RESPIRATORY

RESPIRATORY ANATOMY AND PHYSIOLOGY

Anatomy of respiratory system

Discuss the structure of the chest wall and diaphragm and the implications for respiratory mechanics

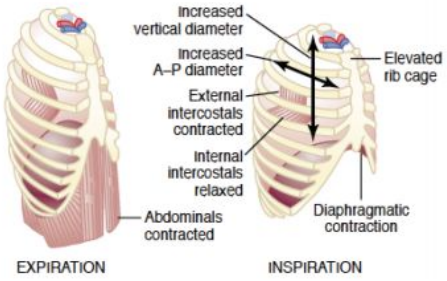
Structure of chest wall + diaphragm

Chest wall

- comprises:
  - Superficial fascia → subcutaneous tissue → deep fascia
  - 12 pairs of ribs + costal cartilages/ 12 vertebrae + intervertebral discs
  - sternum
  - Intercostal muscles
    - External: slope anteroinferiorly; extend from tubercle of rib post → to costochondral junction anteriorly
    - Internal + innermost: slope inferoposteriorly
  - Other muscles: pec major, serratus anterior, serratus posterior superior and inferior, scalenes
  - Superior aperture: T1body, 1st rib + costal cartilage + sup border manubrium
  - Inf aperture: T12 body, 11 + 12th ribs + costal cartilages 7-10, xifisternal joint anteriorly

Diaphragm

- dome shaped muscular structure separating thoracic + abdominal cavities
- consists of: central tendon + peripheral muscles (sternal, costal, lumbar attachments)
- type 1 slow fibres
- 3 perforations:
  - T8 for vena cava
  - T10 for oesophagus
  - T12 for aorta, thoracic duct, azygos vein
- Motor innervation: phrenic nerves C3-5
- Role: inspiratory work + ↑intaabdo pressure (cough, sneeze, vomit) + maintaining LES tone



Relation to respiratory mechanics

Inspiration

- Diaphragm + external intercostal muscles contract
  - contraction of diaphragm → flattens dome → pushes intraabdo contents down → ↑th
  - External intercostals pull ribs anterosuperiorly → ↑cross sectional area of chest → ↑t
- Accessory muscles: sternocleidomastoid + scalenes → elevate sternum + 1st 2 ribs respectively (a
- NB paralysis of external intercostals doesn't have dramatic effect on resp function provided diap

Expiration

- Passive during quiet breathing: diaphragmatic relaxation + elastic recoil of the lungs returns to FRC
- Active during high minute ventilation (>40L/min), expiratory resistance, expulsive efforts
  - Abdominal wall muscles: (rectus abdominus, internal oblique, external oblique, transversus abdominis) contract → ↑intraabsominal pressure + forcing diaphragm up
  - Internal + innermost intercostals contract → pulling ribs downwards + inwards → ↓ thoracic volume

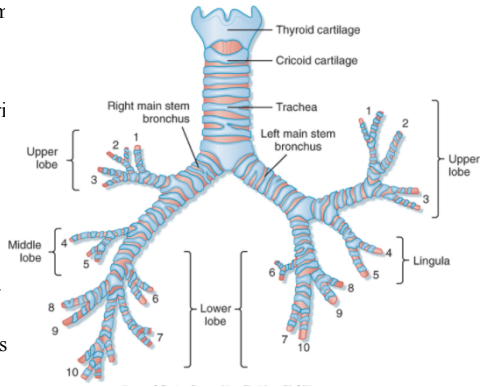
Paralysis of abdominal wall muscles (e.g. spinal injury) has significant affect on resp mechanics:

- Initial phase: spinal shock → flaccid paralysis of abdo wall:
  - intraabdo pressure low, diaphragm moves inferiorly → ↑FRC but..
  - limits tidal vol as contraction of diaphragm only ↑s thoracic vol by small fraction; nursing in supine → abdo contents push diaphragm superiorly
  - Overall: ↓FRC but ↑proportional expansion with respiration → ↑V_T
- Once spastic paralysis occurs the abdo wall is rigid; pt can be sat up

Outline the anatomy of the lower airways

Lower airways

- Trachea to alveolus → airways divide 23 times
  - conduction zone: 1st 16 divisions: trachea → main bronchi → lobar bronchi → segm
  - respiratory zone: last 7 divisions: bronchioles → alveolar ducts → alveoli
- **Conducting zone:**
  - *Trachea*
    - fibrocartilaginous tube supported by incomplete cartilaginous rings anteri
    - from inf end of larynx into thorax
    - bifurcates at level of transverse thoracic plane
    - mean diameter 2cm; length 10cm
    - external pressure 40cmH2O → occlusion of extrathoracic trachea
  - *Bronchi*
    - 1st 4 divisions of trachea
    - R main bronchus: wider; deviates less from axis of trachea (L has tighter
    - 2 main bronchi divide into 5 lobar bronchi → 18 segmental bronchi
    - segmental bronchi travel with branches of pulmonary artery + lymphatics
  - *Bronchioles*
    - embedded in lung parenchyma
    - no cartilage – held open by lung volume
    - resistance to flow negligible due to large cross sectional area
  - *Terminal bronchioles*
  - Flow in conducting zone = turbulent
  - No gas exchange in conducting zone = anatomical dead space ~150ml in adults
  - Blood supply = bronchial circulation
  - Mucus secreted by goblet cells
  - Cilia move staircase of mucus to epiglottis



- **Respiratory zone**
  - Blood supply via pulmonary circulation
  - *Respiratory bronchioles*
  - *Alveolar ducts*
  - *Alveolar sacs*
    - Total surface area: 50-100m2
    - Thin walls: 0.2-0.3um
    - Dense mesh of capillaries 7-10um thick
    - Alveolar-capillary barrier: type 1 pneumocytes + extracellular matrix + pulmonary capillary endothelium
    - Alveoli = composed of 3 types of cells:
      - Type 1 pneumocytes: thin walled optimised for gas exchange; 90% alveolar surface area
      - Type 2 pneumocytes: secrete surfactant → ↓surface tension
      - Alveolar macrophages

Function of lower airways

1. Exchange of O2 + CO2
2. Blood/ gas barrier to diffusion: 50-80m2
3. Other functions:
   a. Clotting mechanism: large number of mast cells containing heparin in interstitium
   b. Defence: lung secretes IgA in bronchial mucus; pulmonary macrophages
   c. Synthetic function: production of surfactant; protein synthesis (collagen and elastin)
   d. Heat regulation / exchange
   e. Pharmacokinetics: route of administration e.g. volatiles; effect site e.g. bronchodilators; route of elimination e.g. volatiles

Control of respiration

Describe the neural and chemical control of ventilation via central and peripheral chemoreceptors and indicate how this is altered by anaesthesia and abnormal clinical states

Control of ventilation

1. Sensors
2. Control centre
3. Effectors

1. Inputs/ sensors

- *i) Central chemoreceptors:*
  - in ventral medulla
  - Stimulus: ↓CSF pH
    - H^+ + HCO3 are ionised → cannot cross BBB
    - CO2 = lipid soluble + freely diffuses into CSF → CO2 + H2O (catalysed by CA) → H2CO3 → H^+ + HCO3
    - H+ diffuses into chemoreceptor tissue → stimulates chemoreceptors to activate resp centre
    - pH → provides indirect measure of PaCO2
  - Special properties:
    - ↑sensitivity: due to ↓buffering (↓protein); CSF pH ~7.32
    - Respond to resp acidosis: PaCO2 regulates ventilation by its effect on CSF pH
    - Cerebral vasodilation: accompanies hypercapnoea → ↑central chemoreceptor mechanism
    - Not stimulated by hypoxia
  - NB CO2 retention: prolonged resp acidosis (e.g. COPD) stimulates active secretion of HCO3 into the CSF
- *ii) Peripheral chemoreceptors*
  - in carotid bodies (CN IX) + aortic arch (CN X)
  - Stimulus:
    - ↓PaO2:
    - ↑PaCO2: rapid (1-3s), but weaker (~20% of response) cf central chemoreceptors
    - acidaemia (↓pH): carotid bodies only
    - hypotension: ↓perfusion
- *iii) Mechanoreceptors/ stretch receptors*
  - stimulate apneustic centre (via VA) to ↓inspiratory volumes = Hering-Breuer reflex
- *Other stimulants*
  - Juxtacapillary Rs: non-myelinated C fibres in alveolar walls; tissue damage/ oedema/ emboli → VA → ↓HR, apnoea, rapid shallow breathing, bronchoconstriction
  - Irritant Rs: nociceptive, chemoreceptive, noxious gases → stimulates respiration
  - Pain Rs
  - Thalamus: ↑core temp
  - Limbic system: emotional responses
  - Cerebral cortex: conscious control
  - Muscle spindles: ventilatory response to exercise

2. Respiratory centre

- located in the medulla + pons
- 4 groups of neurones
- ***Medullary centre:***
  - Respiratory pattern generation + coordination of voluntary + involuntary demands
  - Located in reticular formation below floor of 4th ventricle:
  - ***1. Dorsal resp group***
    - inspiration
    - Inspiratory UMNs project to CL anterior horn cells
  - ***2. Ventral resp group (VRG)***
    - Inspiratory + expiratory neurons (4 nuclei)
    - Controls intercostal muscles: initiate forced expiration + ↑force inspiration
    - Botzinger complex: resp pacemaker
- ***Pontine centres***
  - **2. Apneustic centre**: lower pons; modifies DRG to prevent overexpansion
  - **3. Pneumotaxic centre**/ pontine respiratory group: upper pons; modifies DRG to ↓depth of inspiration

3. Effectors

- Diaphragm, intercostals, abdominal muscles, accessory muscles

Ventilatory response to ↓PaO2

- PaO2 <60mmHg → peripheral chemoreceptors rapidly stimulate respiratory centre → significantly ↑MV
- resp response further augmented in presence of hypercapnoea
- severe, prolonged hypoxaemia → depressive effect on resp centre → apnoea

Ventilatory response to ↑PaCO2

- ↑PaCO2: activates both peripheral + central chemoreceptors
- ↓arterial pH: activates carotid bodies
- ↑CSF PCO2: → ↓central chemoreceptor ECF pH → activates central chemoreceptors

What effects do anaesthetic drugs have on the resp system:

Anaesthesia and the lung

- Many of the drugs used have effects on:
  - medullary resp centre
  - peripheral chemoreceptors
  - airways
- Effects classified by drug class:
  - Volatile anaesthetic agents
    - Dose dependent effects on resp system
      - ↑RR; ↓VT
      - blunted vent response to hypercapnoea: enflurane > des > iso > sevo > halo
        - exception: N2O (no effect) and ether (may ↑MV)
  - IV anaesthetic agents
    - Initial resp stimulation: following induction → brief period of resp stimulation → ↑RR + ↑VT
    - Then resp depression: ↓VT, apnoea
    - Depression of protective airway reflexes
    - Specific to certain drugs
      - Propofol: abolish peripheral chemoreceptor response to hypoxaemia
      - Ketamine: preserves airway reflexes + spont vent
  - Opioids
    - Resp centre depression → ↓RR, blunting of vent respons to ↑PaCO2
    - Antitussive action
    - Histamine release: bronchospasm
    - Chest wall rigidity
  - Benzos: Resp centre depression → ↓RR, blunting vent response to ↑PaCO2
  - NMBD
    - Resp muscle paralysis
    - Specific to certain drugs:
      - Atracurium: histamine release → bronchospasm
      - Sux: sux apnoea (in pts with ↓[plasma cholinesterase]
  - NSAIDs: Bronchospasm
  - LA: High spinal: weakness of intercostal muscles

Effects of GA on the lungs

- airway devices:
  - Laryngospasm, bronchospasm, inadequate humidification
  - Loss of physiological PEEP
  - ↑WOB: due to ↑resistance to gas flow (depends on internal radius as determined by Poiseuille)
  - ↑dead space
- lung volumes
  - FRC ↓ due to: supine position + relaxation of chest wall muscles
  - Anaesthesia → FRC < CC → hypoxaemia
- Atelectasis
  - Absorption atelectasis
  - Compression atelectasis: ↓diaphragmatic tone + compression from abdominal contents
- V/Q relationships
  - Low lung vols → closure of small airways (CC encroaching on FRC)
  - ↑tendency for atelectasis
  - PPV → alters intrathoracic pressure, ↓RV preload, changing pulmonary capillary dynamics
  - Impairment of HPV by volatile anaesthetic agents

GA and post operative respiratory function

- Common complications: atelectasis, bronchospasm, pneumonia, pulmonary oedema, pneumothorax, ventilatory failure
- Causes
  - Upper abdo / thoracic:
    - highest risk of post op pulmonary complications:
    - ↓FRC, basal atelectasis, V/Q mismatch → hypoxaemia, ↓lung vol → ↑WOB
  - Inadequate analgesia
    - Inadequate cough / limited inspiration → exacerbates atelectasis + predisposes to secretion retention + pneumonia

Describe the physiological factors that ↑RR: PAST QUESTION

- RR = period to time taken to complete inspiration + expiration; number of breaths per minute; normal RR = 12-16bpm
- RR is controlled by the resp centre within the medulla
- Control system can be split into: sensors; modulator; effectors

3 main factors that govern RR

1. **Neural control**
   - Voluntary: cerebral cortex → resp MNs → resp muscles → ↑RR
   - Involntary control: stress, fear, pain → autonomic inputs → pontine + medullary resp centres → resp MNs → resp muscles → ↑RR
2. **Chemical control**
   - Stimuli: ↑PaCO2, ↓PaO2, ↓pH (acidosis)
   - ↑PaCO2
     - Central chemoreceptors: ventral medulla: ↑PaCO2 → CO2 diffses across BBB → forms H2CO3 → dissociates into H+ → ↓pH sensed by central chemoreceptors → sigal to medullary resp centre → ↑RR
     - Peripheral chemoreceptors (carotid bodies, aortic arch): ↑PaCO2 → VA afferent to medullary resp centre → ↑RR
   - ↓PaO2
     - sensors: carotid bodies + aortic arch
     - weak activation when PaO2 <100mmHg
     - strong activation when PaO2 <60mmHg → overrides PaCO2 signal → ↑↑RR
   - ↓pH
     - sensor: carotid body: ↓pH → ↑carotid body firing → VA afferent → stimulate emdulalry resp centre → ↑RR
3. **Mechanical control**
   - Muscle/ tendon stretch Rs
   - Pulmonary Juxtacapillary Rs: pulmonary stretch / engorgement of pulmonary capillaries → VA C afferents → ↑RR
   - Irritant Rs (nose, larynx, trachea, bronchi) → VA afferent → ↑RR + bronchoconstriction
   - Arterial baroreceptors: ↓MAP → high pressure baroreceptors → direct stimulation of resp centres → ↑RR

Mechanics of breathing

Describe the properties of surfactant and relate these to its role in influencing respiratory mechanics

Surface tension

- surface tension = tendency of a fluid to ↓its surface area
  - related to attraction between particles in fluid, relative to particles outside the fluid
  - described by LaPlace's Law: P = 2T/ r → where P is pressure; T is surface tension; r is radius
- High surface tension causes 3 problems:
  - 1. ↓radius → ↓compliance → ↑work to expand alveoli
  - 2. Smaller alveoli empty into bigger alveoli → ↓ radius → ↑transmural pressure to remain inflated
  - 3. Transudation of interstitial fluid: due to inward force of surface tension → pulmonary oedema

Surfactant

- produced by type II pneumocytes in alveolar wall
- composed of:
  - 85% phospholipid (DPPC is most important)
  - 5% neutral lipid
  - 10% protein
- 3 main roles
  1. ↓surface alveolar tension
  2. stabilization of small alveoli:
  3. prevention of fluid transudation
- mechanism:
  - Surfactant = amphipathic
  - hydrophobic + hydrophilic end → molecules align along air-liquid interface → disrupting attractive bonds between water molecules → ↓surface tension
- Surface tension varies with the reciprocal of the radius of the alveolus
  - Greater effect during expiration (low surface area): ↓alveolar radius → surfactant molecules closer together → ↑intermolecular repulsive forces → further ↓surface tension
  - As alveoli expand → repulsion between DPPC molecules ↓ as they spread out

What happens if there is no surfactant?

- Lungs would be non-compliant + atelectasis + pulmonary oedema because the alveoli would become filled with transudate
- These are pathological features of infant respiratory distress syndrome

Note on Laplace law:

- An alveolus with a small radius will have a greater pressure inside it than a larger alveolus → if these 2 alveoli are connected together the smaller alveolus will collapse into the larger alveolus. Also the inward force created by this surface tension will tend to suck fluid into the alveoli (transudation)

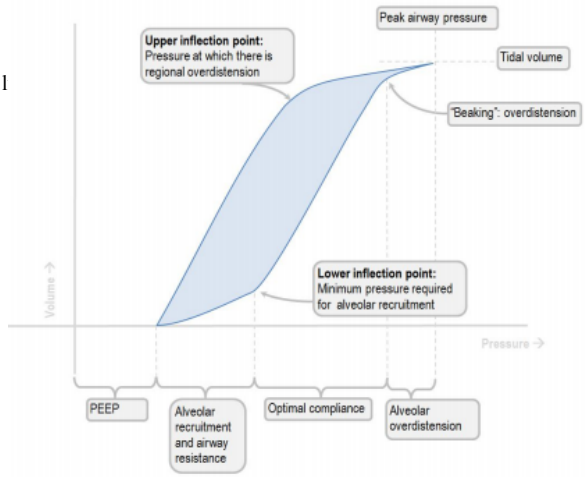
Define compliance (static, dynamic and specific) and relate this to the elastic properties of the lung

Compliance:

- **Compliance = Δvolume for a given Δpressure**
- Inverse of elastance: force at which lung recoils for a given distension
- respiratory compliance = function of *lung* and *chest wall* compliance: **$1/C_T = 1/C_L + 1/C_w$**

Respiratory system compliance

1. **Lung compliance:**
   - Δvolume / Δtranspulmonary pressure
     - Transpulmonary pressure = Palv – Pintrapl
       - Created by resp muscles → pressure gradient across l
       - Palveolar = plateau pressure
       - Pintrapl = ~oesophageal pressure
   - Lung compliance determined by:
     - Elastic recoil of lung connective tissue
     - Surface tension within alveoli (importance of surfactant)
   - Plotted on pressure-vol curve → forms hysteresis
   - In health: 200ml/cmH2O
2. **Chest wall compliance**
   - Δvolume / Δtransthoracic pressure (= intrapleural – atmospheric pressure)
   - Chest wall = elastic → pulls against pleural space ~5cmH2O.
   - In health: 200ml/cmH2O
3. **Total compliance**
   - Calculated from alveolar-ambient gradient; ~100ml/cmH2O



Types of compliance

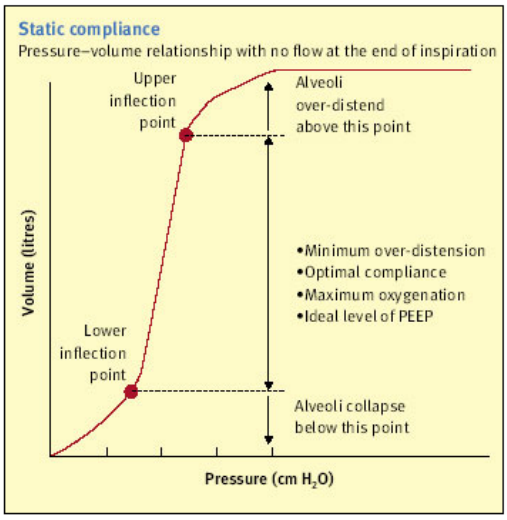
1. **Static compliance**
   - Δvolume per Δpressure when there is **no** airflow
   - Measurement = slope of the lung pressure/ vol curve
     - Pt inspires at increments → Pintrapl ~ = oesophageal balloon catheter
     - Results plotted on pressure-volume graph
   - ↓intrapleural pressure: ↓lung vol → pressure-vol curve flat = ↓lung compliance
   - Normal intrapleural pressure (-5 to -10cmH2O): ↑compliance at FRC
   - ↑intrapleural pressure:. ↑alveoli inflation + near elastic limit → ↓compliance
2. **Dynamic compliance**
   - continuous pressure + vol measurements throughout resp cycle
   - Affected by: airways resistance; RR; inspiratory time; autoPEEP
   - NB dynamic compliance is always lower than static due to time constants
3. **Specific compliance**
   - compliance per unit volume of lung; or compliance / FRC = 0.05 per cmH2O

