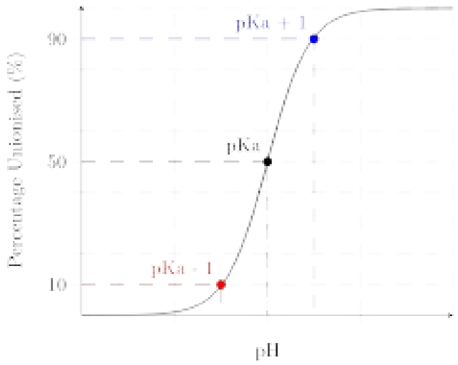
Renal & Acid-Base

Ionised potential vs pH - Acids:



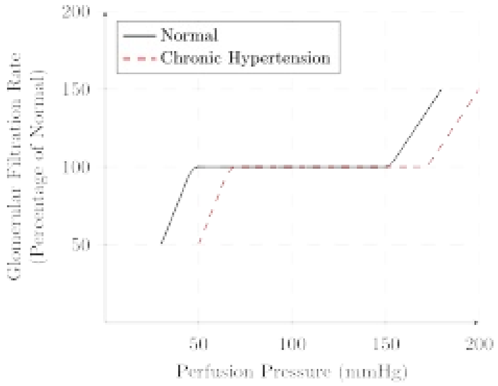
- **A**cids are ionised **a**bove their pKa

Ionised potential vs pH - Bases:



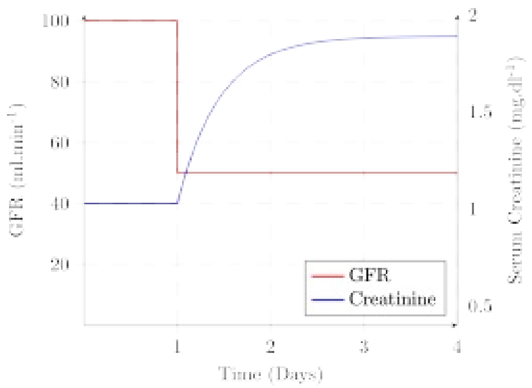
- **B**ases are ionised **b**elow their pKa

Glomerular Filtration and Mean Arterial Pressure:



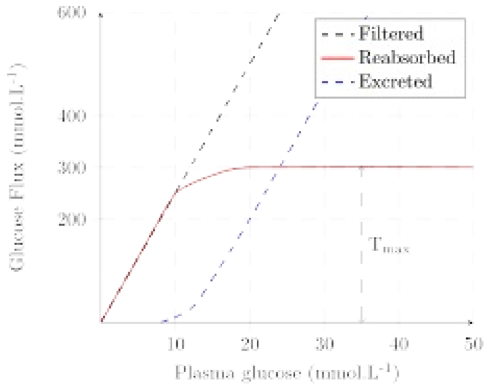
- GFR is autoregulated for a MAP between 60 and 160mmHg

Glomerular Filtration Rate and Serum Creatinine:



- At steady-state, GFR and serum creatinine are inversely proportional
- Following a step-change in GFR, it will take ~48 hours before steady-state is achieved again
  During this period, estimates of GFR using serum creatinine will be less accurate.

Glucose Flux:

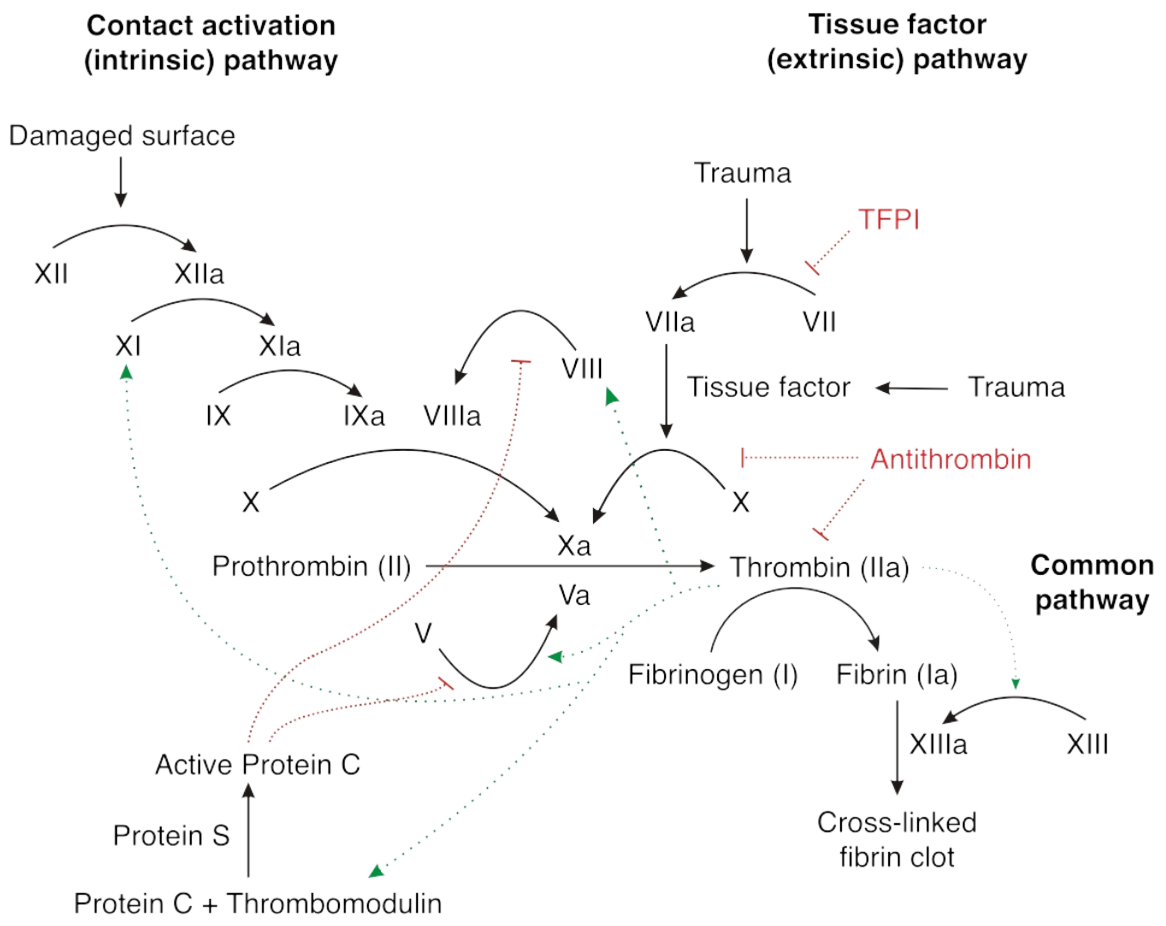


- As glucose is freely filtered at the glomerulus, filtered plasma glucose will be directly proportional to serum glucose
  This relationship is given by the dotted black line.
- Under normal circumstances, all filtered glucose will be reabsorbed
  This relationship is given by the overlap of the red and dotted black lines.
- When glucose filtration exceeds glucose reabsorption, glucose will begin to be excreted in urine.
  This is given by the dotted blue line.
  - The serum concentration of a substance at which this occurs is known as the transport maximum, or $\mathbf{T_{max}}$
    In reality, some glucose will be filtered before T_{max} is reached. This is due to the different affinity of S-GLUT channels, and is the cause of the gentle curves seen on the plots of reabsorption and excretion.
    - The serum concentration at which glucose starts to appear in urine is known as the threshold concentration

- The difference between threshold concentration and T_{max} is known as **splay**

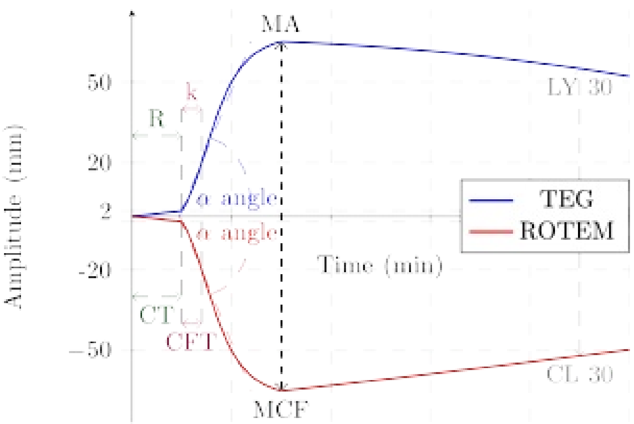
Haematology

Coagulation Cascade:



- The coagulation cascade is covered in detail under clotting

Thromboelastography:

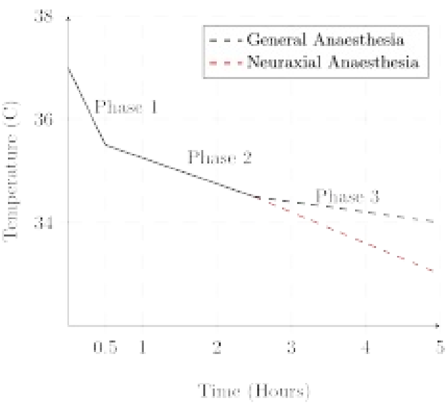


- TEG/ROTEM can be used to guide coagulopathy treatment as:
  - Prolonged R time
    Indicates decreased clotting factor concentration; **give FFP**.

- Decreased α-angle/prolonged K time
  Decreased rapidity of fibrinogen cross-linking; **give fibrinogen**.
- Decreased MA (may be associated with prolonged K time)
  Decreased maximal clot strength; **give platelets** or **DDAVP**.
- Decreased CL 30/CL 60
  Fibrinolysis; **give antifibrinolytic**.

Other

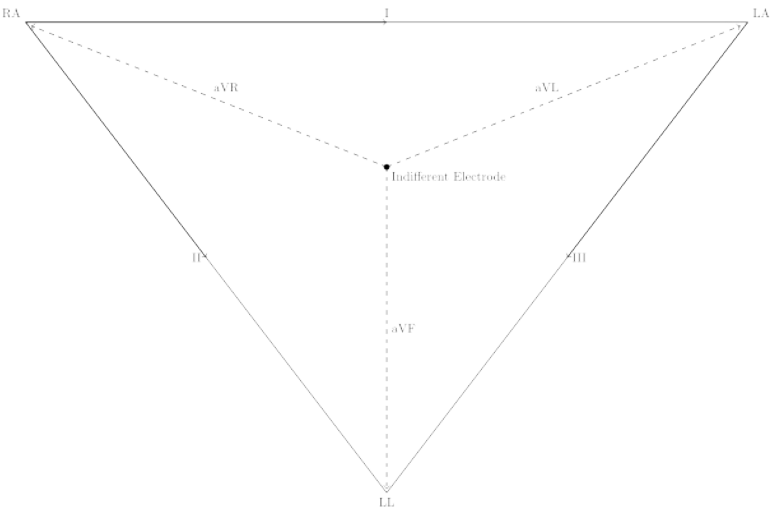
Heat Loss Under Anaesthesia:



- Heat loss under anaesthesia occurs in three phases:
  1. Rapid reduction: 1-1.5°C in 30 minutes
  2. Gradual reduction: 1°C over 2-3 hours
  3. Plateau: Further heat loss attenuated by metabolic heat reduction
     - Does not occur in neuraxial anaesthesia as vasoconstrictive responses are prevented by sympathectomy

Equipment & Measurement

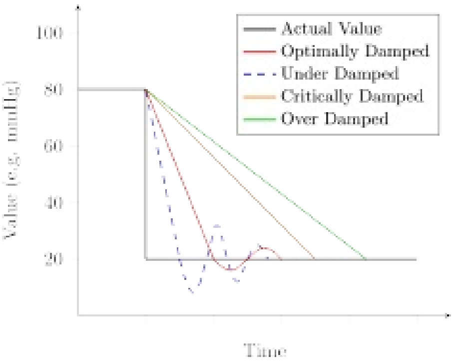
Einthoven's Triangle:



- Einthoven's triangle demonstrates the relationship between different limb leads and augmented leads on the ECG
- Understanding the triangle means one can identify misplaced ECG electrodes by the changes in ECG morphology
  - e.g. if the RA and LA electrodes are switched:
    - Lead I will invert its polarity

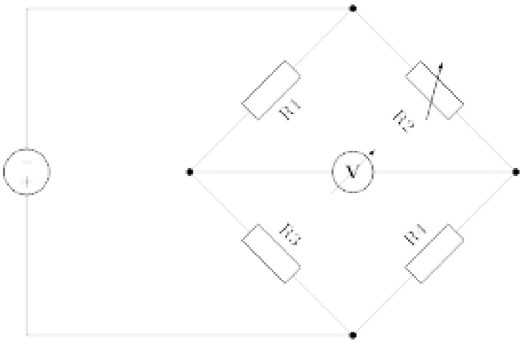
- Lead II and III will be switched
- Leads aVL and aVR will be switched
- Lead aVF will be unchanged

Damping Coefficients:



- Following a step-change:
  - An optimally-damped waveform will return to baseline with one overshoot and one undershoot
  - An under-damped waveform returns to baseline rapidly but overshoots and undershoots several times
  - A critically damped waveform returns to baseline as fast as possible without overshooting
  - An over-damped waveform returns to baseline slower than a critically damped waveform, and does not overshoot

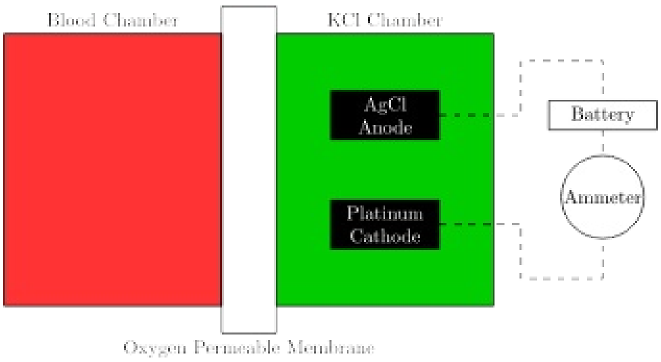
Wheatstone Bridge:



- Covered in detail under Wheatstone bridge

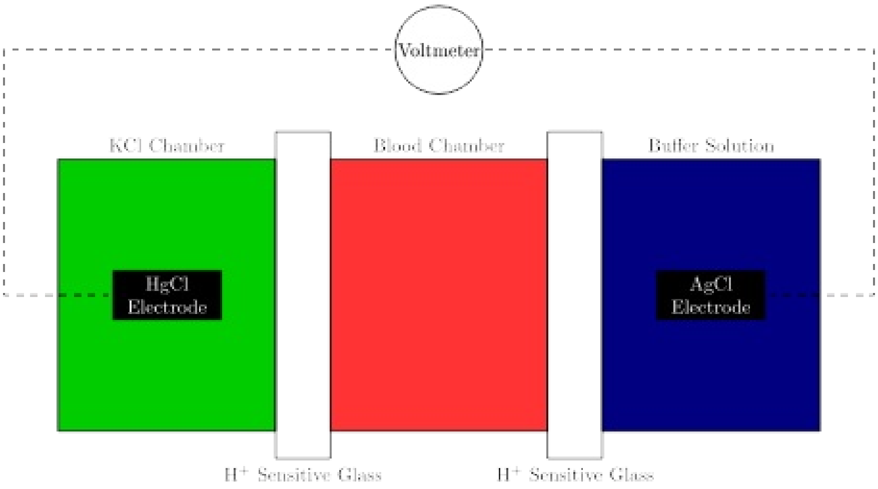
Gas Analysis

Clark Electrode:



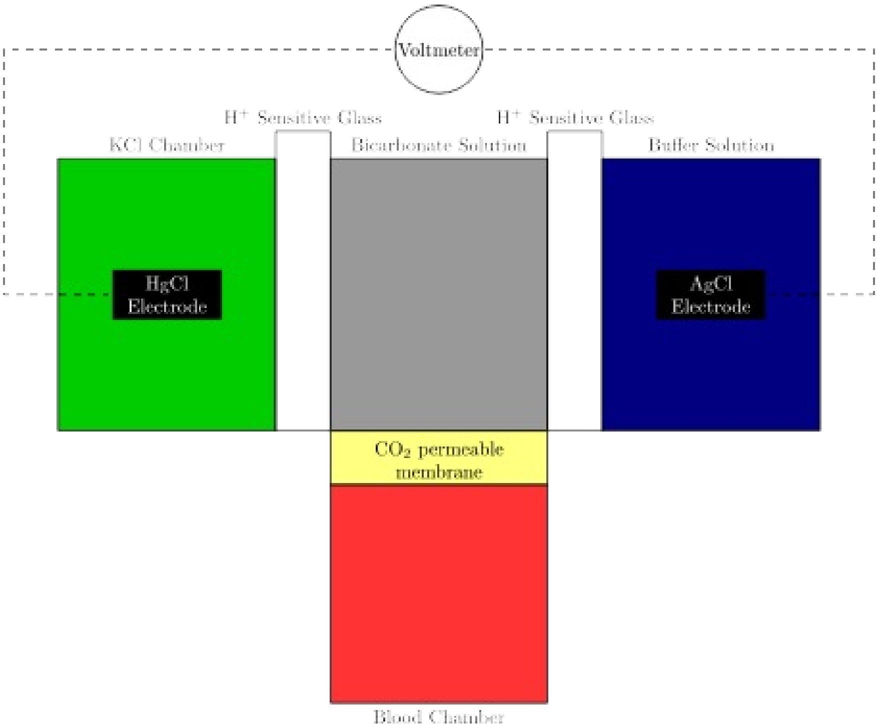
- Covered in detail under Oxygen Tension

pH Electrode:



- Covered in detail under pH Measurement

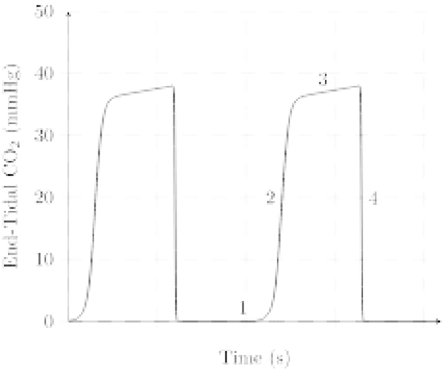
Severinghaus Electrode:



- Covered in detail under Carbon Dioxide Tension

Capnography

Capnograph:



- The capnograph waveform consists of four components:
  1. Baseline
     Inspiration and early dead-space expiration (containing no CO_2).
  2. Alveolar exhalation
  3. Alveolar plateau
     Highest point is defined as E_TCO_2.
  4. Inspiration
- Variations on the waveform are covered under E_TCO_2 Waveform Variations

References

1. Wigger's Diagram (with some modifications) from Wigger's Diagram. 21/3/2012. (Image). By DanielChangMD (revised original work of DestinyQx); Redrawn as SVG by xavax. CC BY 3.0 , via Wikimedia Commons.
2. Clotting Cascade 22/4/2007. (Image). By Joe D (Own work). CC BY 3.0 , via Wikimedia Commons.

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Laws and Equations

This appendix is a list of the key laws and equations common to many topics:

General Laws

- **Fick's Law of Diffusion**
  Diffusion of a substance across a membrane is given by:
  $\dot{V} = \frac{A \times D \times \Delta P}{T}$, where:
    - = Area of the sheet
    - = Diffusion constant, which is proportional to the **solubility** of the gas and inversely proportional to the square root of the molecular weight, i.e. $D \propto \frac{Sol}{\sqrt{MW}}$
    - = Thickness of the sheet
- **Hagan-Poiseuille Equation**
  Calculates the flow for a given pressure different of a particular fluid. May also be rearranged to calculate pressure or resistance.
    - Given by the equation:
      $Q = \frac{\pi P r^4}{8 \eta l}$, where:
        - Q is the flow
        - P is the driving pressure
        - η is the dynamic viscosity
        - L is the length of tubing
        - r is the radius
    - Has several limitations:
        - Only models laminar flow
        - Fluid must be incompressible
          Not technically valid for air, but provides a good approximation when used clinically.
        - Fluid must be Newtonian
        - Fluid must be in a cylindrical pipe of uniform cross-section
- **Reynolds Number**
  Reynolds Number is a dimensionless index used to predict the likelihood of turbulent flow. R < 2000 is likely to be laminar, R > 2000 is likely to be turbulent. Given by the equation:
    - , where:
        - v is the linear velocity of fluid in m/s
        - d is the fluid density in PaS
        - r is the radius in m
        - n is the viscosity in m^2/s