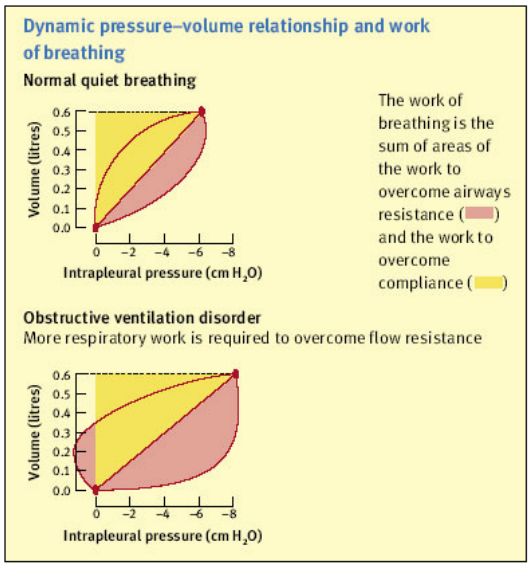
Factors that ↑ and ↓compliance

	↑compliance	↓compliance
Lung compliance	- Aging - asthma - COPD	- ↓lung size (e.g. neonates) - extremes of lung volume - supine posture → ↓FRC - pulmonary fibrosis; pneumothorax - pneumonia/ atelectasis - APO - pulmonary HTN
Chest wall compliance	- collagen disorders	- obesity - pregnancy - kyphoscoliosis → ↑chest wall rigidity - prone position

Within same lung, different alveoli have different compliance
Upright lung:

- alveoli at apex more distended at baseline due to gravity of lung tissue → operate on less compliant part fo VP curve → smaller ↑in vol during resp cycle
- alveoli at base less distended at baseline → more compliant part of VP curve → larger ↑ in vol during resp cycle





Hysteresis:

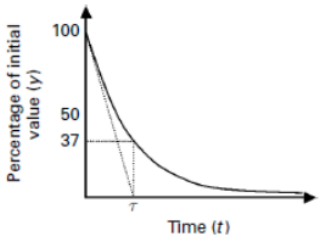
- hysteresis = measurement differs depending on whether the value measured is ↑or ↓
- Lung vol plotted against Pintrapl during inspiration + expiration → pressure vol loop

- Compliance different in inspiration + expiration
  - area of the loop represents the amount of energy expended as heat in overcoming the resistive forces
- Dynamic hysteresis
  - airway resistance ↑s when velocity of gas flow ↑s
- Static hysteresis
- No resistive component → hysteresis is due to viscous resistance of surfactant and the lung

Discuss 'fast' and 'slow' alveoli, including the concept of 'time constants'

A time constant = time taken for an exponential process to be 63% complete were the initial rate continued

- An exponential process; complete after 3 time constants
- In ventilation: time constant = a measure of the rate of filling of that lung unit
- Affected by:
  - lung compliance (Δvol per Δpressure)
  - resistance (airway pressure per unit flow)
  - inflation pressure
- Time constant = resistance to alveolar filling x compliance of alveolus
- used in: time of insp + exp; elimination of inhaled anaesthetics; ΔPaO2 and PaCO2 after Δin ventilation



The "normal" lung unit

- At a constant inflation pressure, the time constant = resistance x compliance
- normal resistance for lung tissue = 2cmH2O/L/sec; and resp system compliance (lung and chest wall) is 100ml/H2O
- t = 2cmH2O/L/sec x 100ml/cmH2O = 0.2seconds
- therefore: alveolar filling follows an exponential process such that it is 63% complete after 0.2s, and 95% after 0.6s

Slow and fast time constants

- different lung units have different resistances / compliances
  - **↓resistance + ↓compliance → short time constant → "fast alveoli"**
    - ↓compliance = empty/ fill rapidly e.g. atelectasis, pulmonary oedema, consolidation, fibrosis
  - **↑resistance + ↑compliance → long time constant → "slow alveoli"**
    - ↑resistance: lung units take longer to fill
- Factors that influence time constants can be divided into:
  - Factors that influence R e.g. asthma/ COPD → ↑R → ↑time constant
  - Factors that influence C e.g. pulmonary fibrosis → ↓compliance → ↓time constant
  -

Clinical significance

- time constants equal: pressure in each unit is identical throughout inspiration + distribution → dynamic compliance = independent of RR
- time constant uneven: slow alveoli don't finish filling before onset of expiration → redistribution of gas from fast to slow alveoli = **pendelluft effect**
  - distribution of inspired gas → dependent on RR;
  - ↑RR proportion of V_T delivered to slow alveoli ↓ (fast alveoli preferentially inflated) → shunt in slow alveoli → ↓% of lung participating in ventilation + gas exchange → ↑V/Q mismatching; global ↓dynamic compliance

Describe the elastic properties of the chest wall and plot pressure-volume relationships of the lung, chest wall and the total respiratory system

See above

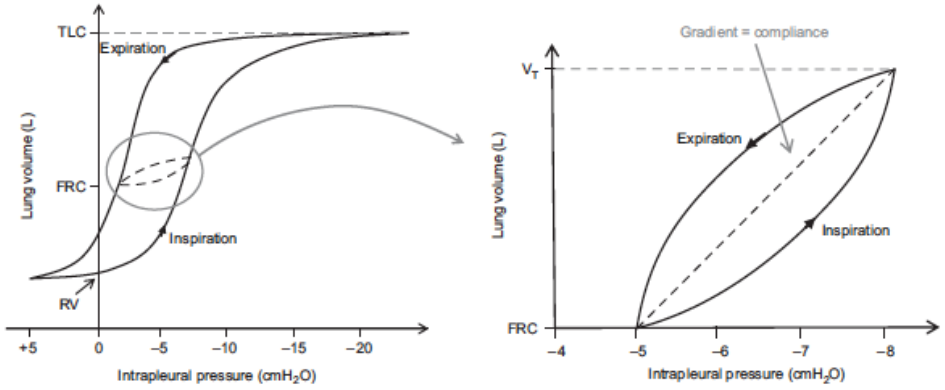


Figure 19.1 Static compliance curve. TLC: total lung capacity; V_T: tidal volume; FRC: functional residual capacity; RV: residual capacity.

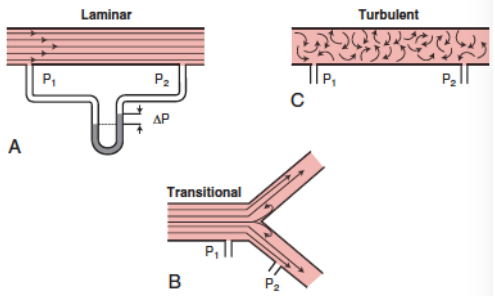
Explain the physics of gas flow and the significance of the relationship between resistance and flow in the respiratory tract

Resistance

- airways resistance = resistance caused by air moving through the airways
- Airway resistance = ΔP/ Q
  - ΔP = driving pressure = mouth – alveolar pressure gradient
  - Q = rate of air flow
  - Measured in cmH2O/L/sec
  - Normal range at FRC of 0.5 – 2cmH2O/L/sec
- Flow = function of pressure gradient, resistance, + type of flow.
- Mouth pressure: measured with manometer
- Alveolar pressure: body plethysmograph
- Airway resistance peaks at 5th generation → rapidly ↓s with each division thereafter due to ↑total cross sectional area

Types of flow

- Laminar, turbulent, or transitional
- The type of flow predicted by **Reynolds Number**
  - 2rdv/n where r = radius; d = density; v = velocity; n = viscosity
  - gives ratio of inertial to viscous forces
  - <2000 = laminar flow; >4000 = turbulent



Laminar flow

- occurs in straight smooth-walled tubes
- air/ gas moves in concentric tubes parallel to walls → velocity of air at centre = 2x at walls
- for laminar flow, resistance is ***independent*** of flow rate
- resistance to laminar flow is governed by **Hagan-Poiseille** equation
  - $R = 8\eta L/\pi r4$
  - where R is resistance; n = viscosity; l = length of tube; r = radius
  - Therefore resistance is:
    - proportional to: **viscosity** of gas; **length** of tube
    - inversely proportional to: **radius**
    - ***independent of density***
    - also proportional to **velocity**: **P = k x v** where P = pressure, k = constant, v = velocity (flow rate)
  - As length + viscocity remain constant → resistance in laminar flow due to Δ**radius** (airway caliber)
    - ↓intramural radius: oedema, ↑mucous, wall hypertrophy
    - smooth muscle tone: bronchospasm (↓r), connective tissue loss, B2 agonist (↑r)
    - external compression: tumour, haemorrhage, PTX, dynamic airways compression with forced expiration

Turbulent flow

- gas movement disorganized → formation of eddies → ↑resistance
- occurs in large airways: nose, pharynx, larynx, trachea
- Resistance in turbulent flow ***dependent*** on flow rate
  - Resistance to turbulent flow is more affected by:
    - ***density***
    - minimal contribution from viscosity
    - ↑ with ↓vessel radius; depends on degree of turbulence
- Factors that → turbulent flow
  - ↑RR: ↑gas velocity → turbulent flow in large bronchi
  - upper airway obstruction → ↑velocity around obstruction

Transitional flow

- occurs through most of the airways
- air flow = mixture of laminar + turbulent flow
- due to multiple bifurcations + ↓smoothness 2o cilia, mucus, debris
- pressure determined by both: flow rate + square of flow rate

Summary of factors affecting airways resistance

- Airway radius - laminar flow
- Rate of gas flow - turbulent flow:
- Indirectly: Lung vol → ↑lung vol → ↓airways resistance 2o radial traction on intra-thoracic bronchi + -ve transpleural pressure

Describe the factors affecting airway resistance and how airway resistance may be measured

See above

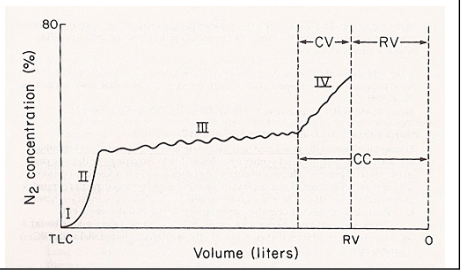
Describe closing capacity and its relationship to airway closure and explain its clinical significance and measurement

Closing capacity:

- volume at which small airways begin to close
- begins in dependent parts of lung (base)
- **CC = RV + closing volume**
- Normal lung: CC < FRC → no airway closure during normal tidal breathing
- If CC > FRC → dependent airway closure + gas trapping during normal tidal breathing → V/Q mismatch. Causes:
  - ↓FRC
  - ↑CC: ↑age (CC > FRC in supine pt age 44 and standing pt age 66); smoking; disease (emphysema/ asthma - gas trapping)

Measurement of closing capacity:

- requires measurement of RV + CV
- CV: measured using single breath nitrogen test (Fowlers)
  - Inspiration of 100% O2 from RV → expired [N2] during slow expiration measured with rapid N2 analyser → plotted against vol of gas expired
  - 4 phases:
    - phase 1: gas from anatomical dead space expired: 100% O2
    - phase II: dead space + alveolar gas expired; basal empty first
    - phase III: plateau; all gas is alveolar
    - phase IV: ↑[N2] at CV when apical alveoli empty (higher apical [N2])
- RV:



Note on closing volume

Closing volume (CV) = lung volume from beginning of airway closure to the end of max expiration

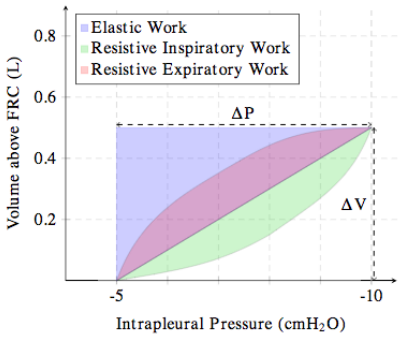
- i.e. the beginning of phase IV of the washout curve to RV
- Closing vol = CC – RV
- Note: this is distinct from the closing capacity (which is the difference between the onset of phase IV and zero lung vol)
- Normal = ~7ml/kg or 10% of vital capacity
- normal values:
  - 15-20% of VC
  - 10% of FRC in young adult

- 40% of FRC at 40yrs

Describe the work of breathing

- WOB = Energy used by the respiratory muscles during ventilation
- Work = pressure x volume (measured in Joules)
- represented as area on pressure-vol loop (dynamic compliance curve)
- Tidal breathing at rest: <2% BMR; O2 requirement = 3ml/min

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



WOB can be divided into:

1. **Inspiratory work**
   - Active
   - Elastic + resistive work
2. **Expiratory work**
   - Usually passive (uses potential energy stored during inspiration)
   - Resistive work

Inspiratory elastic work

- ~65% of total work
- work done on inspiration to overcome:
  - surface tension of lung (70%)
  - elastic properties of lung/ lung elastic recoil (30%)
- stored as elastic potential energy → used on expiration

Inspiratory + expiratory resistive work

- ~35% of total work; lost as heat
- energy required to overcome frictional forces: includes
  - 1. Airway resistance: between gas molecules
    - depends on **type of flow** + **airway calibre**
    - turbulent flow (↑RR; upper airway obstruction, ↑airway density) → ↑airway resistance than laminar flow
    - ↓airway calibre (radius) (e.g. bronchoconstriction, dynamic airway compression, ETT) → ↓calibre → ↑WOB
  - 2. Tissue resistance e.g. interstitial lung disease
- Usually potential energy stored from insp work is sufficient to perform expiratory resistive work → expiration can become active in pathological conditions e.g. COPD, asthma

Minimising WOB:

- Elastic work:
  - PEEP: keep lung vol at FRC and maximise number of ventilated alveoli
  - Positioning: optimise lung volume
  - Surfactant: minimise surface tension
  - Optimise RR: elastic WOB ↓s with ↑RR
- Resistive work
  - ↓RR: RR directly proportional to resistive work
  - ↑laminar flow: more efficient than turbulent flow; can be ↑ by ↓gas density e.g. heliox
  - ↑radius: ↑lung vol; bronchodilators

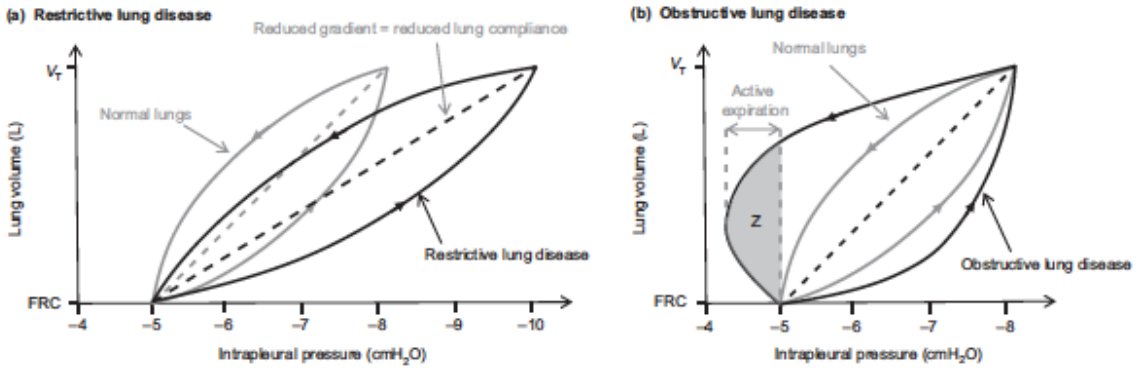


Figure 20.2 Pressure–volume loops: (a) restrictive lung disease; (b) obstructive lung disease.

Describe altered lung mechanics in common disease states

CICM - Describe the inspiratory and expiratory process involving the chest wall, diaphragm, pleura and lung parenchyma L1

- Δ lung vol occur due to Δ pressures
- respiration relies on the thoracic cavity being airtight, with trachea being only method gas can enter or exit the chest

Intrapleural pressure

- the pressure in the space between the visceral and parietal pleura, or (physiologically) between the lungs and the chest wall
- usually negative: -5cmH2O at rest
- varies with vertical distance in the lung
  - Gravity pulls lung parynchema inferiorly: intrapleural pressure is therefore more -ve in apex (-10cmH2O at FRC); less negative at the base (-3cmH2O at FRC)
  - This changes the degree of inflation at FRC: apical alveoli are maximally inflated; basal alveoli are hardly inflated
- During inspiration; the pleural pressures change evenly throughout the lung, however the basal alveoli are better ventilated because they have greater compliance

Inspiration

- Diaphragm + external intercostal muscles contract
  - contraction of diaphragm → flattens dome → pushes intraabdo contents down → ↑thoracic vol and generates –ve intrathoracic pressure which is transmitted through pleural space to lungs → expanding lungs and causing a pressure gradient between the mouth and small airways → gas flow into lungs
  - External intercostals pull ribs anterosuperiorly → ↑cross sectional area of chest → ↑thoracic vol and –ve pressure
- Accessory muscles: sternocleidomastoid + scalenes → elevate sternum + 1st 2 ribs respectively (active in hyperventilation)

- → intrapleural pressure becomes more negative: ~-8cmH2O
- When Ppl >Pel → lungs expand
- Alveolar pressure (PA) becomes subatmospheric → inspiration occurs
- At end inspiration:
  - Ppl = Pel
  - PA = Patmospheric

Expiration

- Passive during quiet breathing: diaphragmatic relaxation + elastic recoil of the lung parenchyma to return the lung to FRC
- Thoracic vol ↓s → Ppl falls to -5cmH2O
- Elastic recoil of the lung causes it to collapse until PA = Patmospheric
- Active during high minute ventilation (>40L/min), expiratory resistance, expulsive efforts
  - Abdominal wall muscles: (rectus abdominus, internal oblique, external oblique, transversus abdominis) contract → ↑intraabdominal pressure + forcing diaphragm up
  - Internal + innermost intercostals contract → pulling ribs downwards + inwards → ↓ thoracic volume

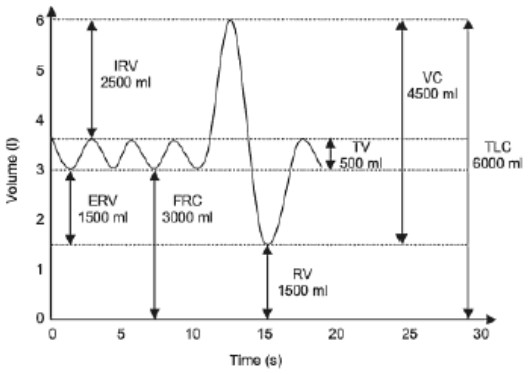
Pulmonary gas volumes and ventilation

Discuss lung volumes and capacities, their measurement and normal values

A lung capacity = sum of ≥2 lung volumes; therefore a derived value

4 lung volumes:

1. V_T: vol of air inspired per breath during normal quiet breathing: **7ml/kg** or ~500ml
2. **IRV**: vol of additional air that can be inspired above VT: **45ml/kg** or ~2500ml
3. **ERV**: vol of additional air that can be expired following normal tidal exhalation: 1500ml or **10-15ml/kg**
4. **RV**: vol of air that remains in lungs following max exhalation (i.e. after ERV): 1500ml or **15-20ml/kg**



4 lung capacities

1. VC
   a. Vol of air from max exhalation to max inhalation
   b. VC = ERV + V_T + IRV
   c. ~60ml/kg or ~4500ml
   d. VC <15ml/kg suggestive of need for ventilation
2. Inspiratory capacity: **IC = V_T + IRV**; 3000ml
3. Total lung capacity: TLC = RV + ERV + V_T + IRV = 6000ml or 80ml/kg
4. **FRC**
   a. Vol of air in lungs at end of normal expiration
   b. **FRC = RV + ERV** = 3000ml normal adult; **30ml/kg**

Measurement of lung volumes

A lung volume is measured directly: spirometer or gas dilution

- ERV, VT, and IRV
  - Measured directly using spirometry (flow meter)
  - Any capacity which is the sum of these (IC, VC) can therefore be calculated
- RV
  - cannot be exhaled so cannot be measured by spirometry → therefore FRC and TLC cannot be calculated by spirometry
  - RV measured by:
    - Gas dilution: relies on conservation of mass + poor He solubility + no He diffusion across alveolar capillary border
    - Body plethysmography: relies on Boyles law
    - N2 washout

Physiological importance of FRC

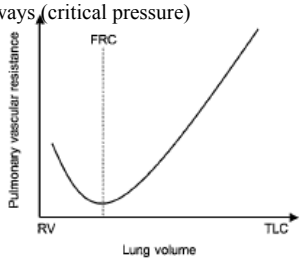
1. Gas exchange: buffers swings in PAO2; allows pulmonary circulation to be oxygenated throughout resp cycle
2. O2 reserve: allows continual oxygenation of blood during apneic periods
3. ↓WOB:
   a. WOB = function of lung resistance and compliance
   b. Compliance: lung sits on steepest part of compliance curve at FRC → <FRC some alveoli collapse; >FRC some alveoli overdistended
   c. Prevention of alveolar collapse: prevents atelectasis
4. Maintain lung volume + closing capacity
5. Minimise RV afterload
   a. >FRC compression of intra-alveolar vessels occurs → ↑PVR
   b. <FRC extra-alveolar vessels collapse → ↑PVR\
6. Maintain lung volume above closing capacity
   a. If closing capacity > FRC → shunt

↓FRC	↑FRC
- position: supine → ↓1L - ↑intraabdo pressure: obesity, pregnancy, acute abdomen, laparoscopic surgery - anaesthesia - ↓age - lung disease: pulmonary fibrosis, pulmonary oedema, atelectasis, ARDS	- PEEP: - Emphysema: lung elastic tissue destroyed → ↓inward elastic recoil - ↑age: ↑quantity of lung elastic tissue - asthma: air trapping + high intrinsic PEEP

Physiological consequences of ↓FRC by 1L in adult (40-50% decrease)

- **↓O2 store + PAO2 buffer**
  a. ↓effect of pre-oxygenation with 100% O2 as absolute gas vol are ↓
  b. ↑risk hypoxaemia during induction
  c. ↑breath to breath variation in PaO2
- **↑WOB**

b. Once CC >FRC → airway closure + gas trapping in normal breathing → ↑pressure required to open airways (critical pressure)
c. ↑elastic work → lungs move from steep to flatter part of compliance curve → less efficient
d. ↑resistance work ↑AWR due to ↓caliber of airways



- **↑V/Q mismatch**
  a. due to dynamic airways closure, gas trapping, atelectasis
  b. ↑shunt
  c. ↓PaO2
- **↑PVR**
  a. PVR minimal at FRC
  b. ↓FRC → ↓radial traction on extra-alveolar vessels → ↓radius vessels → ↑PVR
  c. will ↑west zone 4 (↑pressure on extra-alveolar vessels by poorly inflated lung) → atelectasis
  d. ↑atelectasis (↑with supine position)

Changes to FRC that occur with anaesthesia

- FRC = vol of air in the lungs at the ene dof expiration when elastic recoil of lungs = outward force of chest wall + diaphragm tone
- FRC = ERV + RV (in erect pt = 30ml/kg → ~3000mls)

Changes during anaesthesia

- rapid ↓FRC 15-20% on induction: due to ↓cross sectional area of rib cage (~200mls), diaphragm position (~30mls), ?pooling blood in thoracic cavty
- max drop in 1st few mins → remains steady throughout anaesthesia
- remains for several hrs post waking
- ↓whether or not pt paralysed

Effects of changes depend on:

- patient factors:
  a. preexisting disease: ↓chest/ lung compliance;
  b. ↑age/ obesity/ pregnancy
- surgical factors
  a. abdo surgery/ pneumoperitoneum
  b. thoracic/ 1 lung ventilation
- anaesthetic factors
  a. Δposture
     i. supine: ↑pressure of abdo contents on diaphragm → ↓FRC ~500-1000ml. effect ↑by ↑BMI, pulmonary vascular congestion (HF), trendelenberg
     ii. prone: least impact
     iii. head down: ↓FRC
  b. Induction of GA: ↓tone in ext. intercostals + ↑tone abdo muscles
  c. Paralysis: ↑cephalad position of diaphragm
  d. Excessive IV fluids: pulmonary oedema
  e. High FiO2: loss of N2 splinting → absorption atelectasis → ↓FRC
  f. Rapid shallow breathing: ↑alveolar surface tension, ↓compliance, ↑atelectasis, ↓FRC
  g. PEEP: prevents atelectasis → preserves FRC

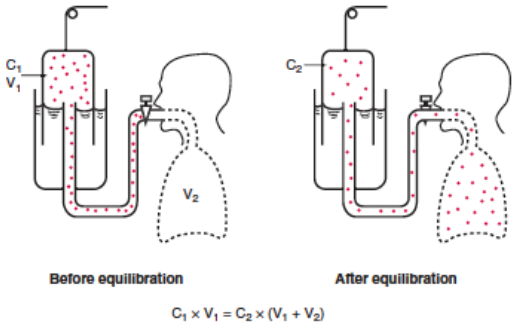
Measurement in more detail:

1. ERV, VT, and IRV

- measured directly using spirometry
- Spirometer = flow meter
  - Pt exhales as fast as possible through flow meter
  - Flow-time curve is produced
  - This curve can be integrated to find volume
- Any capacity which is the sum of these (IC, VC) can therefore be calculated

2. RV

- cannot be measured by spirometry as it cannot be exhaled → therefore FRC and TLV cannot be calculated
- RV can be measured using: gas dilution, body plethysmography, or N2 washout
- **1. Gas dilution**
  - Relies on 2 principles:
    - 1. Conservation of mass
    - 2. Poor He solubility → does not diffuse across alveolar-capillary barrier
  - Only communicating gas can be measured – therefore will underestimate FRC in gas trapping
  - At end tidal expiration a spirometer containing known [He] is opened to pt → He equilibrates between lungs + spirometer → expired [He] measured
  - From law of conservation of mass:
    - C1V1= C2V2
      - Before equilibration
        - C1 = initial concentration in spirometer
        - V1 = initial vol of spirometer
      - After equilibration:
        - total vol (V2) = V1 + FRC
        - C2 = amount of He in spirometer (lower)
        - He cannot diffuse across he alveolar capillary barrier to the amount of He before equilibration = amount of He after equilibration
    - C1V1 = C2 (V1 + FRC)
    - FRC = V1 x (C1-C2) / C2



- **2. Body plethysmography**
  - Relies on: Boyles law – at constant temperature, the vol of a fixed mass of gas is inversely proportional to its absolute pressure: PxV = a constant
  - Pt sits in airtight box → pt inhales against closed mouthpiece → resp effort ↑AP diameter of thoracic cage → ↑ lung vol. Gas remaining in lung expands → as lung vol ↑s → vol in body plethysmograph ↓s by equal amount

- 1st the Δvol in box is calculated:
  - before closure of mouthpiece, box pressure (P1) and box vol (V1) are known
  - after inspiration against closed mouthpiece, box pressure P2 is measured
  - V2 = V1 - ΔV
  - P1V1 = P2 (V1-ΔV)
- Then the lungs are considered:
  - Before closure of mouthpiece, mouthpiece pressure (P3) is known
  - Mouthpiece coses at end of tidal expiration, so initial lung vol (V3) is FRC
  - After inspiration, mouthpiece pressure P4 is measured
  - ↑in lung vol = ↓ in box vol = ΔV (already calculated from above)
- Therefore: P3xFRC = P4 (FRC + ΔV)
- All values except FRC are known → therefore FRC can be calculated:
  - FRC = P4ΔV/ P3-P4

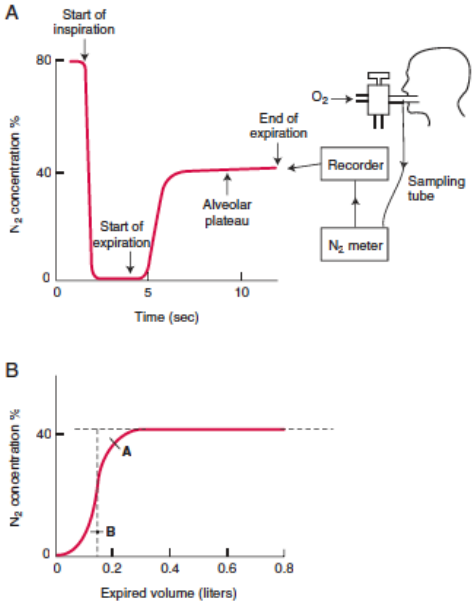
- **3. N2 washout method**
  - N2 makes up 79% of dry inspired air
  - Spirometer circuit with N2 analysewr
  - At end of tidal expiration (i.e. FRC), pt breathes 100% O2 → as pt breathes in and out, N2 is replaced by O2 → test finishes when expired N2 is <1%
  - Total vol of expired N2 is calculated from total vol of expired gas x concentration of N2 within collected gas
  - FRC = total expired N2 col x [N2]f / [N2]i where [N2f] is final fractional N2 concentration of expired gas and [N2]i is the initial fractional N2 concentration of expired gas

Body plethysmograph vs. helium dilution technique:

- Body plethysmograph measures total vol of gas in lung, including trapped behind closed airways (not communicating with mouth)
- Helium dilution method measures only communicating gas or ventilated lung vol
- In young, normal subjects these vols are virtually the same, but in patients with lung disease, the ventilated vol may be considerably less that the total vol because of gas trapped behind obstructed airways

Discuss dead space, its measurement and apply the Bohr equation and alveolar gas equation

Dead space = any vol of gas entering the resp system which does not participate in gas exchange.



1. Anatomical

- VDanat: volume of conducting airways; ~150ml
- Affected by:
  - **Lung vol:** ↑vol → radial traction on airway walls → ↑airway diameter
  - **Posture**: supine → ↓lung vol → ↓airway diameter
  - **Airway caliber**: (bronchoconstriction ↓VDanat; bronchodilation ↑VDanat)
  - **Age**/ size
- Measurement: **Fowlers** method:
  - Inspiration of 100% O2 from RV → expired [N2] during slow expiration measure expired
  - 4 phases:
    - 1: gas from anatomical dead space expired: 100% O2
    - II: dead space + alveolar gas expired; basal empty first
    - III: plateau; all gas is alveolar
    - IV: ↑[N2] at CV when apical alveoli empty (higher apical [N2])

2. Alveolar dead space

- VDalv: ventilated alveoli that are not perfused (i.e. V/Q mismatch)
- negligible in normal lungs as V/Q well matched
- ↑VDalv
  - ↓PAP: hypovolaemia; RVF; ↑RV afterload (IPPV, PE, MI)
    - ↓PAP → insufficient perfusion of lung apices → high V/Q ratio
    - ↑intrathoracic pressure (IPPV) → ↓VR → ↓PAP
  - ↑alveolar pressure: PEEP, positioning
    - ↑alveolar pressure → in apex causes compression of pulmonary capillaries → ↓alveolar perfusion (West zone 1)
    - ↑intrathoracic pressure → ↓VR → ↓PAP
- Measurement
  - Cannot be measured directly
  - As VDphys = VDanat + VD alv: → VDalv can be calculated if VDphys (Bohr) + VDanat (fowlers) are known

3. Physiological

- VDphys = anatomical + alveolar dead space
- Normal value: 2-3lm/kg i.e. 30% of VT
- Calculated using Bohr equation
  - calculates the ratio of physiological dead space to tidal vol:
  - $V_D/V_T = PaCO2 – P_{ET}CO2 / PaCO2$
    - V_D: physiological dead space vol
    - V_T: tidal vol
    - PECO2: partial pressure of CO2 in expired air
    - VD/VT ~0.2-0.35 i.e. ~30%
  - Principle: all CO2 comes from alveolar gas ie from alveoli that are ventilated + perfused; none from dead space

Alveolar gas equation

- allows PAO2 to be estimated from variables that are easily measured
- PAO2 = FiO2 – (PaCO2 / R)
- R = resp quotient where R = vol of CO2 produced / vol of O2 consumed
  - R is dependent on metabolic substrates used for metabolism: fat, protein, carbohydrate
  - Normal value = 0.8
- PAO2 is therefore dependent on:
  - FiO2
  - Barometric pressure
  - Alveolar ventilation

Pulmonary circulation

Outline the anatomy of the pulmonary and bronchial circulations

Pulmonary circulation

Pulmonary arteries

- R + L pulmonary arteries arise from pulmonary trunk at level of the sternal angle.
- carry poorly oxygenated (venous) blood to lungs for oxygenation
- pass to root of lung → branch to superior lobe → enter hilum → descends posterolateral to main bronchus → divides into lobar + segmental a to supply each lobe + bronchopulmonary segment of the lung
- Pulmonary capillaries
  - Line walls of alveoli to form a mesh
  - Diameter: 7-10um
  - Very thin walls fused to the BM of the alveolar epithelium
- Histology:
  - Pulmonary arteries: thin walls; little smooth muscle; large amount of elastin
  - Pulmonary capillaries: lined with endothelial cells

Pulmonary veins

- 2 on each side; carry well oxygenated (arterial) blood from pulmonary capillaries to LA
- Intrasegmental veins drain blood from adjacent bronchopulmonary segments
- Main vein drains each bronchopulmonary segment
- Pleura
  - Veins from parietal pleura → join systemic veins in adjacent parts of the thoracic wall.
  - Veins from visceral pleura → drain into the pulmonary veins

Bronchial circulation

Bronchial arteries

- Supply:
  - Structures making up the root of the lungs
  - Supporting tissues of the lung
  - Visceral pleura
- L bronchial arteries arise from the thoracic aorta
- R bronchial artery may arise from an intercostal artery or bronchial artery
- Small bronchial arteries:
  - Provide branches to the superior oesophagus → pass along posterior aspects of main bronchi, supplying them and their branches as far distally as the resp bronchioles
- The most distal branches of bronchial arteries anastomose with branches of pulmonary arteries in walls of bronchioles + in visceral pleura
- Occasionally additional bronchial vessels arise from the descending aorta and travel in the pleural ligament
- Histology: same as that of other systemic arteries

Bronchial veins

- drain blood from bronchial artery supply i.e. 1° proximal part of root of lungs. Remainder drained by the pulmonary veins
- The R bronchial vein drains → into the azygous vein
- The L bronchial vein drains → into the accessory hemiazygous vein or L superior intercostal vein

Discuss the difference between the pulmonary and systemic circulations

The pulmonary circulation differs from the systemic circulation in several major respects:

	Systemic circulation	**Pulmonary circulation**
Anatomy:	Thick walled arteries – smooth muscle + elastic Abundant autonomic (esp. SY) innervation → PVR highly regulated by ANS	2 pulmonary arteries; 4 pulmonary veins Thin walled capillaries Extensive ANS innervation, but less effect
Function	1. Offloads O2 / loads CO2 2. Acid/base 3. metabolic: absorbs + delivers nutrients; toxins, drugs; excretes waste products 4. produces factors for coagulation	1. Loads O2 and unloads CO2 2. Acid/base via CO2 3. Filters blood 4. Metabolic: activates ATI, inactivates bradykinin, takes up 5HT Or… Filtration Immune Reservoir (blood) Metabolic: ACE, alpha1-antitrysin Thermoregulation Inhalational agents in Take up drugs Synthesis (surfactant)
Pressure and flow		
Pressures	120/80 MAP 100mmHg ↑pressure, ↑resistance circuit	25/8 MAP 15mmHg ↓pressure, ↓resistance, ↑capacitance Blood flow 5L/min (i.e. entire CO) achieved with MPAP 15mmHg
Atrial pressure	Right 2mmHg	Left 5mmHg
Pressure drop inlet-outlet	~100mmHg	10mmHg
Major point of resistance	Arterioles	Evenly spread across pulmonary circulation
Blood flow	5L/min	5L/min
Nature of flow	Continuous (windkessel)	Pulsatile
Factors affecting flow and resistance		
	Determined primarily by arterioles affected by: 1. Hypoxia and hypercarbia (↓pH)	1. ↑resistance at high lung vol (compression of alveolar caps) + low lung vol (narrowing of extra-alveolar vessels)

	2. myogenic feedback: ↑pressure = ↑contraction = ↑resistance 3. Circulating factors	2. hypoxic + hypercarbic (↓pH) vasoconstriction (↑HPV) 3. ↑Pa or Pv pressures → ↓resistance due to recruitment + distension of capillaries. Excessive pulmonary pressures → ↑ fluid transudate, ↑institial pressures, ↑resistance 4. flow dependent on arterial, venous, and airway pressures 5. Circulating factors - constrict: NA, A, DA, ATII, TXA2 - dilate: ACh, PGE2, PGI2, histamine
Resistance	20mmHg/L/min	5mmHg/L/min
Autonomic regulation	Principle determinant of SVR	SY stimulation at cervical ganglia ↓pulmoanry blood flow
Posture	Hydrostatic pressures	West zones – low resistance circuit so large effect of gravity on circulation; lung apex to base 30-40cmH2O

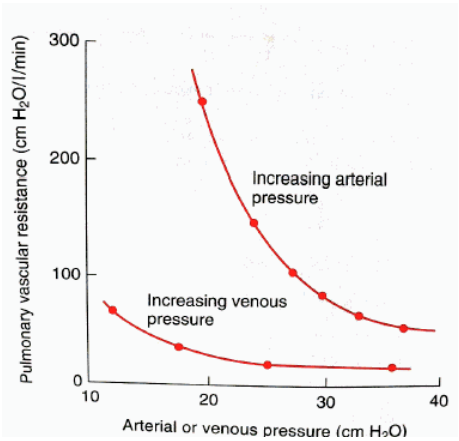
Discuss pulmonary vascular resistance and the control of pulmonary vascular tone

Physiological features of pulmonary vasculature

1. **Pressure**
   a. Pressures within pulmonary blood vessels
      i. ↓pressure (MPAP ~15mmHg) + ↓resistance → thin walled vessels; optimal for gas exchange
      ii. ↓ pressure → ↓ likelihood of transudation into the alveoli (pulmonary oedema)
      iii. Pulmonary capillary pressures = hydrostatically dependent → zones 1-4
   b. Pressures around pulmonary blood vessels
      i. Pulmonary capillaries surrounded by gas → ↓support from endothelium → collapse / distend
      ii. Pressure in alveoli is usually close to atmospheric pressure
2. **No autoregulation**
3. Metabolic needs of bronchi are met by independent systemic circulation (**bronchial circulation**)

Pulmonary vascular resistance

- PVR = impedance to blood flow through lungs i.e. from RV to LA
- Pulmonary circulation = low pressure/ low resistance system
- PVR can be calculated using **Ohms law**:
  - Pressure difference across vascular system = total flow x vascular resistance. Therefore
  - Vascular resistance = pressure difference / total flow. Therefore
    - PVR = MPAP – PCWP / CO = 2mmHg/L/min
    - SVR = (MAP - mean RA pressure) / CO = ~20mmHg/L/min
  - Typical values
    - MAP = 100mmHg
    - Mean RA pressure = 2mmHg
    - CO = 5L/min
    - MPAP = 15mmHg
    - PCWP = 5mmHg



Determinants of PVR:

1. **Pulmonary artery pressure**
   a. ↑MPAP → ↓PVR due to 2 mechanisms:
      i. Recruitment: ↑pressure → collapsed pulmonary capillaries reopened
      ii. Distension: ↑vascular pressure → open capillaries further distended
2. **Lung volume**
   a. Functionally: 2 different types of pulmonary blood vessels:
      i. Alveolar capillaries: little CT; ↑alveolar pressure → compression
      ii. Extra-alveolar vessels: not exposed to alveolar pressure; can be pulled open by radial traction of surrounding parenchyma
   b. Δshape of alveolar and extra-alveolar vessels account for ΔPVR at different lung volumes
      i. FRC: PVR lowest
      ii. ↑lung vol: ↑PVR 2° blood flow resistance within alveolar capillaries (stretched + distorted); extra-alveolar vessels contribute little resistance to blood flow as ↑lung vol → ↑radial traction → ↓resistance
      iii. ↓lung vol: ↑PVR due to resistance to flow in extra-alveolar vessels (narrow)
3. **HPV**
   a. response to hypoxia → acts to ↓V/Q mismatch
   b. ↓PaO2 → vasoconstriction → ↑local vascular resistance → redirect blood flow to better ventilated alveoli
   c. mediated by NO (potent arteriolar vasodilator released when PAO2 <70mmHg) + O2 sensitive K channels (stimulated by alveolar hypoxia) → opening of Ca2+ channels → vasoconstriction
   d. Examples of HPV:
      i. Foetal circulation
      ii. Pneumonia
      iii. High altitude
      iv. Cardiogenic pulmonary oedema: due to gravity there is ↑pressure at lung bases → transudation → HPV → upper lobe diversion
   e. Factors that modify HPV
      i. ↑by: acidosis, hypercapnia
      ii. ↓by: alkalosis, hypocapnoea, vasodilators, bronchodilators, volatile agents
4. **Gravity**
   a. Zone 1: PVR very high
   b. Zone 2: PVR high
   c. Zone 3: PVR low
5. **Neural control**
   a. A-adrenergic vasoconstrict; b-adrenergic vasodilate
   b. Cholinergic vasodilates via endolehtlium and nitric oxide → activate cGMP to ↓intracellular Ca2+
6. **Humoral control**
   a. Catecholamines predominantly vasoconstrict
   b. TXA2, PGD2, PGE2, PGFalpha vasoconstrict; PCI2 vasodilates
   c. Histamine, serotonin vasoconstrict

Ventilation/ perfusion relationships

Explain the vertical gradient of pleural pressure and its significance

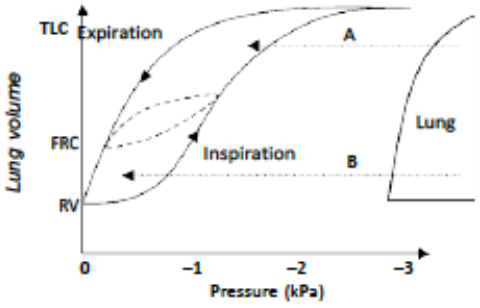
Intrapleural pressure

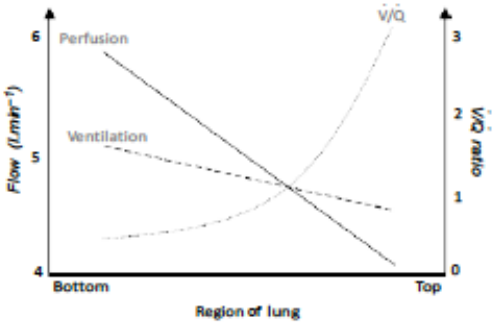
- = pressure between visceral + parietal pleura or between lungs + chest wall
- at rest = -5cmH2O due to outwards recoil of chest wall + inwards recoil of lungs

Vertical gradient of pleural pressure

- Intrapleural pressure varies with the vertical distance in the lung
- due to **gravity** pulling lung parenchyma inferiorly
- At FRC
  - apex: -10cmH2O
  - base: -3cmH2O

	Apex	**Base**
At FRC	Alveoli in apex larger than base - ↑traction from interstitium - Maximally inflated - Pintrapl = -10cmH2O - On flatter part of compliance curve – point A	Basal alveoli - More compressed due to effect of gravity - Hardly inflated - Pintrapl -2cmH2O - on steep part of compliance curve – point B
During inhalation	- Less expansion due to ↓compliance - -10cmH2O → -13cmH2O (flat compliance) - small Δvol → ↓flow	- More expansion due to ↑compliance - -2cmH2O → -5cmH2O - Larger Δvol → ↑flow i.e. etter ventilated



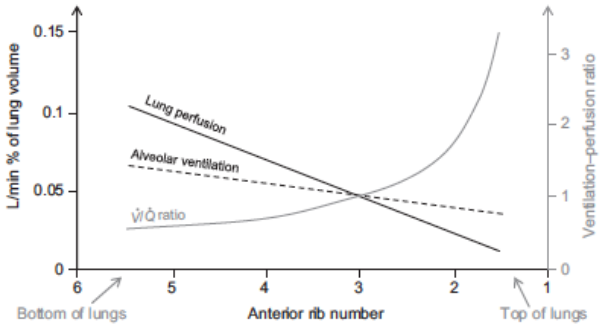


Positioning

- Supine: vertical difference between apex + base abolished → anterior lung higher than posterior → perfusion in posterior lung > anterior lung
- lateral position: perfusion in dependent lung > non-dependent lung

Discuss normal ventilation-perfusion matching

- Optimal gas exchange occurs when the ventilation and perfusion to each alveolus is matched i.e. **V/Q ratio = 1**
- Unequal V/Q → inefficient gas exchange
  - Excessive ventilation → excessive work
  - Inadequate ventilation → inadequate gas exchange



Normal lung:

- Perfusion = 5L/min; alveolar ventilation = 4L/min → normal V/Q ratio = 0.8
- Considerable regional variation

Gravity

- Ventilation and perfusion: bases > apex due to gravity
- **V/Q ratio ↑s from bottom to top of lungs**
  - Base: V/Q ratio: 0.6 (perfusion > ventilation)
  - Apex: V/Q ratio >3 (ventilation > perfusion)
- Gravity has ↑effect on *perfusion* than on ventilation
- **Perfusion**
  - effect of gravity on pulmonary capillary pressure
  - difference in pulmonary capillary pressure between apex and base is equivalent to hydrostatic pressure exerted by a column of blood
  - distance from apex to base = 30cm → 30cmH2O
  - Altered by: exercise; body position
- **Ventilation**
  - Weight of lung parenchyma → intrapleural pressure more –ve at apex than base
  - FRC: intrapleural pressure -10cmH2O at apex and -3cmH2O at base → apical alveoli nearly fully inflated vs. basal alveoli hardly inflated → compliance basal alveoli > apical
  - Inspiration: insp muscles ↓Pintrapl by 3cmH2O throughout pleural cavity. Δpressure → ↑Δvol at base → base better ventilated

Pathological causes of abnormal V/Q ratio

1. perfused but not **ventilated** → V/Q ratio <1 (V/Q scatter)
   - Most common cause of hypoxaemia
   - Causes: pneumonia, atelectasis; ARDS; airway obstruction; COPD; one lung ventilation
   - Poorly V alveoli with normal Q have ↓PAO2: ↑FiO2 → ↑PAO2 → ↑PAO2-PaO2 gradient across alveolar-capillary barrier
2. ventilated but not **perfused** → V/Q ratio (>1)
   - Causes: PE; ↓RV SV (hypovolaemia, RV infarction, pericardial tamponade)
3. V/Q = 0 (shunt)

Methods used to measure ventilation perfusion inequalities:

- Regional defects in ventilation or perfusion:
  - V/Q scan
    - Radiolabelled tracer + gamma camera
    - Perfusion: radiolabelled (Tc99m) dye
    - Ventilation: radioactive gas (Xe)
    - images show gross areas of V/Q mismatch e.g. PE
- Physiological uniformity of ventilation:
  - Single breath N2 washout test
  - Multiple breath N2 washout
- A-a gradient

Assessment	
Perfusion	**Ventilation**
• CXR • lung scan • spiral CT + contrast • pulmonary angiography • Xe^{133} washout • calculation of V_D/V_T • $P_{a-ET}CO_2$ difference	• clinical assessment • CXR • single breath N_2 test • N_2 washout • Xe^{133} • venous admixture • $P_{A-a}O_2$ difference • pulmonary function tests

Effect of V/Q mismatch on O2 transfer + CO2 elimination

A lung with V/Q inequality isn't able to transfer as much as O2 and CO2 as a lung that is uniform

↑ V/Q mismatch impairs both CO2 and O2 transfer, but to different degrees

- O2 uptake is more markedly affected because of the shape of the O2 uptake curve
  - Alveoli with low V/Q and consequently lower PO2 cause a substantial ↓ in the O2 concentration of blood leaving poorly ventilated alveoli.
  - Alveoli with a high V/Q and PO2 produce only a small ↑ in O2 concentration
- CO2 elimination is less affected by V/Q mismatch
  - This is partly due to the more linear relationship between PCO2 and CO2 concentration and mostly due to the importance of PaCO2 in determining ventilatory drive
  - Any ↑ in PaCO2 resulting from V/Q mismatch will result in an ↑ in ventilation to normalize the PaCO2
  - A ↑in total ventilation is effective in ↑ the elimination of CO2 from both well and poorly ventilated alveoli, so PaCO2 is easily normalised

Discuss West's zones of the lung

Wests zones take into account the effect of alveolar pressure on pulmonary blood flow

- West built on gravitational model of ventilation and perfusion
- upright lung divided into 3 zones → arterial, venous, alveolar pr

1. **Zone 1 (apex): PA > Pa > Pv**
   a. Alveolar pressure > arterial pressure
   b. Alveolus compresses capillary → no blood flow occ
   c. Ventilation but no perfusion = dead space; V/Q ratio
   d. Occurs when:
      i. Alveolar pressure high: PEEP
      ii. Arterial pressure low: shock, hypovolaem
      iii. NB doesn't exist in normal lungs as PAP
2. **Zone 2: Pa > PA >Pv**
   a. Arterial P > alveolar P > venous P
   b. Blood flow occurs intermittently during the cardiac cycle: systolic Pa > PA, but diastolic Pa is <PA
   c. Alveolar pressure acts as starling resistor
   d. Flow is proportional to the Pa-PA gradient
      i. When Pa falls below PA (e.g. diastole) then no blood flow occurs
3. **Zone 3 (base): Pa > Pv > PA**
   a. Arterial pressure > venous pressure > alveolar pressure
   b. Due to gravity
   c. Blood flow contiguously throughout cardiac cycle
   d. Flow is proportional to the Pa – Pv gradient

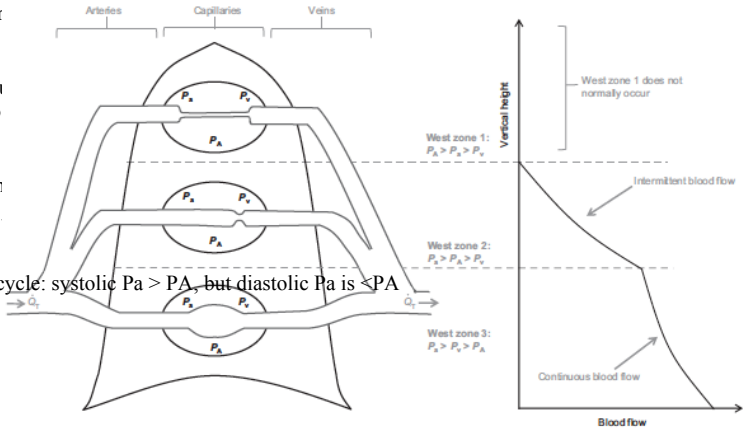


Figure 15.1 West zones of the lung.

Describe the shunt equation

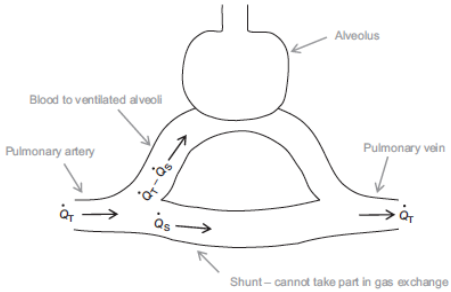
Shunt

- blood reaches systemic circulation without being oxygenated via passage through the lungs
- deoxygenated venous blood passes directly into arterial system and mixes with arterial blood → ↓PaO2
- classified as physiological or pathological
  - **1. Physiological**:
    - **i) Anatomical**
      - Bronchial circulation: drain into pulmonary veins
      - Thebesian veins: drain directly into L heart chambers
    - **ii) Functional**
      - Local V/Q mismatch → not true shunt
  - **2. Pathological**
    - Intracardiac: e.g. VSD
    - Large communicating vessels: e.g. pulmonary AVM; PDA
    - Intra-pulmonary shunts: pulmonary oedema, pneumonia, bronchial obstruction, one lung ventilation

Measurement

- shunt cannot be directly measured
- **Shunt equation** used to calculate proportion of CO that is shunted from venous to arterial system

- In form of ratio = shunt fraction (normal = 2-5%)
  - $\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$
    - where Qs = shunt blood flow;
    - QT= cardiac output
    - CcO2 = pulmonary end capillary O2 content → assumed to be 100% saO2
    - CaO2 = arterial O2 content → calculated from ABG
    - CvO2 = mixed venous O2 content → calculated from CVC (PAC)



- How to derive the shunt equation
  - 1. Consider pulmonary blood flow:
    - total pulmonary blood flow = QT
    - blood flow to unventilated alveoli (shunt) = Qs
    - therefore blood flow to ventilated alveoli = QT – Qs
  - 2. Consider vol of O2
    - vol of O2 in pulmonary vein = vole of O2 in ventilated capillary + vol of O2 in shunt capillaries
    - written mathematically: QTCaO2 = (QT – Qs)CcO2 + QsCvO2
  - 3. Multiply and rearrange:
    - multiply out brackets: QTCaO2 = QTCcO2 – QsCcO2 + QsCvO2
    - rearranging gives: QsCcO2 – QsCvO2 = QTCcO2 – QTCaO2
    - or: Qs(CcO2 – CvO2) = QT(CcO2 – CaO2)
    - which gives the shunt equation: $\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$

Physiological consequences of a shunt:

1. **Effect on CO2**
   a. No CO2 can diffuse from shunted blood → CO2 might be expected to ↑, however:
   b. In spont breathing pt → ↑PaCO2 → ↑resp drive → ↑alveolar ventilation = no ↑in PaCO2 unless:
      i. Shunt fraction is large and
      ii. Pt unable to ↑alveolar ventilation to compensate
2. **Effect on O2**
   a. PaO2 ↓s ∝ shunt fraction
   b. As shunted alveoli = ventilated but not perfused → true shunt is unresponsive to ↑FiO2
   c. For an alveoli with V/Q between 0-1 (V/Q mismatch or V/Q scatter but not true shunt):
      i. There is ventilation, but ↓perfusion → blood partially oxygenated
      ii. ↑PAO2 will ↑oxygenation (assuming no diffusion limitation):
         1. administration of supplemental O2
         2. hyperventilation
         3. as per the alveolar gas equation
   d. For an alveoli with V/Q of 0 (true shunt)
      i. There is no perfusion. Regardless of ↑PAO2 → PaO2 will not improve
      ii. May get small ↑in PaO2 due to ↑dissolved O2

Venous admixture:

- Volume of mixed venous blood that would need to be added to pulmonary end capillary blood to produce the observed difference between arterial PO2 and pulmonary end capillary PO2
- Calculated value, and not actual amount

Discuss regional ventilation-perfusion inequalities, venous admixture and the effect on oxygenation and carbon dioxide elimination

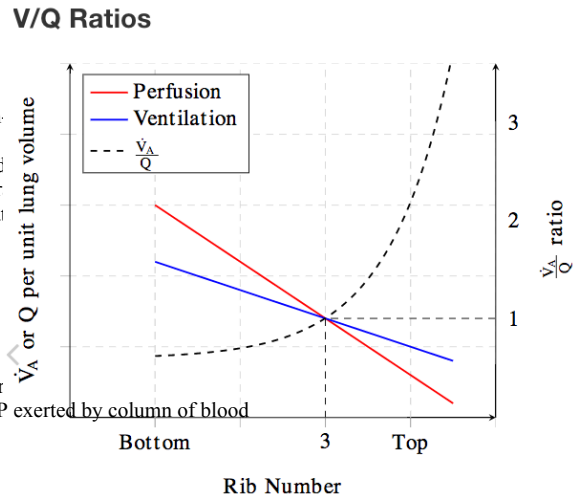
- Optimal gas exchange occurs when the ventilation and perfusion to each alveolus is matched i.e. V/Q ratio = 1
- Unequal V/Q → inefficient gas exchange
  - Excessive ventilation → excessive work
  - Inadequate ventilation → inadequate gas exchange

Normal lung:

- Perfusion = 5L/min; alveolar ventilation = 4L/min → normal V/Q ratio = 0.8
- Considerable regional variation

Distribution of ventilation

- **In erect pt at FRC**: ventilation bases > apex due to *gravity*
  - Weight of lung parenchyma → compresses lung below (**base**); stretches non-
  - Pintrap -10cmH2O at **apex** vs -3cmH2O at **base**
    - apical alveoli nearly fully inflated vs. basal alveoli hardly inflated
    - Inspiration: insp muscles ↓Pintrapl by 3cmH2O throughout pleur
    - Δpressure → ↑Δvol at base → basal alveoli compliance + ventilat
- **Right lung** better ventilated than L (R lung bigger)
- **Lateral position**
  - Dependent lung better ventilated in spont breathing pt
  - Non-dependent lung better ventilated in IPPV pt



Distribution of perfusion

- pulmonary circulation = ↓pressure circulation → gravity has ↑effect pulmonary capillar
- Difference in pulmonary cap pressure between apex + base = equivalent to hydrostatic P exerted by column of blood
- Distance from apex to base = 30cm → 30cmH2O

V/Q ratios

- V and Q: bases > apex due to gravity
- Gravity has greater effect on *perfusion* than on ventilation
- V/Q ratio ↑s from bottom to top of lungs
  - Base: V/Q ratio: 0.6 (perfusion > ventilation)
  - Apex: V/Q ratio >3 (ventilation > perfusion)

V/Q mismatch

- Occurs when V/Q ≠1
- V/Q >1 (dead space)
  - I.e. ventilated but not perfused
  - Causes: PE; ↓RV SV (hypovolaemia, RV infarction, pericardial tamponade)
- V/Q 0-1 (V/Q scatter)
  - perfused but not **ventilated** Most common cause of hypoxaemia
  - Causes: pneumonia, atelectasis; ARDS; airway obstruction; COPD; one lung ventilation
  - Poorly V alveoli with normal Q have ↓PAO2: ↑FiO2 → ↑PAO2 → ↑PAO2-PaO2 gradient across alveolar-capillary barrier
- V/Q = 0 (shunt)
  - Mixed venous blood entering systemic circulation without being oxygenated → ↓PaO2

Effect of V/Q mismatch on O2 transfer and CO2 elimination

↑ V/Q mismatch impairs both CO2 and O2 transfer, but to different degrees

- O2 uptake is **↑affected** 2° shape of O2 uptake curve
  - Alveoli with ↓V/Q + ↓PO2 → substantial ↓O2 concentration of blood leaving poorly ventilated alveoli.
  - Alveoli with a ↑V/Q and ↑PO2 → produce only a small ↑ in O2 concentration
- CO2 elimination is **less** affected by V/Q mismatch
  - more linear relationship between PCO2 and [CO2] + importance of PaCO2 in determining ventilatory drive
  - Any ↑PaCO2 2° V/Q mismatch → ↑ in ventilation to normalize PaCO2
  - A ↑total ventilation → ↑elimination of CO2 from both well + poorly ventilated alveoli → so PaCO2 is easily normalised

Venous admixture

- Vol of mixed venous blood that would need to be added to pulmonary end capillary blood to produce the observed difference between arterial PO2 and pulmonary end capillary PO2
- Calculated value, and not actual amount
- Sources of blood contributing to venous admixture
  - True shunt:
    - Normal: bronchial venous blood; thebesian veins
    - Pathological: VSD
  - V/Q mismatch
    - Normal: blood that perfused alveoli with V/Q <1 → blood not fully oxygenated
    - Abnormal: COPD, pulmonary fibrosis, pneumonia

Outline methods used to measure ventilation-perfusion inequalities

Methods used to measure ventilation perfusion inequalities:

- Regional defects in ventilation or perfusion:
  - V/Q scan
    - Radiolabelled tracer + gamma camera
    - Perfusion: radiolabelled (Tc99m) dye
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Assessment	
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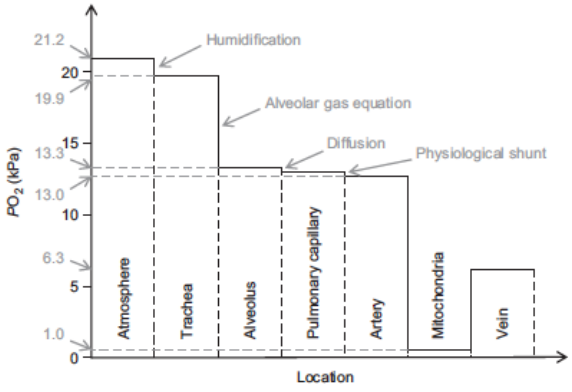
Diffusive transfer of respiratory gases

Describe the oxygen cascade

- stepwise reduction in PO2 as O2 passes from the environment to the tissues
- Critical purpose = maintain mitochondrial PO2 above the level required to supply energy for tissue metabolism

Steps of the cascade:

1. **Dry atmospheric air:** 160mmHg
   a. PO2 = PB x FiO2
   b. O2 is 21% at sea level
   c. PO2 = 760mmHg x 0.21 = 160mmHg
2. **Humidified tracheal gas:** 149mmHg
   a. Gas humidified during inspiration
   b. heated to 37° with 100% relative humidity
   c. $P_{SVPwater}$ at 37° = 47mmHg
   d. Boyles Law:
      i. PO2 = $P_B - P_{SVPwater}$) x FiO2
      ii. PO2 = 0.21 x (760 – 47)
      iii. PO2 = 150mmHg
3. **Alveolar gas:** 100mmHg
   a. P_AO2 mainly dependent on FiO2, PB, and alveolar ventilation – as described by the AGE
   b. P_AO2 = FiO2 (P_B - $P_{SVPwater}$) – PaCO2 / R
   c. Or PAO2 = PiO2 – PaCO2/ R
   d. P_AO2 = 150 – 40 / 0.8
   e. P_AO2 = 100mmHg
4. **Arterial blood:** normal PaO2 = 100mmHg
   a. The difference in PAO2 and PaO2 = A-a gradient
   b. A-a gradient = PAO2 – PaO2 = PiO2 – (PaCO2 / R) – PaO2
   c. Step reduction in PO2 between alveolus and systemic arteries. Due to 3 factors:
      i. Diffusion across alveolar-capillary barrier (if diffusion limited)



ii. Shunts: anatomical
iii. V/Q mismatch

5. **Mitochondria:** 5mmHg
   a. lower than arterial due to metabolic activity of tissues
   b. Pasteur point: PaO2 at which oxidative phosphorylation ceases: 1mmHg
6. **Venous blood**
   a. PO2 > mitochondrial PO2
   b. Mixed venous blood quoted as 40mmHg
   c. Higher than mitochondria as not all arterial blood travels through capillary beds

NB:

- O2 content is what is important for cellular function
- Partial pressure determines rate and extent of gas transfer
- Important concepts:
  - Daltons Law: the partial pressure of a gas is proportional to its fractional area of the total vol of a dry gas mixture
  - Ficks law of diffusion
  - Shunt equation

Alveolar gas equation

- allows PAO2 to be estimated from variables that are easily measured
- **PAO2 = FiO2 – (PaCO2 / R)**
- R = resp quotient where R = vol of CO2 produced / vol of O2 consumed
  - R is dependent on metabolic substrates used for metabolism: fat, protein, carbohydrate
  - Normal value = 0.8
- PAO2 is therefore dependent on:
  - FiO2
  - Barometric pressure
  - Alveolar ventilation

Describe the alveolar exchange of oxygen and carbon dioxide

- CO2 produced in tissues as a byproduct of aerobic metabolism
- CO2 produced at basal rate of 200ml/min (at STP)

Haldane and Bohr

- important physiological mechanisms in tissues / lungs re gas exchange + acid-base balance
- **Bohr effect**
  - describes how ΔPCO2 and pH affect O2 transport:
  - **↑PaCO2 / ↓pH** → Hb O2 binding affinity ↓s → shifts OHDC to ***right*** → facilitates **release of O2** (i.e. O2 offloaded where needed
- **Haldane** effect:
  - ↑ability of deoxygenated Hb to carry CO2
  - result: metabolic waste products are transported away from tissues to lung

Tissues/ lungs

- Metabolically active tissues produce H+ and CO2 → Bohr effect means that additional O2 is offloaded at ↑metabolically active tissues
- According to the Haldane effect, the newly formed deoxyHb is better at binding H+ and carrying CO2 than oxyhb → metabolic waste products transported away from tissues to lung
- In the lungs: ↑PO2 → O2 molecules bind to deoxyHb → ability to bind H+ and CO2 ↓s (**reverse of Haldane effect**). In consequence
  - Release of H+ → H ions combine with HCO3 → H2CO3 → liberates CO2
  - CO2 diffuses into alveoli + away from blood → HbO2 binding affinity ↑s, facilitating loading fo O2 onto Hb ions (**reverse of Bohr effect)**

Factors that affect the transport of O2 and CO2 from the alveolus to the blood

- transport via diffusion through blood gas barrier + rate of reaction with blood
- Factors
  - **Fick's law of diffusion**: diffusion constant ∝ solubility of the gas, and inversely ∝ square root of MW
    - Surface area: alveoli have ↑SA → allows max exposure of blood to gas within alveoli
    - Membrane thickness: rate of transfer inversely ∝ membrane thickness
    - MW of gas: CO2 and O2 are small, uncharged molecules
    - Solubility: CO2 20x more soluble than O2 in blood → much faster rate of transfer
    - Concentration gradient
      - Molecules will diffuse down concentration gradient
      - Conc gradient between alveolar gas and blood = dependent on partial pressure of gas within each compartment
      - Partial pressure of alveolar gas = the individual pressure exerted by each gas
  - Rate of perfusion + diffusion limitation
    - Concentration gradients for both gases maintained with rapid flow through of blood through the pulmonary circulation
    - O2 exchange usually perfusion limited: Hb fully loaded by 0.25s
    - CO2 exchange is ventilation limited

Discuss diffusion capacity and its measurement

Diffusion capacity is a measure of the rate at which a gas can diffuse across the blood gas barrier

- DL = Vgas / (P1-P2)

The diffusion of molecules across a semi-permeable membrane **is governed by 5 factors**:

1. **Fick's law:** rate of diffusion is directly ∝ concentration gradient (or partial pressure). Dependent on:
   - Partial pressure of gas in alveolus: affected by
     - Atmospheric pressure
     - FiO2
     - Alveolar ventilation
   - Partial pressure of gas in blood: affected by
     - Solubility
     - Binding of gas to Hb
     - Formation of carbamino compounds

$$\text{Rate of diffusion} = \frac{\Delta P \times A \times s}{T \times \sqrt{MW}}$$

2. **Grahams law:** rate of diffusion is inversely ∝ square root of MW

3. **Surface area:** (directly ∝) Affected by:
    - Parenchymal volume: body size, pathology; V/Q mismatch; pulmonary blood volume; posture
4. **Membrane thickness:** (inversely ∝)
5. **Solubility:** (directly ∝)

Measurement of diffusing capacity

- CO
    - Diffusion limited
    - Normal blood concentration is nearly zero
    - DL = Vgas / (P1-P2)
    - Vital capacity breath of 0.3% CO → held for 10s then exhaled → inspired and expired CO are measured
    - Difference is the amount of CO which is now bound to Hb
- At rest diffusing capacity is 25ml/min/mmHg
- Diffusing capacity is ↓ in:
    - Thickened alveolar-capillary barrier: interstitial lung disease
    - ↓surface area: emphysema, PE, lobectomy/pneumonectomy
- Factors that ↑ diffusion capacity
    - Exercise (due to pulmonary vasodilation and alveolar recruitment)
    - Blood-gas barrier area: lung size, alveolar recruitment, capillary distension

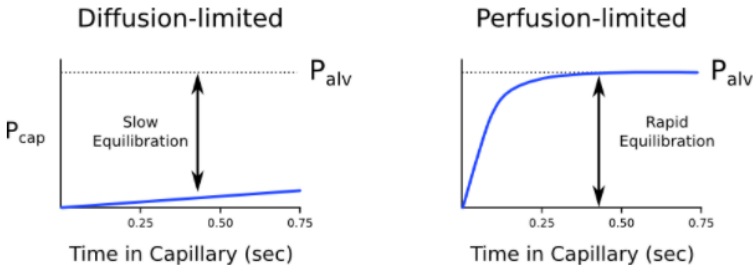
CICM - Explain perfusion-limited and diffusion-limited transfer of gases L1

Diffusion through tissues is described by Fick's law

- **Fick's law of diffusion =**
  - ΔP = pressure gradient across membrane
  - A = area of membrane
  - S = solubility of substance
  - T = thickness of membrane
  - MW = molecular weight of substance

$$\frac{\Delta P \times A \times S}{T \times \sqrt{MW}}$$

- The rate of diffusion of a gas through a tissue is:
  - directly ∝:
    - surface area of the barrier
    - solubility of the gas
    - concentration gradient (partial pressure difference)
  - Inversely ∝:
    - Membrane thickness
    - Square root of MW



Diffusion vs. perfusion limited

Transfer of gases can be diffusion or perfusion limited dependent on the rate limiting step

Diffusion limited

- Occurs in gases which do not reach equilibration of Pa and PA
- The rate of gas diffusion across the alveolar membrane limits its transport away from the lung.
- Rate limiting step = rate of diffusion
- E.g. CO
  - CO binds so avidly to Hb (250x that of O2) → virtually no CO dissolved in plasma → PaCO rises only slightly
  - Even when RBC traversed entire length of pulmonary capillary, there is still substantial partial pressure difference across alveolar-capillary barrier → equilibrium of PaCO and PACO never reached

Perfusion limited

- Characterized by complete equilibration i.e. Pa = PA
- amount of gas transferred between alveolus and capillary = dependent on amount of blood passing through the capillary
- rate limiting step = rate of blood flow
- E.g. **N2O**
  - N2O rapidly diffuses across alveolar-capillary barrier
  - Insoluble; does not bind to Hb; only carried in plasma in dissolved form
  - PaN2O = PAN2O (<0.07sec); well before RBC has traversed pulmonary capillary
  - ↑diffusion rate will not ↑blood transport away from the lungs → limiting factor = rate of blood flow/ perfusion
- e.g. CO2 (ventilation limited i.e. perfusion limited in reverse)

Is the transfer of O2 perfusion or diffusion limited?

- Can behave as **both** perfusion and diffusion limited
- O2 diffusion takes 0.25s; pulmonary capillary transit time is 0.75s
- **Normal** conditions
  - Transfer of O2 across the alveolar capillary barrier is **perfusion** limited
  - Equilibrium is reached between alveolar and capillary PO2 before the RBC has traversed the pulmonary capillary
- Conditions where transfer of O2 may become **diffusion** limited
  - **Disease of the alveolar capillary barrier**
    - Pulmonary fibrosis: thickening of alveolar-capillary barrier → ↓rate of diffusion
    - Exercise: ↑CO → ↓RBC transit time
    - Altitude: ↓PaO2

Gas transport in the blood

Discuss the carriage of oxygen in blood, the oxyhaemoglobin dissociation curve, oxygen stores in the blood and their clinical significance and implications

Carriage of O2 in the blood

O2 is carried either bound to Hb or dissolved in solution

- **1. Dissolved O2 (2%)**
  - obeys **Henry's Law**: amount dissolved ∝ the partial pressure. For each mmHg of PO2, there is 0.003ml O2/100ml blood → therefore normal arterial blood with PO2 of 100mmHg contains 0.3ml O2/100ml
- **2. Bound to Hb (98%)**
  - each gram of fully saturated Hb can bind 1.34ml of O2 (= **Hufners constant**)
  - 98% O2 in blood = bound to Hb, a protein tetramer with an iron-porphyrin ring attached to each chain
  - O2 coordinates with each Fe atom → inducing a conformational change → promotes binding of O2 to the other Fe atoms.
  - total O2 binding capacity of Hb in blood (at normal p, temp, and PCO2) = 1.39ml/g → giving a total O2 carrying capacity of blood which an Hb of 150g/l of 20.8ml/100ml
- Normal arterial blood has a PO2 of 100mmHg and is 97.5% saturated
- Venous blood has a PO2 of 40mmHg and is 75% saturated

O2 content

- CaO2 = (Hb x sats x 1.34) + (PaO2 x 0.003)
- 1.34 = Hufners constant at 37degrees
- 0.03 = solubility coefficient for O2 in water
- O2 content per 100mL arterial blood = 20ml; venous blood = 15ml

RBCs

- small, flexible, biconcave discs
- cell membrane contains carbohydrate based antigens (ABO) and transmembrane proteins (Rhesus)
- No nucleus; no mitochondria (therefore aerobic metabolism not possible – entirely dependent on glucose and glycolytic pathway)

Hb

- large, ion containing protein contained within RBCs
- HbA
  - Most common form of adult Hb (95%)
  - Quaternary structure comprising 4 polypeptide globin subunits (2 alpha and 2 beta chains) in tetrahedral arrangement
  - 4 globin chains held together with weak electrostatic forces
  - each globin chain has its own haem group – an ion containing porphyrin ring with iron in the ferrous state (Fe2+)
  - O2 molecules are reversibly bound to each haem group through a weak coordinate bond to the Fe ion
  - In total: 4 O2 molecules can be bound to each Hb molecule – one for each heme group

Different structures of Hb molecules

- the structure of the globin chains can vary
- In HbA (adult Hb): the globin portion contains 2 alpha and 2 beta chains
- Foetal Hb (HbF): contains 2 alpha and 2 gamma chains
- HbA2: contains 2 alpha and 2 delta; present in 2-3% of the population
- In health, HbF is replaced by HbA within 6 months of birth

Disorders of Hb synthesis

- ↓ production of normal globin chains eg thalassaemia
  - Thalassaemia results from ↓ synthesis of alpha or beta chains
  - Thalassaemia major = pt is homozygote and there is no production of HbA → severe anaemia + usually fatal before adulthood
  - Thalassaemia minor = pt is heterozygous; can produce some HbA → mild anaemia
  - Most commonly originates from Mediterranean, Indian, or Southeast Asian populations
- Abnormal globin chains e.g. sickle cell anaemia

Determinanet of tissue O2 delivery

- Diffusion from alveolus to blood: Fick's law of diffusion and factors affecting rate
- Diffusion from capillaries into tissues and cells: partial pressure difference

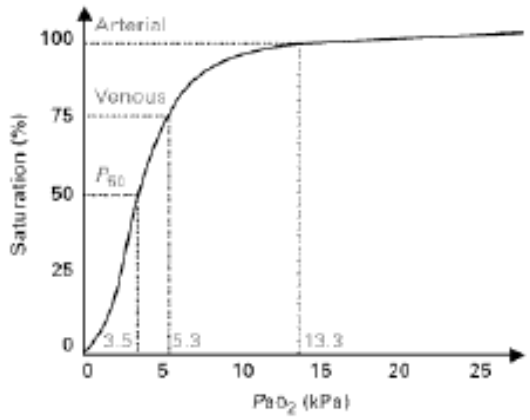
Oxyhaemoglobin dissociation curve

Oxyhaemoglobin dissociation curve

- OHDC describes the relationship between SaO2 and PaO2 at 37 degrees
- Demonstrates cooperative binding of Hb:
  - ↑in O2 affinity of Hb with each successive O2 binding
    - 1st O2 molecule = difficult to bind – 2O strong electrostatic charges to be overcome to achieve conformational changes in Hb molecule: ***tense*** conformation → βchains far apart
    - once 1st O2 has bound confirmation of Hb changes → βchains closer together → 2nd O2 has ↑binding affinity → ↓energy to bind
    - 4th molecule binds 300 times more easily than 1st
    - once 4th O3 bound → Hb in ***relaxed*** state
  - The max amount of O2 that can be combined with Hb is the O2 capacity → all available binding sites are occupied by O2
- Importance of sigmoidal shape
  - Upper portion is flat: if PO2 in alveolar gas ↓s slightly, loading of O2 will be little affected. I.e. a small ↓ in PO2 at normal O2 levels → causes only a slight ↓ in arterial saturation
  - However, where O2 levels are already low, and on the steep part of the curve, the same small ↓ in PO2 will cause a sharp ↓ in SaO2
- O2 concentration: (1.39 x Hb x sats) + (0.003 x PO2)
- Oxygen saturation of Hb = the % of the available binding sites that have O2 attached:
  - (O2 combined wit Hb / O2 capacity) x 100
  - In arterial blood, O2 sats are usually >97%. This corresponds to a PO2 of 100mmHgand is on the flat part of the curve
  - In venous blood, the saturations are ~75% This corresponds to the start of the steep part of the curve and a PO2 of ~40mmHg

Factors that may alter the OHDC

- Position of OHDC is described by P50 value = the PO2 at which 50% of Hb is bound to O2; corresponds to PaO2 of 26mmHg
- **Right shift**
  - ↓affinity of O2 for Hb → O2 ↑easily offloaded (i.e. for a given PO2, SaO2 is lower)
  - ensures ↑tissue oxygenation in states of ↓perfusion
  - Causes: **↑PCO2; acidosis; ↑2, 3, DPG; exercise; ↑temp; HbS**
  - **Bohr effect**: Δ PCO2 and pH affect O2 transport → ↑PaCO2 and ↓pH sabilises deoxyHb → facilitates release of O2 → right shift
- **Left shift**
  - Left shift → ↑O2 binding affinity
  - Causes; ↓PaCO2; alkalosis; ↓2, 3, DPG; hypothermia; methaemoglobin; HbF



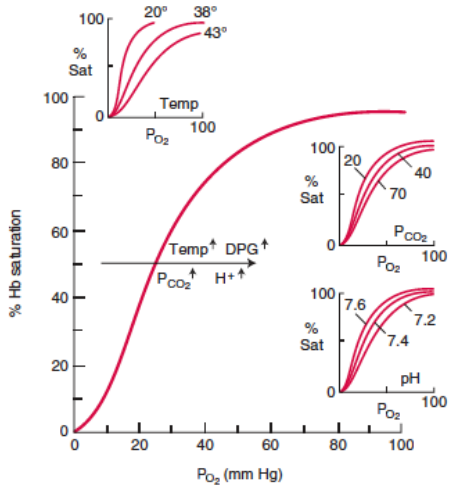
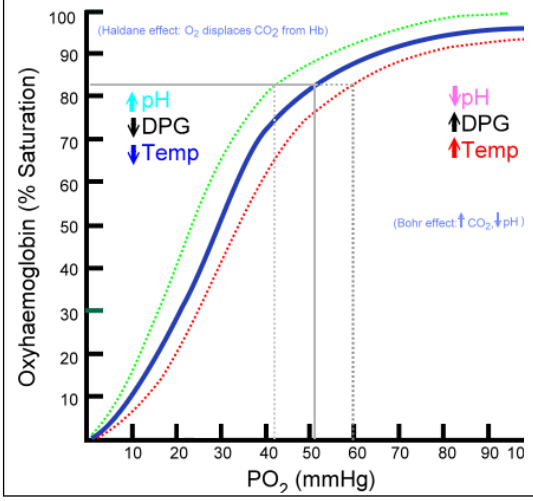
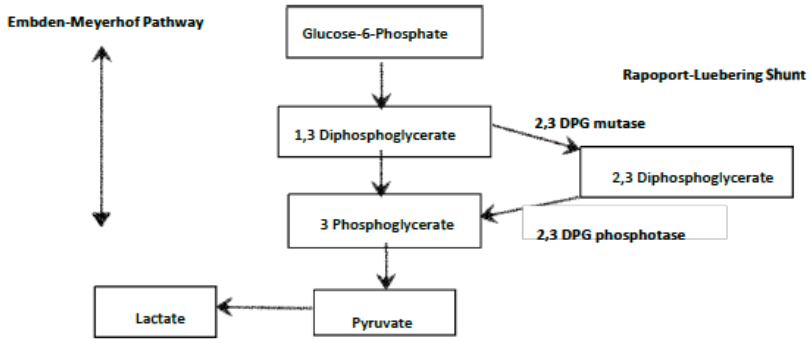


Figure 6-3. Rightward shift of the O_2 dissociation curve by increase of H^+, P_{CO_2}, temperature, and 2,3-diphosphoglycerate (DPG).