Cell Physiology

- **Nernst Equation**
  Calculates the electrochemical equilibrium for a given ion:
  $E\ (mV) = \frac{R.T}{z.F} ln \frac{[ion]_{outside}}{[ion]_{inside}}$, where:
  - is the equilibrium potential for the ion
  - is the gas constant (8.314 $J.deg^{-1}.mol^{-1}$)
  - is the temperature in Kelvin
  - is Faraday's Constant
  - is the ionic valency (e.g. +2 for Mg^{+2}, -1 for Cl^{-})
- **Goldman-Hodgkin-Katz Equation**
  Calculates the membrane potential for given values of intracellular and extracellular ionic concentrations:
  $E\ (mV) = \frac{R.T}{F} ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$, where:
  - is the permeability constant for the ion, x
    If the membrane is impermeable to x, then $P_x = 0$.
- **Henderson-Hasselbalch**
  Calculates the pH of a buffer solution:
  $pH = pK_a + log \frac{[A^-]}{[HA]}$, where:
  - is the pH of the solution
  - is the pKa of the buffer
  - is the concentration of base
  - is the concentration of acid

Respiratory Laws

- **Modified Bohr Equation**
  The ratio of dead space to tidal volume ventilation equations the arterial - mixed-expired CO2 difference, over the arterial CO2. $\frac{V_D}{V_T} = \frac{PaCO_2 - PE'CO_2}{PaCO_2}$
- **La Place's Law**
  The larger the vessel radius, the larger the wall tension required to withstand a given internal fluid pressure. For a thin-walled sphere, Wall Tension (T) is half the product of pressure and radius, i.e. $T = \frac{P.r}{2}$
- **Alveolar Gas Equation**
  The alveolar PO2 is equal to the PiO2 minus the alveolar CO2/the respiratory quotient, i.e.:
  $PA_{O_2} = Pi_{O_2} - \frac{PA_{CO_2}}{R}$

Gas Laws

- **Boyle's Law**
  $PV = K$, i.e. pressure and volume are inversely related at constant temperature and pressure.

- Boyles Law can be used to work out how many litres of gas are remaining in gas cylinder, e.g.:
    - A standard C cylinder is 1.2L in size
    - Normal cylinder pressure is ~137bar, and atmospheric pressure is ~1bar
      $$P_1 . V_1 = P_2 . V_2$$
      $$137. 1.2 = 164$$
    - Therefore, the cylinder contains ~164L of oxygen
    - This can be used to calculate the volume of gas remaining in the cylinder during use, using the volume of the cylinder (fixed) and the current pressure as measured at the regulator

- **Charle's Law**
  $V = KT$, i.e. volume and temperature are linearly related when pressure is constant.

- **Gay-Lussac's Law/The Third Gas Law** $P = k. T$, i.e. pressure and temperature are linearly related when volume is constant.

- **The Universal Gas Equation**
  $PV = nRT$, i.e. combination of Boyle's, Charle's law combining each variable and the universal gas constant, R (8.13).

- **Henry's Law**
  The number of molecules of dissolved gas is proportional to the partial pressure of the gas at the surface of the liquid

- **Graham's Law of Diffusion**
  Diffusion rates through orifices are inversely proportional to the square root of the molecular weight

- **Dalton's Law of Partial Pressures**
  In a mixture of gases, each gas exerts the pressure that it would exert if it occupied the volume alone.