2,3DPG

- Formed by RBC during glycolysis
- Binds to beta chains of deoxy-Hb
- DPG binds strongly with beta chains → changing protein conformation → ↓O2 affinity
- ↑2,3DPG → ↑unloading of O2 from Hb → ↑ tissue supply
- Factors ↑DPG:
    - High altitude: aclimatisation response
    - Anaemia
    - Alkalosis
    - Chronic hypoxaemia
    - Exercise
    - Pregnancy
    - Hyperthyroidism
- Factors ↓DPG
    - Stored blood: DPG ↓ in stored blood: storage ↓ glycolysis (only issue with MTP); levels return to normal after 24-48hr





Haemoglobin and DPG

Normal adult Hb (HBA) consists of 2 alpha and 2 beta chains composing a tetramer

- each chain surrounds a porphyrin ring and Fe ion
- An O2 molecule can coordinate with each Fe ion → inducing a conformational change in the tetramer from its tense (T, deoxy) to relaxed (R, oxy) state
    - requires the breakage of salt links within each chain and extrusion of 2,3DPG (2,3 bisphosphoglycerate) from a site where it binds both beta chains
    - 2,3,DPG has a major effect on the affinity of Hb for O2. It is present within erythrocytes at ~the same molar concentration as Hb. It is a highly negatively charged molecule :
        - which in the tense state of Hb occupies a site in the center of the tetramer where it binds 3 positively charged sites on each B chain.
        - This binding must be broken when Hb binds O2
        - This greatly ↓s the affinity of Hb for O2
        - In the complete absence of 2,3DPG, Hb is 50% saturated at 1mmHg PO2 instead of at 26mmHg

Discuss the carriage of carbon dioxide in blood, the carbon dioxide dissociation curve and their clinical significance and implications

CO2 is a byproduct of aerobic metabolism in mitochrondria

- non-polar
- small molecule
- able to diffuse across membranes
- Blood musc transport CO2 from site of production (active tissue) to site of elimination (lungs)

Role of Hb

- main O2 carrying compound
- **Bohr** effect: ↓pH or ↑PaCO2 → ↓Hb affinity for O2
- **Haldane** effect: deoxy-Hb is able to carry more CO2 than oxy-Hb

CO2 is carried in 3 ways in blood:

1. **Dissolved CO2 (5%)**
   - Obeys Henry's Law: vol of CO2 dissolved in plasma is proportional to tl
   - Solubility coefficient ~20x > O2: ~0.06ml/100ml/mmHg
   - As a result → dissolved CO2 plays a significant role in its carriage
2. **As HCO3 (90%)**
   - CO2 + H2O ←→ H2CO3 ←→H^+ + HCO3 (via CA)
   - CA only present within RBC
   - CO2, H2O, and HCO3 can cross RBC membrane; H^+ cannot.
     - CO2 diffuses into RBC → forms H^+ + HCO3
     - HCO3 diffuses out of RBC into plasma
     - Cl shift: maintains electroneutrality (**Hamburger effect**): mediated by Cl/HCO3 exchanger
     - Deoxy Hb is a better buffer for H+ than oxyhb (30% of Haldane effect) → venous RBC can carry more CO2 in the form of HCO3 than arterial RBC
3. **Combined with Hb and other proteins as carbamino compounds (5%)**
   - Deoxy-Hb forms carbamino complexes with CO2 more readily than oxy-Hb (70% of Haldane effect)
   - CarbaminoHb: CO2 binds to terminal amine group of Hb molecule = HbNH2 + CO2 >--→ HbNHCOOH2

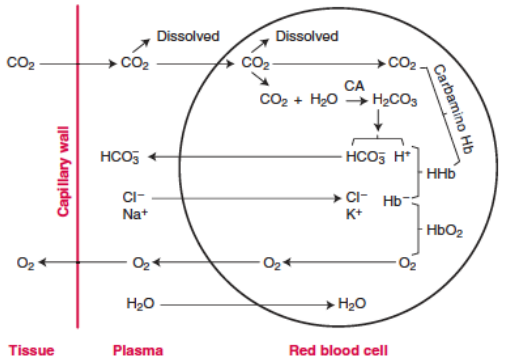


Figure 6-5. Scheme of the uptake of CO_2 and liberation of O_2 in systemic capillaries. Exactly opposite events occur in the pulmonary capillaries.

CO2 dissociation curve

- Describes relationship between PaCO2 and total CO2 content (NB difference from OHDC which relates PO2 and SaO2)
- diagrammatic representations of the **Haldane effect**: deoxygenated blood carries ↑CO2 than oxygenated blood
- Typically drawn as 2 curves: arterial and venous
  - Arterial PaCO2 = 40mmHg; and CO2 content = 48ml/100ml blood
  - Venous CO2: 45mmHg; content 52ml/100ml blood
- The position of the dissociation cuve is dependent on HbO2 saturation → the Haldane effect
- **Haldane effect**
  - For a given PCO2, CCO2 ↑s as PO2 ↓s i.e. shifts the CO2 blood curve to the left
  - This is due to:
    - ↑affinity of deoxy-Hb for H+ and
    - The ↑ability of deoxy-Hb to form carbamino compounds
- Important features:
  - At physiological PCO2: the dissociation curve is ~ linear
  - As PCO2 ↑s → CO2 content ↑s due to ↑fraction of dissolved CO2

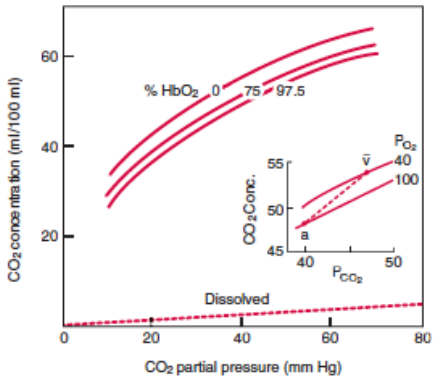


Figure 6-6. CO_2 dissociation curves for blood of different O_2 saturations. Note that oxygenated blood carries less CO_2 for the same P_{CO_2}. The *inset* shows the "physiological" curve between arterial and mixed venous blood.

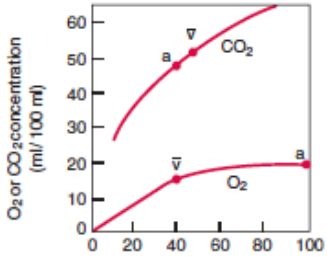


Figure 6-7. Typical O_2 and CO_2 dissociation curves plotted with the same scales. Note that the CO_2 curve is much steeper. *a* and *v̄* refer to arterial and mixed venous blood, respectively.

How is the Haldane effect related to the Bohr effect?

- **Bohr effect:** ↑CO2 or ↓pH → shifts P50 of Hb to ↑PO2 values i.e. shifts OHC to **right** → Hb having a ↓O2 binding affinity
- **Haldane and Bohr** = important physiological mechanisms in peripheral tissues and lungs with regard to gas exchange and acid-base balance
  - Metabolically active tissues produce H+ and CO2 → Bohr effect means that additional O2 is offloaded at most metabolically active tissues
  - According to the Haldane effect, the newly formed deoxyHb is better at binding H+ and carrying CO2 than oxyhb → the metabolic waste products are therefore efficiently transported away from the tissues to the lung
  - In the lungs: PO2 is high → O2 molecules bind to deoxyHb → ability to bind H+ and CO2 ↓s (reverse of Haldane effect). In consequence
    - Release of H+ → H ions combine with HCO3 → form H2CO3 → liberates CO2
    - Liberated CO2 diffuses into alveoli and away from the blood → HbO2 binding affinity ↑s, facilitating loading fo O2 onto Hb ions (reverse of Bohr effect)

Effects of hypocapnia	Effects of hypercapnia
- ↑TPR - cerebral vasoconstriction - placental vasoconstriction	- cerebral vasodilation - ↑ICP - ↑CNS SY outflow

- ↓CO - ↓ICP - ↑pain threshold - hypoventilation - resp alkaloss - left shift of the HbO2 dissociation curve - hypokalaemia → ICF shift - ↓HCO3 reabsorption by the kidney - ↓plamsa ionized Ca2+ → tetany	- ↑CO and BP (indirect effect) - direct depressant effect on CVS - cardiac arrhythmias - hyperventilation - resp acidosis - right shift of HbO2 dissociation curve - hyperkalaemia - ↑HCO3 resbaorption by kidney

O2 and CO2 stores in the body

Oxygen

- 70kg male contains ~1.5L of O2, split between:
  - 850ml in blood
    - 20.4ml of O2 per 100ml blood: divided up as
      - 20.1ml bound to Hb
      - 0.3ml dissolved
    - 250ml bound to myoglobin
    - 450ml contained in FRC (21% of 2.4L)
  - FRC: 270ml
  - Dissolved in body fluids: 45mL
  - Myoglobin 200ml: haem containing O2 bidning protein present in skeletal muscles

CO2:

- CO2 is produced in the mitochrondria during the citric acid cycle as a product of aerobic metabolism
  - Entry of substrate (CHO, FFA, ketone, aas) in force of AcetylCoA with movement of electrons through enzymatic reactions → forms CO2 + FADH, NADH, H+
  - Final movement of electrons via reduced compounds through ETC → moves electrons through intermediaries of lower and lower potential until combines with O2 to form H2O + ATP
  - Amount of CO2 produced depends on energy substrante (CHO vs. FA vs. ketone vs. aa)
- Transport of CO2
  - Hb loaded with O2 arrives at active tissue
    - ↑CO2, ↓O2, ↑temp working tissue → R shift in OHDC (Bohr effect) → ↑offloading O2 → formation of deoxyHb
  - transported dissolved (10%), HCO3 (60%), carbamino compounds (30%)
- 120L of CO2 in the body
  - 1.8L/kg (1.6L/kg of which is in relatively inaccessible compartments)
- Blood content of CO2 ~2.5L
- Normal elimination (and, at steady state, production) of CO2 is 200ml/min

Refer to above learning points

Pulmonary function tests

CICM - Describe the measurement and interpretation of pulmonary function tests, including diffusion capacity. L1

- PFTs are used to quantify an individual pts respiratory physiology.
- clinical uses are:
  - dx of respiratory disease
  - grading severity + guide pharmacological mx
  - estimation of surgical risk esp. thoracic
- Spirometer is used. Classified as:
  - Volume sensing
  - Flow sensing

Measurement

Spirometry can measure:

- All static lung volumes and capacities except RV, TLC, and FRC
- Dynamic spirometry i.e. lung measurements that depend on flow rate:
  - FEV1
  - Forced vital capacity (FVC)

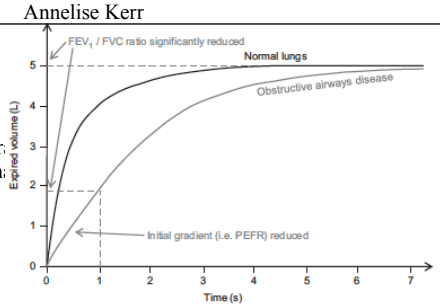
- Peak expiratory flow rate (PEFR)
- Expiratory flow volume curve
- Flow volume loops

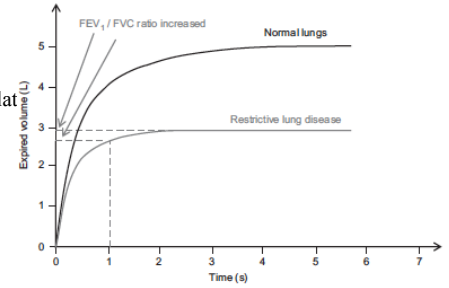
Forced spirometry

- simple bedside test used for dx of restrictive and obstructive lung disease
- From full inspiration, pt breathes out as hard and fast as possible into spirometer to full expiration → expir
- 2 parameters measured: FEV1 and FVC. These are compared with predicted values based on normal pts m

Obstructive vs. restrictive lung disorders

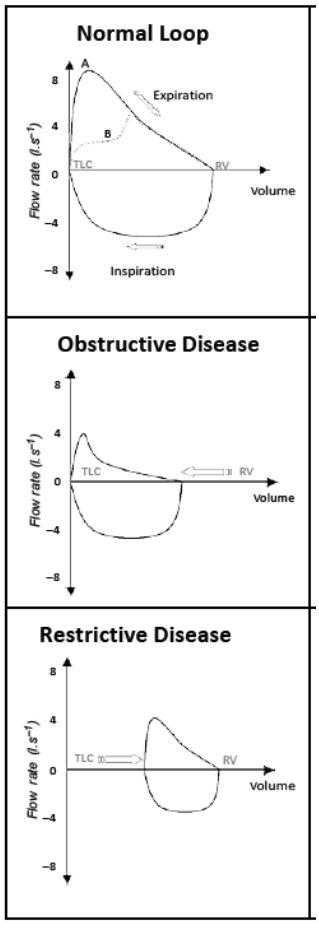
- **obstructive** airways disease (asthma, COPD)
  - FEV1 <80% predicted
  - FEV1/FVC ratio <0.7
  - Severity of disease can be assessed using FEV1
    - Mild: FEV1 50-79% predicted
    - Moderate: FEV1 30-49% predicted
    - Severe: FEV1 <30% predicted
  - Differentiation between asthma and COPD is based on reversibility of airway obstruction.
    - Forced spirometry performed before and 15mins post administration of bronchodilat significant airway reversibility → asthma
- **Restrictive** lung diseases (fibrosis, kyphoscoliosis, resp muscle weakness)
  - FEV1 <80% predicted
  - FVC <80% predicted
  - FEV1/FVC ratio >0.7 ("normal" or high)





Expiratory flow volume *curve*

- expiratory flow plotted against expired volume
- shape of curve: due to airway radius at different lung volumes:
- Upward slope
  - steepness of upward slope = effort dependent;
  - steepness of downward slope = effort independent (flow rate limited + declines 2o to dynamic airways compression)
- dynamic airways compression
  - starling resistor mechanism
  - during forced expiration → ↓lung vol/ airway (↓intra-airway pressure)
  - when intrapleural pressure > airway pressure → airway compression → ↓calibre of airways
  - ↓calibre → ↑resistance (Hagan-Poiseiulle)



Normal curve:

- Max inspiration to 80ml/kg (TLC)
- At TLC → minimal airways resistance due to radial traction on airways
- Max driving pressure due to ↑elastic energy stored in lung tissue
- Quick rise to max flow rate (8L/sec): intrapleural P > airway pressure
- Straight downward slope (dynamic airways compression)
- Max flow to RV
- Flow ceased due to airways closure
- FEV1/FVC >0.7

Obstructive disease

- ↑TLC and RV due to hyperexpansion/ gas trapping
- upward slope less steep due to ↓calibre of airways
- ↓PEFR due to ↑airways resistance at any vol
- concave loop: compression of major airways with premature airways closure + rapid ↓flow rate; fast then slow alveolar emptying
- FEV1/FVC <0.7
- ↑RV due to gas trapping

Restrictive lung disease

- ↓TLC due to restrictive effect - ↓lung compliance
- upward slope same as normal lung
- down slope (FEV1) steeper than normal due to ↑elastic recoil
- RV unchanged due to later CC due to ↑radial traction
- FEV1/FVC >0.7

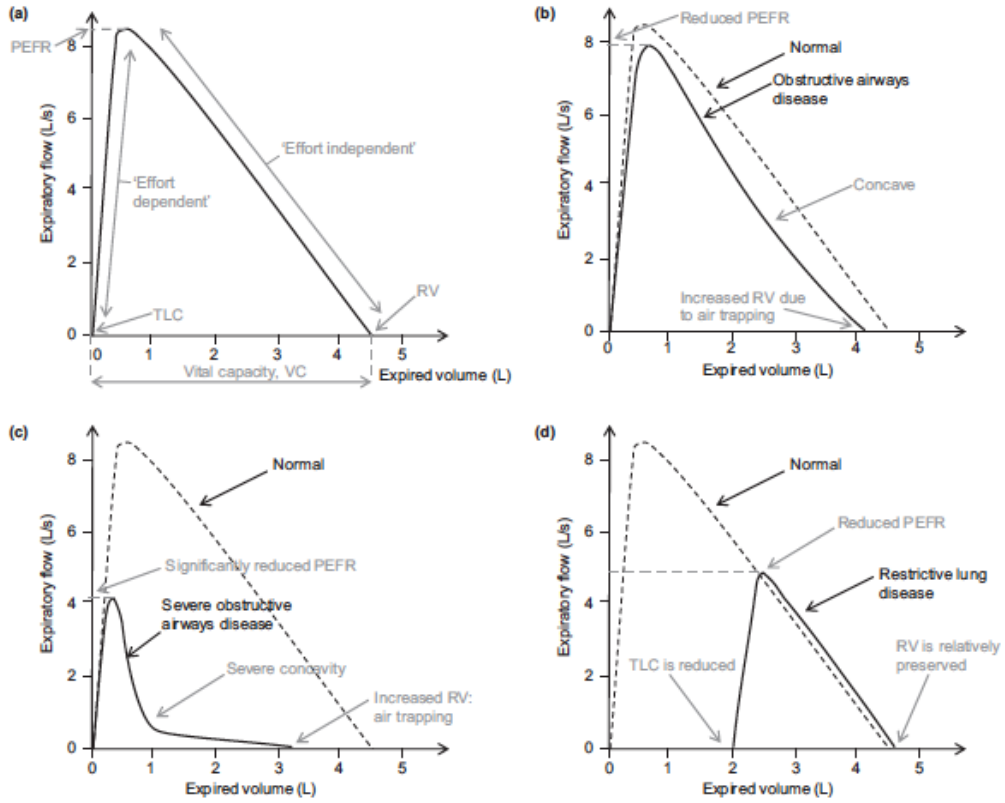


Figure 12.3 Expiratory flow–volume curve: (a) normal; (b) mild obstructive airways disease; (c) severe obstructive airways disease; (d) restrictive lung disease.

Flow volume *loop*

- inspiratory flow vol curve + expiratory flow vol curve
- used if diagnostic uncertainty about location of airway obstruction
- obtained using spirometry
    - pt blows into mouthpiece that records flow + volume
    - exhales maximally then inhales maximally: RV to TLC
    - from TLC exhales with max effort to RV to record FEV1, forced mix expiratory flow rate (25-75%) and FVC
    - normal FEV1/FVC >0.7
    - obstructive: FEV1/FVC <0.7
    - restrictive: FEV1/FVC >0.7 (both FEV1 and FVC ↓)

Pathology

- **obstructive airways disease:**
    - exp portion: ↓PERF; concave; ↑RV
    - insp portion: unaffected
- **restrictive airways disease**
    - exp portion: ↓PEFR, normal appearance of effort independent potion; ↓VC; ↓TLC → right shifted loop
- variable extrathoracic airway obstruction
    - e.g. vocal cord palsy
    - extrathoracic = level above 6th tracheal ring
    - "variable" = airway obstruction moves with Δairway pressure throughout resp cycle
    - lung volumes unchanged
    - insp: lesion pulled into trachea → ↓insp flow
    - exp: lesion pushed out of trachea → exp flow unaffected
- variable intrathoracic obstruction
    - e.g. tumour
    - "intrathoracic" = airway obstruction at or below 6th tracheal ring
    - insp: airway calibre ↑s → insp flow unimpeded
    - exp: airway calibre ↓s → exp flow ↓

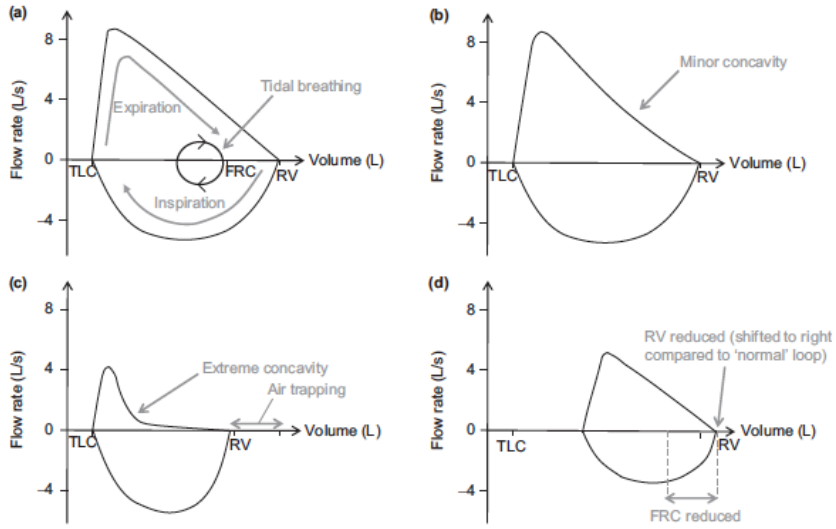


Figure 12.5 Flow–volume loops (a) normal; (b) mild small airways obstructive disease; (c) severe small airways obstructive disease; (d) restrictive lung disease.

Applied respiratory physiology

Discuss the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure

PEEP and IPPV

- **PEEP**
  - +ve airway pressure at end of expiration
  - iPEEP = intrinsic PEEP, autoPEEP, dynamic hyperinflation
- **IPPV:**
  - artificial ventilation which requires insertion of cuffed tube into trachea → prevents gas escape + provides airway protection → tube connected via flexible tubing to ventilator
  - +ve pressure then applied to respiratory system → allowing flow of gas into conducting airways down to alveolus

Physiological effects of PEEP

- **Respiratory effects**
  - **PEEP** and **IPPV**:
    - ↑lung vol + ↑FRC by amount ∝compliance of the system
    - ↑oxygenation via alveolar recruitment
    - ↑lung compliance via alveolar recruitment → ↓WOB
    - may ↑proportion of West Zone 1 physiology (PA > Pa → dead space ventilation)
  - **IPPV**:
    - Major physiological difference from spont vent = range of airway and intrathoracic pressures involved
    - Spont vent: small pressure excursions above and below atmospheric pressure in airway pressure
    - IPPV: much ↑airway pressures in inspiration (15-25mmHg); much of this pressure is transmitted to ↑intrathoracic pressure
    - Less effective in maintaining V/Q ratio: atelectasis; ↓FRC (→ shunting); ↑alveolar + anatomical dead space
    - Risk of barotrauma
    - Long term complications (e.g. ICU): bronchopulmonary dysplasia; O2 induced lung injury; tracheal stenosis; nosocomial lung infection
  - **PEEP**
    - ↑PaO2 in diseased lung
    - ↓CO
    - ↑O2 flux
    - not useful in healthy lungs
- **Cardiovascular**
  - ↑intrathoracic pressure → ↓filling R heart
  - ↓VR due to RA compression → ↓RV filling pressure, ↓LV filling, ↓CO
    - these changes are more marked in hypovolaemia
  - also ↓LV afterload by ↓LV transmural pressure (NB effects in normal pt are minimal)
  - ΔPVR and RV afterload
    - PEEP has variable effects on RV afterload depending on how it changes lung vol
    - low lung vol: PEEP → ↓PVR as PEEP stretches open extra-alveolar vessels
    - high lung vol: PEEP → ↑PVR as PEEP compresses alveolar vessels
- **Peripheral vascular**
  - ↓UO due to ↓CO and ↓RBF + ADH release due to ↓atrial stretch and ANP release
  - ↑hepatic blood flow due to ↑CVP and ↓CO
- **Renal**
  - ↓renal perfusion 2o to hypoperfusion from ↓CO
  - humeral effects: ↓ANP secretion; stimulation of RAAS; ↑vasopressin production → ↓urine output + Na + water retention

Also can consider the effects of general anaesthetic with IPPV

Also can consider the effects of general anaesthetic with IPPV

1. Effect of drugs on resp system

- Volatile anaesthetic agents
  - Dose dependent effects on resp system
  - ↑RR, but with ↓VT

- blunted ventilatory response to hypercapnoea
- IV anaesthetic agents
  - Initial resp stimulation: following induction of anaesthesia → resp stimulation → ↑VT and ↑RR
  - Subsequent resp depression: ↓VT and apnpoea
  - Depression of protective airway reflexes
- Opioids
  - Depression of respiratory centre → ↓RR + blunting of response to hypercapnoea
  - Antitussive
  - Histamine release
  - Chest wall rigidity
- Benzos
  - Depression of resp centre → ↓RR and blunting of response to hypercapnoea
- Depolarising and non-depolarising muscle relaxants
  - Resp muscle paralysis

2. Effect of general anaesthesia on lungs

- airway devices:
  - Laryngospasm, bronchospasm, humidification
  - Loss of physiological PEEP
  - ↑WOB: due to ↑resistance to gas flow (depends on internal radius as determined by Poiseuille)
  - ↑dead space
- lung volumes
  - FRC ↓ due to: supine position + relaxation of chest wall muscles
  - Anaesthesia → FRC < CC → hypoxaemia
- Atelectasis
  - Absorption atelectasis
  - Compression atelectasis: ↓diaphragmatic tone + compression from abdominal contents
- V/Q relationships
  - Low lung vols → closure of small airways (CC encroaching on FRC)
  - ↑tendency for atelectasis
  - PPV → alters intrathoracic pressure, ↓RV preload, changing pulmonary capillary dynamics
  - Impairment of HPV by volatile anaesthetic agents

Note on: Tidal volume

- Must consider respiratory system compliance when setting tidal vol or inspiratory pressures.
- If a tidal vol is set, then the pressure generated for a given vol is reliant upon compliance
- If tidal vol set and compliance is low → then the pressure applied to deliver that vol may be too high and associated with risk of barotrauma. This may also occur if a high inspiratory pressure (>40cmH2O) has been set
- Barotrauma occurs as a result of excessively high alveolar pressures and can manifest as pneumothorax, pneumomediastinum, surgical emphysema, or acute lung injury

Discuss the physiological effects of hypoxaemia, hyper and hypocapnia, and carbon monoxide poisoning

Hypoxia:

- hypoxia = O2 deficiency at the tissues
- O2 delivery = CO x arterial O2 content
  - = HR x SV x (1.34 x Hb x SpO2 + PaO2 x 0.003)
- Conditions that need to be fulfilled for cells to utilize O2 for aerobic metabolism
  a. Adequate PaO2
  b. Adequate O2 carrying capacity (Hb concentration)
  c. Adequate CO and arterial flow
  d. Adequate mitochondrial function
- Hypoxia therefore classified in terms of failure of ≥1 of the following:
  - i) hypoxaemic hypoxia
  - ii) anaemic hypoxia
    - impaired O2 delivery due to low Hb
    - CO poisoning
      - classified as subset of anaemic hypoxia as carboxyHb ↓s the effective amount of Hb in solution
      - CO has 210x affinity for Hb than O2 → CO rapidly displaces O2 from Hb and is liberated slowly
      - No ↑ in resp drive since PaO2 is unchanged
  - iii) ischaemic hypoxia
    - due to impaired CO resulting in impaired O2 delivery
  - iv) histotoxic hypoxia due to impaired tissue oxidative processes → preventing utilisation of delivered O2
    - E.g. cyanide poisoning → inhibits cytochrome oxidate and prevents oxidative phosphorylation

Hypoxaemia

- hypoxaemia = low partial pressure of O2 in blood
- ↓PaO2 and ↓SpO2 = PaO2 <60
- Classified according to aetiology
  - Hypoventilation
    - Leads to ↓PAO2 → ↓O2 partial pressure gradient across alveolar-capillary barrier → ↓PaO2
    - Leads to ↑PaCO2 (VA and PaCO2 are inversely related)
  - Diffusion limitation
    - ↓alveolar surface area
    - ↑alveolar capillary barrier thickness: pulmonary fibrosis; ARDS
    - NB diffusion limitation is rarely a cause of hypoxaemia
  - Shunt
    - Physiological: anatomical; functional
    - Pathological: intracardial; large communicating vessels; intrapulmonary shunts
    - V/Q mismatch

Effects

- Respiratory:

- ↑PaCO2 + ↓PaO2 →
  - Detected by peripheral chemoreceptors (carotid + aortic bodies) →
  - stimulate ventilation via action on carotid and aortic body chemoreceptors →
  - stimulates respiratory centre → significantly ↑minute ventilation
  - hyperventilation stimulated at PaO2 <55mmHg, maximal at PaO2 <30mmHg
- ventilatory response further augmented in presence of hypercapnoea
- NB severe prolonged hypoxaemia has a depressive effect on the respiratory centre → apnoea
- HPV

- Neuro:
  - cerebral acidosis (via anaerobic metabolism) → stimulates central pH receptors → ventilation
- Cardiovascular
  - Systemic vasodilation: ↑CO2, ↓MAP
  - Acidosis + ↑2,3DPG → shift HbO2 dissociation curve to right
- acid base changes
  - Hypoxia → anaerobic metabolism → lactate production → base deficit + ↓HCO3
- Renal
  - ↑EPO and Hct in chronic hypoxia

Physiological causes of early post-operative hypoxaemia

- hypoxaemia = presence of abnormally low pO2 levels in arterial blood
  - differs form hypoxia, which is O2 deficiency at the tissues
  - Hypoxaemia can lead to hypoxia → deranged tissue function
- Normal PaO2 varies with age; estimated via PaO2 = 100 - (age/3) → therefore 75-100
- Causes of early post op hypoxaemia
  - Hypoventilation
    - As per alveolar gas equation
    - Normally MV ↑ linearly with ↑PaCO2, however immediately post op: residual effects of inhaled anaesthetics, opioids, sedative/ hypnotic drugs can ↓this response
    - May have residual NMB
  - Low inspired FiO2 for patient needs
    - ↑VO2 will require ↑DO2 to maintain PaCO2
    - fever, shivering, hypermetabolic states may ↑VO2
  - Diffusion hypoxia
    - Rapid diffusion of nitrous oxide into alveoli at end of NO anaesthetic → dilutes alveolar gas + causes transient ↓PAO2 + PACO2
    - In pt breathing room air can cause arterial hypoxaemia + ↓PaCO2 can ↓resp drive
  - V/Q mismatch/ scatter (shunt vs. dead space)
    - Post op can be due to:
      - Airway collapse (atelectasis) or obstruction
      - R to L shunting
      - Consolidation / aspiration / fluid (pulmonary oedema)
  - Diffusion barrier

	Neurological	**Respiratory**	**Cardiovascular**
↑PaCO2	- Cerebral vasodilation → ↑CBF → ↑ICP - Convulsant at high PaCO2 - CNS depression when >100-150mmHg - Autonomic: ↑SY outflow; ↑sensitivity to PSY tone via ↓AchE activity in acidosis	- Control: ↑CO2 stimulates central + peripheral chemoreceptors → ↑resp drive - Pulmonary vasoconstriction - R shift of OHDC	- Peripheral vasodilation - SY stimulation: ↑HR - Myocardial depression (intracellular acidosis) - Arrhythmogenic *Other* Renal: chronic hypercapnia → renal compensation by retention of HCO3 Endocrine: SY response → ↑s BSL and ↑K
↓PaCO2	Cerebral vasoconstriction → ↓ICP ↑neural excitability at low PaCO2	- Resp depression - L shift of OHDC	Myocardial depression Intracellular alkalosis
CO poisoning Subset of anaemic hypoxia	Headache + confusion Weakness, dizziness, N+V Convulsions, coma, death	- No ↑ in resp drive since PaO2 unchanged - ↓O2 carrying capacity → hypoxaemia	- 210x affinity for Hb than O2 - CO rapidly displaces O2 from Hb - ↓O2 carrying capacity of blood - L shift OHDC - ↓O2 concentration at a given PaO2 → ↓DO2

Discuss the effect of the following on ventilation: • Changes in posture • Exercise • Altitude • Anaesthesia • Ageing • Morbid obesity

Altitude

- Physiological effects of altitude related to:
  - ↓atmospheric pressure
  - ↓temperature
  - ↓relative humidity
  - ↑solar radiation
- Barometric pressure ↓s with distance above the earths surface in an approx exponential manner
  - ↓air pressure → proportional ↓in PO2
  - at 3000m → alveolar PO2 = 60mmHg
  - at 5400 → consciousness lost in unacclimatised individuals
  - Mt Everest summit (8848m) → inspired PO2 only 43mmHg

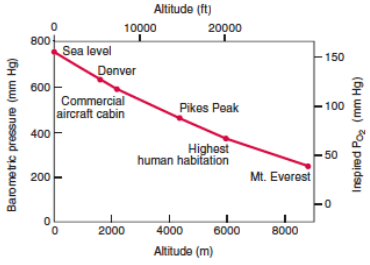


Figure 9-2. Relationship between altitude and barometric pressure. Note that the PO_2 of moist inspired gas is about 130 mm Hg at 1520 m (5000 ft) (Denver, CO) but is only 43 mm Hg on the summit of Mount Everest.

Acclimatization:

- **Respiratory**
  - Hyperventilation
    - ↓PaO2 compensated by ↑minute ventilation
    - most important feature of acclimatization
    - limits of compensation reached on 100% O2 at 13 700m
    - Mechanism

- Hypoxic (↓PaO2) stimulation of peripheral chemoreceptors
- Resulting ↓PaCO2 + alkalosis →
- Compensation is limited by resp alkalosis = Braking effect
- The resp alkalosis stimulates compensatory movement of HCO3 out of CSF + renal excretion HCO3

- OHDC: L shift due to alkalosis → ↑2,3,DPG → R shift curve and return to normal
- HPV
- ↑pulmonary capillary hydrostatic pressures → fluid transudation + pulmonary oedema

- **Cardiovascular**
  - ↑PVR due to HPV
  - ↑SNS outflow → ↑HR
  - ↓SV due to: ↓preload. ↓plasma vol due to pressure diuresis + insensible losses from hyperventilation + ↓relative humidity
  - ↑myocardial work:
    - ↑HR
    - ↑viscosity of blood due to ↑Hct
    - ↑RV afterload from ↑PVR
    - pulmonary oedema
- **Haematological**
  - Polycythaemia
    - Hypoxia → EPO → stimulates BM → ↑RBC concentration → ↑Hb → ↑O2 carrying capacity
    - ↑blood viscosity → ↑risk thrombotic events
  - ↑number of capillaries per unit vol in peripheral tissues
- **CNS**
  - Acute mountain sickness: due to hypoxaemia and alkalosis; headache, fatigue, dizziness, palpitations, insomnia, loss of appetite, nausea
  - Chronic mountain sickness: ill defined syndrome characterised by marked polycythemia, fatigue, severe hypoxaemia

Hyperbaric
- ↑ambient pressure
- 2-3 atmospheres absolute (i.e. 1-2 atmospheres above normal atmospheric pressure)
- ↑partial pressure of gases (↑O2 carried in blood rather than bound to Hb)
  - Boyles and Daltons law: ↑partial pressure in blood; for each 100mmHg ↑ pressure in alveolar, can dissolve 0.3mmHg further O2 in blood
- occurs most commonly in underwater diving: ↑respired gas density, ↑PaO2, ↑WOB, ↑physiological dead space

Hyperbaric O2 therapy
- involves ↑ PO2 to very high level
- useful in:
  - Severe CO poisoning: most of the Hb is bound to CO and therefore unavailable to carry O2. By ↑ inspired PO2 to 3atm in special chambers, the amount of dissolved O2 in arterial blood can be ↑ to about 6ml/100ml and the needs of the tissues can be met without functioning Hb
  - Gas gangrene (clostridial myonecrosis): anaerobic bacteria cannot live in a high PO2 environment
  - Decompression sickness
  - Arterial gas embolism

Define humidity and outline the importance of humidification

Define humidity:
- Humidification describes the amount of water vapour present in air
- Absolute humidity: the mass of water vapour per unit volume of a gas
- Humidity at saturation: the max mass of water which can be present in a gas per unit vol at a specified temperature
- Relative humidity: the ratio of absolute to saturation humidity at a specified temperature expressed as a percentage
- Mechanism:
  - Nose optimised for humidification: septum + turbinates ↑SA and create turbulent flow → ↑contact of air with mucosal surfaces
  - Mouth breathing ↓s humidity of inspired air to 60%
  - Fluid lining airway → acts as heat + moisture exchanger
    - Nasopharynx: relative humidity = 90%
    - 2nd generation bronchi: relative humidity = 100% BTPS = water vapour pressure 44mmHg with absolute humidity = 44g/m3

Importance of humidification:
- Optimal function requires relative humidity >75%
- Inspired gas is normally humidified in the nose and mouth before entering the lower respiratory tract
- Inadequate humidification of inspired gas results in:
  - Acute:
    - Impaired ciliary and mucous belt function
    - Tenacious mucus, crusting of secretions
    - ↑airway resistance and ↓compliance
    - heat loss by evaporation
  - Chronic
    - Squamous metaplasia
    - ↓FRC
    - ↑shunt
    - impaired surfactant function
    - atelectasis

Respiratory – other

Describe the composition of ideal alveolar and mixed expired gases

Outline the non-ventilatory functions of the lungs

Filtration (blood/gas)
Immune (macrophages, IgA)
Reservoir (blood/gas)
Metabolic (ACE, alpha 1 antitrypsin, CHO, protein)
Thermoregulation
Inhalational agents
Taking up drugs
Surfactant synthesis

Filtration (blood/gas)
- Blood: receives all CO; venous embolic filtering; microbe filtering
- Airway: particulate matter filtration: impaction/ sedimentation; nasal hairs, mucous production, muco-ciliary escalator

Immune (macrophages, IgA)
- macrophages in alveoli: destroy + remove small inhaled pathogens
- Secretory IgA: prevents binding of bacteria to nasal mucosa
- Mucus layer: protects large airways; exocytosed by goblet cells in response to noxious stimuli (e.g. chemical, inflammatory, neuronal stimulation)
- Cilia: projections of epithelium that beat rhythmically to propel mucus out of airway

Reservoir (blood/gas)
- Blood: vol ~20% (1L)
  - ↑SNS stimulation → constriction of pulmonary vasculature → mobilisation of blood → ↑CO
  - ↑PAP → ↑pulmonary blood vol by ↓PVR due to recruitment + distension
- Gas:
  - Transmission of air to vocalise, cough
  - FRC = O2 reservoir

Metabolic (ACE, alpha 1 antitrypsin, CHO, protein)
- Vasoactive substances: store of ACE → converts ATI to ATII; breaks down bradykinin
- Protein production
- Removal of proteases via alpha1antitrypsin
- Drug metabolism: NA

Thermoregulation
- warming and humidification

Inhalational agents
- administration route for volatile anaesthetics and bronchodilators

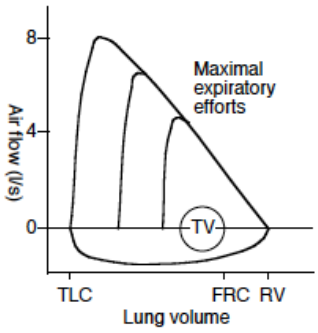
Taking up drugs
- sequestering of drugs
- passive/ active: fentanyl has significant uptake in the lungs
- drugs absorbed in pulmonary circulation are: lipophilic; alkaline (pKa>8)

Surfactant synthesis
- type 2 pneumocytes
- ↓surface tension of alveoli → prevents emptying of smaller alveolar into larger ones and prevents transudation of water into alveolar space

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

CICM - Explain the pathways and importance of the cough reflex L1

- important airway protective reflex
- Major mechanism for clearing foreign material larger than can be carried by the mucociliary elevator
- Involves deep expiration followed by forced expiration against a closed glottis
- **Sensors**
  - Mechanical or chemical irritation of the airway
  - VA afferents have sensitive light touch and corrosive chemical receptors in larynx, trachea, carina, terminal bronchioles, and alveoli
- **Integrators**
  - VA afferents synapse in medulla → trigger autonomic sequence of events
- **Effectors**
  - Epiglottis
  - Abdominal muscles + internal intercostals
  - Vocal cords
- **Stages**:
  - Stage 1: deep inspiration close to vital capacity
  - Stage II: tight closure of the glottis + contraction of expiratory muscles → ↑airway pressure >100mmHg
  - Stage III: forceful expiration through upper airways narrowed by high transmural pressure → high air velocity to dislodge foreign material
- Max expiratory flow rate and velocity which can be generated depends on both expiratory muscle strength and lung vol
  - With normal strength it is limited by lung vol due to airway closure – which makes expiratory flow effort independent as lung vol ↓s