Cardiovascular Equations

- **Fick's Principle**
  Flow of blood through an organ equals the uptake of a tracer substance by the organ divided by the concentration difference of the substance across it, i.e.:
  $$\dot{Q} = \frac{\dot{V}_{O_2}}{Ca_{O_2} - C\bar{v}_{O_2}}$$

- **Starling's Law of Fluid Exchange**
  Flow of fluid across the capillaries is proportional to the hydrostatic pressure difference and the oncotic pressure difference (times the reflection coefficient), all times by the filtraiton coefficient, i.e.:
  $$Net\ flow\ out = K[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

- **Venous Admixture**
  Calculates the shunt fraction by identifying how much mixed venous blood must be added to ideal pulmonary capillary blood to produce the identified arterial oxygen content. $\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{Cc'_{O_2} - Ca'_{O_2}}{Cc'_{O_2} - C\bar{v}'_{O_2}}$

Equipment

- **Doppler equation**
  Calculates the velocity of an object based on the change in observed frequency when a wave is reflected off (or emitted from)

the object:
$V = \frac{\Delta F s}{2 F_0 cos\theta}$ where:

- = Velocity of object
- = Frequency shift
- = Speed of sound (in blood)
- = Frequency of the emitted sound
- = Angle between the sound wave and the object

References

1. Davis & Kenny. Basic Physics and Measurement in Anaesthesia, 5th Edition.
2. Gorman. RAH Diving and Hyperbaric Medicine. Chapter 3: The physics of diving.

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Structures for SAQs

Structured answers are vital:

- Structure aids both learning and recall of information
- A structured format is easy to follow less likely to irritate the drunk/tired/hungover mind of the examiner
- You may get marks for incomplete answers if your structure demonstrates you have an understanding of the topic, even if the details are not filled in

Some questions lend themselves more easily to a particular structure than others, but all questions can be made to fit even a basic structure.

Regulation of Physiological Responses

- Sensor
- Integration
- Effector

Change in Level of a Substance

- Intake
- Distribution
- Elimination

Compare and Contrast (Drugs)

- **C**lass
- **P**harmaceutics
  - Uses
  - Chemical
  - Presentation
  - Heat/light stability
  - Routes of administration
  - Doses
- **P**harmacokinetics
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**limination
- **P**harmacodynamics
  - Main Action
  - Mode of Action
  - Effects (See the physiological approach)
  - Side Effects
  - Toxic effects
    - Allergic
    - Dose-dependent
    - Idiopathic

            - Drug interactions

Describe Why Two Drugs are Used in Combination

- Definition
  Brief, of each drug.
    - Consider the components of anaesthesia that each provides
- Pharmacokinetics
    - Interactions
    - Relative onset
    - Metabolism
        - No effect/Induces/Inhibits
    - Elimination
- Pharmacodynamics
    - Isobologram
      Synergistic/additive/antagonistic.
    - Then list the effects of each drug, and how they are modified by the other
        - e.g. if drugs are synergistic, then decreased doses will be required
            - Increases beneficial effects
            - Decreases adverse effects

Describe the Physiology of...

- Respiratory
    - Bronchodilation/constriction
    - Vasodilation/constriction
    - V_T
    - RR
    - Secretion
    - Laryngeal reflexes
- CVS
    - Preload
    - Contractility/Pump effects
        - Inotropy
        - Chronotropy/rhythm
        - Dromotropy
        - Lusitropy
        - Bathmotropy
        - Nodal effects
        - Coronary Blood Flow
    - Afterload/Pipe effects
        - SBP
        - DBP
        - MAP
        - SVR
        - PVR
    - Intraarterial injection
- CNS
    - Sedation

  - Analgesia
  - Pro/anticonvulsant
  - Amnestic
  - Cerebral Metabolic Rate
  - Cerebral Blood Flow
  - ICP
  - IOP
- Musculocutaneous
  - Blood Flow
  - NMJ
- Endocrine
  - Gynaecomastia
  - Hair
  - Bone
- Renal and GU
  - Renal Blood Flow
  - Nephrotoxicity
  - Bladder tone
  - Uterine tone
- GIT and Hepatic
  - Hepatotoxicity/LFTs
  - Secretions
  - Gastric emptying
  - N/V/D/C
- Haematological
  - G6PD
  - Porphyrias
  - Bone marrow effects
- Immunological
  - Anaphylaxis
  - Histaminergic
  - Neutrophil function
- Metabolic

Anatomical Structure

- Anatomy of the structure
- Relationships
- Relevant surface anatomy
- Layers of dissection

Physics and Measurement

- Definition
- Uses
- Physical principles
- Components
- Calibration
- Advantages/Disadvantages

References

- Dr. Podcast
- Wisdom from drunk, tired, and/or hungover examiners.

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