RESPIRATORY PHARMACOLOGY

Describe the pharmacology of anti-asthma drugs, including beta 2 agonists, corticosteroids, anticholinergics, leukotriene antagonists and theophylline

	B2 agonist – e.g. salbutamol	Antimuscarinic e.g. ipratropium	Theophiline	Aminophylline	Leukotriene antag e.g. montelukast
Chem	Synthetic sympathomimetic amine	Synthetic quaternary ammonium compound / Derivative of atropine	methylated xanthine derivative/ methylxanthines	Ethylenediamine salt of theophylline (methylated xanthine derivative)	
Uses	Asthma / COPD / Preterm labour	Asthma / COPD	Asthma / COPD	Asthma / COPD / Heart failure	Asthma/ allergic rhinitis
Pres	2/4/8mg tablets aerosol 100microg/puff dry powder for inhalation 200/400microg solution for nebulization 2.5/5mg/ml clear, colourless solution for injection 1mg/ml salbutamol sulfate	Solution containing 0.25mg/ml for nebulization MDI delivering 200microg/dose (18microg of which is available to patient)	Capsule IV	Tablets: 100/225/350mg Suppositories Clear solution for injection: 25mg/ml aminophylline	Tablets: 10mg
Action	**Beta-adrenergic agonist (B2>B1)** Stimulation of adenylate cyclase in presence of Mg to **↑intracellular [cAMP]** Directly inhibits antigen-induced release of histamine + slow releasing substances of anaphylaxis from mast cells	Competitive **inhibition of cholinergic Rs** on bronchial smooth muscle → blocking bronchoconstrictor action of VA efferent impulses	Non selectively **inhibit phosphodiesterase** → ↓cAMP hydrolysis → ↑intracellular cAMP → smooth muscle relaxation Relaxes respiratory smooth muscle + ↓response of airways to stimuli	**inhibits Mg2+ dependent phosphodiesterase** (responsible for degradation of cAMP) → **↑intracellular [cAMP]** Interferes with influx of Ca2+ into smooth muscle cells + stabilises mast cells by antagonizing action of adenosine	Blocks binding of **leukotriene** D4 to its receptor Alters inflammatory contribution to asthma
CNS		Nil – unable to cross BBB	↓seizure threshold		
CVS	High doses beta-1 actions → +ve inotrope + chronotropic effects Lower doses B2 predominate → ↓PVR → ↓DBP 10-20mmHg	Inh: Nil IV: ↑HR, ↑BP, ↑CO, ↓CVP	↑inotropy, ↑chronotropy arrhythmogenic (VF)	+ve inotrope + chronotrop → ↑CO, ↓SVR → ↓BP ↓LVEDP + pulm cap wedge pressure arrhythmogenic in ↑↑doses	
Resp	Bronchodilation → ↑PEFR + FEV1 Interferes with HPV	bronchodilation		Bronchodilation → ↑VC ↑sensitivity of resp centre to CO2 ↑diaphragmatic contractility IV: inhibits HPV	Bronchodilation
AS	Uterine relaxation: ↓tone gravid uterus; 10% crosses placenta	Large doses: ↓gastric secretion/ saliva		↑RBF, ↑GFR, ↓renal tubular Na absorption → diuretic	
Other	↓plasma [K+] by shift of ion into cells ↑plasma [FFAs] + glucose stimulates insulin release		Natriuresis Hypokalaemia	Hypokalaemia (2o diuretic) Abnormal LFTs Inappropriate ADH secretion	
Toxicity/ SE	Anxiety, insomnia, tremor, sweating, palpitations, ketosis, lactic acidosis, hypoK, postural hypotension, N+V	Nil anticholinergic SE when given inh		GI + CNS disturbance (convulsations post rapid IV administration) Cardiac dysrhythmias	headache
Route/ dose	Inhalaed: 5mg nebs q4hr; MDI 6-12 puffs PRN IV: <0.5microg/kg/min	Inhalaed via nebs 100-500microg q6hr or 1-2 puffs	IV: 4-6mg load then 0.4mg/kg/hr PO	PO: 900mg/ day in divided doses IV: loading dose 5mg/kg → maintenance 0.5mg/kg/hr	PO: 10mg daily
Onset	5-15mins		Variable; peak plasma time 1-2hr		Peak plasma time 3-4hr
Duration	Up to 4hrs		Variable		
A	10% of inhaled dose reaches bronchial tree	Bioavailability PO 3-30%/ inh 5%		PO: bioavailability 90%	PO: 64% bioavailability
D	8-64% protein bound Vd 150L	Vd 0.4L/kg	40% protein bound Vd 0.4L/kg	50% protein bound Vd 0.4-0.6L/kg	>99% protein bound Vd 8L
M	Liver; major metabolite salbutamol 4-O-sulfate	To 8 inactive metabolites	Liver By CYP450 Metabolites: 1,3 dimethyluric acid, 1-methyluric acid, 3-methylxanthine (active)	Liver Demethylation + oxidation 3-methyl xanthine derivative is active	Liver CYP3A4
E	30% unchanged in urine; remainder in faeces + sulfate derivative in urine clearance 28L/hr elimination ½ life 3-5hrs	Urine / faeces Clearance 12L/hr Elimination ½ life 3hrs	Urine ½ life 4-8hr clearance 1.5ml/kg/min	Urine (10% unchanged) Clearance 1ml/kg/min Zero order kinetics – elimination ½ life varies with dose 1st order kinetics: elimination ½ life 8hrs	Faeces (85%) Urine (0.2%) ½ life 3hr clearance 45ml/min
Special points	Potentiate NDNMBs		Low therapeutic index due to arrhythmias	Clearance ↓HF, liver disease, elderly	

	Hydrocortisone	**Prednisolone**	**Methylprednisolone**	**Dexamethasone**
Chem	Glucocorticosteroid	Synthetic glucocorticosteroid		Synthetic glucocorticosteroid
Pres	Tablets: 10/20mg Vials: white lyophilized powder diluted in water → 100mg of hydrocortisone sodium succinate Topical creams	Tablets: 1 / 2.5 / 5 / 20mg Solution for injection 25mg/ml prednisolone acetate drops	Tablets: 2/4/8/16/32 Injectable suspension 20/40/80mg/ml Powder for injection: 40/125/500/1g/2g	Tablets 0.5/2mg/ oral solution IV dexamethasone sodium phosphate 3.8mg/ml Topical creams
Relative dose equivalent	100mg	25mg	20mg	4mg
Route/ dose	IV: 100-500mg 6-8hrly PO: 10-20mg/day	PO: 5-60mg/day	PO/ IV/ IM	PO 1-9mg IV:
Onset	<2hrs	IV: 5min / PO: 1hr	PO: 1-2hr	IV <5min
Duration	8hrs	18-36hr	PO:36hr IM: 1-4weeks	
A	PO: bioavailabilty 50%	PO: bioavailabilty 80-100%		70% protein bound; high uptake in liver, kidney, adrenals
D	Variable protein binding depending on conc Reversibly bound to albumin (20%) + specific corticosteroid binding globulin (70%) Low conc: 90% proteinbound High conc: 60% protein bound Vd 0.3-0.5L/kg according to dose	Reversibly bound to albumin (20%) and specific corticosteroid binding globulin (70%) Low concs: 90% protein bound High conc: 60% protein bound Vd 0.3-0.7L/kg according to dose	Vd 1L/kg	**Liver**
M	Liver To tetrahydrocortisone	Liver Hydroxylation → conjugation	Liver	**Urine** plasma ½ life 4hrs biological ½ life 50hrs
E	Clearance dose dependent: 150-250ml/min Elimination ½ life 2hrs	11-14% unchanged in urine clearance dose dependent: 170-200ml/min elimination ½ life 2-5hrs	Urine Elimination ½ life 3hr Total body clearance 16L/hr	Glucocorticoids antagonize effects of anticholinesterase drugs
Special points	¼ as potent as predisolone	Prednisone and prednisolone are metabolically interchangeable (only latter is active) Conversion of prednisone to prednisolone is rapid + extensive - occurs as 1st pass effect in liver 4x more potent than hydrocort 6x less potent than dex		PO 1-9mg
Relative mineralocorticoid effect	+++	++	+	+

- Uses
  - Adrenocortical deficiency / Allergy / anaphylaxis / Asthma / Autoimmune disorders / Eczema / chemo / immunosuppression post organ tx
- MoA:
  - Anti-inflammatory
  - Inhibits all stages of inflammatory process by inhibiting neutrophil and macrophage recruitment, blocks effects of lymphokines, inhibits formation of plasminogen activator
  - Control rate of protein synthesis: react with cytoplasmic receptors → form complex that directly influences rate of RNA transcription → directs synthesis of lipcortins
  - Act on HPA axis at receptors on plasma membrane
  - Antiallergic, antitoxic, antishock, antipyretic, immunosuppressive properties
- Effects
  - CNS: ↑excitability
  - CVS: ↑contractility, vasoconstriction by ↑number + stimulating action of a1 + b-adrenoceptors
  - mineralocorticoid effect: Na retention; ↑K excretion; ↑urinary Ca2+ excretion
  - ↑GFR; stimulates tubular secretory activity
  - Profound effects on CHO, protein, lipid metabolism
  - Metabolic effects of steroids: Stimulate gluconeogenesis / inhibit peripheral utilization of glucose / redistribution of body fat/ enhanced lipolysis / ↓conversion of amino acids to protein
  - NB glucocorticoids antagonise effects of anticholinesterase drugs

Outline the pharmacological management of bronchosconstriction in acute severe asthma. Include MoA and potential adverse effects: PAST QUESTION

Glucocorticoids

Asthma = chronic disease characterised by airways hyperresponsiveness

- ↑bronchial smooth muscle tone → bronchoconstriction
- ↑mucous production
- Acute attack → gas trapping/ ↑physiological dead space

Acute management

Drug	Action	Dose/ route	MoA	Adverse effects
Supplemental o2	↑FiO2	Inh	↑FiO2 → ↑alveolar O2 in areas undergoing gas exchange	removal of HPV to non-ventilated units → ↑shunt → ↓O2 content of blood
Adrenaline	Non-specific α/β adrenoceptor agonist	1mg neb 1mg IMI	β2 agonist GsPCR → ↑adenylyl cyclase → ↑cAMP → ↓Ca2+ → ↓bronchial smooth muscle tone + ↓mucous production → ↓airways resistance	2o α/β agonist effects systemically α1: peripheral vasoconstriction → ↑BP; cutaneous constriction β1: ↑HR + ↑MRO2 → arrhythmias/ ischameia nausea/ abdo pain ↓insulin → ↑BSL
Salbutamol	Selective β2 agonist (β2>β1)	Dose: 1mg neb; 1mg IMI	non selective βagonist: GPCR → ↑adenylyl cyclase → ↑cAMP → ↓Ca2+ → ↓bronchial smooth muscle tone + ↓secretions	β1: ↑HR, palpitation β2: stimulation of skeletal muscle → tremor/ sweat/ postural hypotension removal of HPV ↓K via intracellular shift N+V ↑BSL
Ipratropium bromide	Anticholinergic	500ug neb	Competitive inhibition of mAChR (M3) on bronchial smooth muscle → GPCR → blockade → ↓phospholipase C → ↓DAG, IP3, ↓Ca2+ ↓bronchoconstriction effect of VA stimulation Inhibit Ach ↑mediator release from mast cells	Minimal Unpleasant taste
Corticosteroids	Anti-inflammatory	Pred 1mg/kg Hydrocort 100-300mg TDS	Bind to intracellular Rs to augment gene transcription/ translation ↓inflammatory mediators: ↓phospholipase A2 production → ↓arachidonic acid → ↓PG/ leukotrienes/ IL production/ ↓capillary leak + oedema	↑BSL (↑gluconeogenesis) Adrenal suppression: inhibition of HPA Loss of subcut CT ↓platelet affregation (↓arachidonic acid → ↓TXA2)
Methylxanthines Theophylline/ aminophylline	Phosphodiesterase III inhibitor	PO: 900mg divided IV: 5mg/kg bolus → 0.5mg/kg/hr	↓breakdown of cAMP → ↑cAMP → ↓Ca2+ → bronchial relaxation Antagonises adenosine effect on mast cells	CVS: +ve inotrope/ chronotrope → ↑CO, ↓SVR → ↓BP Inhibition of HPV → supplement O2 CNS stimulant → ↑risk seizure ↑gastric acid production ↓gastric motility Diuretic: ↓Na+ reabsorption; ↑K excretion
Volatile anaesthetics	Non-adrenergic Non-cholinergic	Titrated	↓smooth muscle tone	
Heliox			↓density + specific gravity than air/ O2 ↓WOB; improves oxygenation	↓inspired O2
MG2+	Ca2+ channel blockade	20mmol IV	Smooth muscle relaxation → CCB → ↓Ba2+	Sedation/ hypocalcaemia

Outline the pharmacology of drugs used to treat pulmonary hypertension including nitric oxide - ACUTE

- PAH is a disease of the small pulmonary arteries
- Defined as: mean PAP >25mmHg at rest and >30mmHg with exercise
- Results in progressive ↑vascular resistance → refractory systemic arterial hypotension, severe hypoxaemia, RV failure, cardiogenic shock, and death
- Pathophys: ↑ in vasoconstrictor substances (thromboxane, endothelin) + ↓ in vasodilatory substances (NO, prostacyclin) + smooth muscle cell proliferation + in situ thrombosis
- Acute PAH is characterised by a sudden ↑ in PAP
    - **Most common causes of acute PAH are: sepsis, massive PE, and ALI**
    - Other causes: idiopathic, LHF, pulmonary or vascular disease, thromboembolism
- Dx: cardiac catheterization
    - This involves establishing the pressures are elevated and then introducing either NO, adenosine, or the prostacycline epoprostenol and measuring the change in pressure.

Treatment

- Aimed at acutely relieving RV pressure overload + preventing RV dysfunction.
- Mechanisms of PAH include:
    - Vascular thromboembolism
    - Endothelial dysfunction
    - Hypoxic vasoconstriction
    - Pulmonary vascular remodeling
    - Smooth muscle proliferation
    - In situ thrombosis
- Goal of rx: avoid acute pulmonary vasoconstriction, halt progression of vascular remodeling, reverse early vascular remodeling

	Nitric oxide	Prostacyclin e.g. iloprost	Endothelin R antagonist e.g. bosentan	Phosphodiesterase type 5 inhib e.g. sildenafil
Chem	NO Inorganic gas Produced by L-arginine	prostacycline analogue		
Uses	Selective pulmonary **vasodilator** in pulmonary HTN ARDS Severe R sided HF	Pulmonary HTN	Pulmonary artery HTN Idiopathic pulmonary fibrosis	Pulmonary artery HTN Erectile dysfunction
Pres	Aluminium cylinders containing NO + nitrogen (pure NO is toxic + corrosive)	Ampule containing 10microg/ml or 20microg/ml	Tablets 62.5mg/ 125mg	
Action	NO produced in vivo by NO synthase 00< diffuses into vascular smooth muscle layer → stimulates ↑expression of guanylate cyclase → ↑ production of cGMP → ↑smooth muscle relaxation ↓platelet aggregation + ↓angiogenesis	Synthetic analogue to prostaglandin PGI2 relaxation of vascular smooth muscle by stimulating production of cAMP + inhibit growth of smooth muscle cells	Endothelin-1 has direct vasoconstrictor effect; stimulates proliferation of vascular smooth muscle, fibrosis, and inflammation Competitive antagonist of endothelin-1 → inhibition of vasoconstriction	Inhibits PDE-5 → ↑cGMP → ↓ pulmonary vasculature relaxation through ↑ sensitivity to NO actions
CNS	No ↑ CBF Physiological role as a NT within ANS + CNS			
CVS	Inhibits platelet aggregation + adhesion	Platelet inhibitor	↓ BP	
Resp	preferentially dilates vessels of well perfused alveoli → improvement in V/Q matching inhibits HPV			
AS				
Other	Insulin release modulated by NO			
Toxicity/ SE	Exposure to 500-2000ppm → methaemoglobinaemia + pulmonary oedema Discontinuation can lead to rebound arterial hypoxaemia + pulmonary HTN Inhaled NO + high FiO2 → oxidized to NO2 (pulmonary toxin) Severe hypotension if dose reaches systemic circulation	jaw pain, cramp; sudden or abrupt withdrawal → rebound pulmonary HTN; caution in bleeding	↑ALT/AST; hepatotoxicity ↓Hb resp infection, headache, oedema, flushing	Headache, flushing, dyspepsia, insomnia
Route/ dose	Inhalation; 5-20ppm	IV/ subcut: teprostinil Inhaled: iloprost 2.5microg → 5microg >q2h	PO: 62.5mg BD then ↑ to 125mg BD	PO 5-20mg TDS IV 2.5-10mg TDS
Onset		Peak serum time <5min	Peak plasma time 3-5hr	<60mins
Duration		30-60min	24hr	2-4hr
A	Highly lipid soluble Diffuses freely across CMs	60% protein bound	50% bioavailability	bioavailability 40%
D		Vd 0.8L/kg	98% protein bound / VD 18L	
M	Combins with oxy-Hb → methaemoglobin + nitrate	Beta-oxidation of carboxyl side chain Metabolite: tetranor-iloprost (inactive)	Liver via CYP3A4 and 2C9 into 3 metabolites	Liver via CYP3A4 and forms active metabolite
E	70% excreted as nitrate in urine <48hrs ½ life <5s	½ life 20-30min urine (70%); faeces (10%)	½ life 5hrs/ total clearance 4L/hr Faeces	½ life: 4hrs Excretion: 80% faeces, 20% urine
Special points	Delivering with ↑FiO2 not recommended → combines with NO to form toxic NO2 Abrupt cessation can cause profound ↓PaO2 + ↑PAP ?downregulationof endogenous NO or guanylate cyclase activity Must monitor [nitrogen dioxide] during treatment CI in neonates know to have circulation dependent on R to L shunt		dose dependent derangement in LFTs → transaminitis; strongly induces CYP3A4 and 2C9 and can therefore ↓efficacy of other drugs metabolised by this pathway avoid use in liver impairment	contraindicated in pts taking nitrates → profound hypotension; headache

Discuss oxygen therapy including methods of delivery, indications and contraindications, physiological and pathophysiological effects

	Oxygen
Chem	O2; present in normal air at 21%
Uses	Hypoxia CO poisoning; anaerobic infections; air-gas embolism; decompression sickness; radiotherapy injury
Pres	colourless, odourless, tasteless drug
Action	- essential role is in the process of oxidative phosphorylation → energy required for cellular function - Elemental O2 is combined with H ions via mitochrondrial cytochrome oxidase; energy released is used for the synthesis of ATP - ↓PVR, ↓mean PAP - Haldane effect: binding O2 displaces CO2
Toxicity/ SE	Dry mucous membranes; Absorption atelectasis Acute lung injury ↓resp drive ↓HR, ↓DBP, ↓CO due to myocardial depression Acute O2 toxicity: altered mood, vertigo, loss of consciousness, convulsion Chronic O2 toxicity: conc >60% for prolonged periods: tracheal irritation, substernal pain; pulmonary congestion, atelectasis, ↓VC Toxicity results from an ↑ production of reactive species such as superoxide anion, singlet O2, and hydrogen peroxide
Route/ dose	Inhaled; ECMO Variable: nasal prongs, face mask Fixed: via closed circuit or fixed intake valves e.g. venture which entrain air at a set proportion
A	Freely permeable through normal alveolar tissue
D	Transported bound to Hb + dissolved
M	Metabolised with glucose to form energy, CO2, H2O Metabolism = 3 step process of glycolysis, krebs cycle, and oxidative phosphorylation
E	As CO2 and water
Special points	