RESPIRATORY ANATOMY AND PHYSIOLOGY

Anatomy of respiratory system
Discuss the structure of the chest wall and diaphragm and the implications for respiratory mechanics
Outline the anatomy of the lower airways

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
What effects do anaesthetic drugs have on the resp system:
Describe the physiological factors that

Mechanics of breathing
Describe the properties of surfactant and relate these to its role in influencing respiratory mechanics
Define compliance (static, dynamic and specific) and relate this to the elastic properties of the lung
Discuss ‘fast’ and ‘slow’ alveoli, including the concept of ‘time constants’
Describe the elastic properties of the chest wall and plot pressure-volume relationships of the lung, chest wall and the total respiratory system
Explain the physics of gas flow and the significance of the relationship between resistance and flow in the respiratory tract
Describe the factors affecting airway resistance and how airway resistance may be measured
Describe closing capacity and its relationship to airway closure and explain its clinical significance and measurement
Describe the work of breathing
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

Pulmonary gas volumes and ventilation
Discuss lung volumes and capacities, their measurement and normal values
Discuss dead space, its measurement and apply the Bohr equation and alveolar gas equation

Pulmonary circulation
Outline the anatomy of the pulmonary and bronchial circulations
Discuss the difference between the pulmonary and systemic circulations
Discuss pulmonary vascular resistance and the control of pulmonary vascular tone

Ventilation/ perfusion relationships
Explain the vertical gradient of pleural pressure and its significance
Discuss normal ventilation-perfusion matching
Discuss West's zones of the lung
Describe the shunt equation
Discuss regional ventilation-perfusion inequalities, venous admixture and the effect on oxygenation and carbon dioxide elimination
Outline methods used to measure ventilation-perfusion inequalities

Diffusive transfer of respiratory gases
Describe the oxygen cascade
Describe the alveolar exchange of oxygen and carbon dioxide
Discuss diffusion capacity and its measurement
CICM - Explain perfusion-limited and diffusion-limited transfer of gases L1

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
Oxyhaemoglobin dissociation curve
Discuss the carriage of carbon dioxide in blood, the carbon dioxide dissociation curve and their clinical significance and implications
O2 and CO2 stores in the body

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

Applied respiratory physiology
Discuss the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure
Discuss the physiological effects of hypoxaemia, hyper and hypocapnia, and carbon monoxide poisoning
Discuss the effect of the following on ventilation: Changes in posture Exercise Altitude Anaesthesia Ageing Morbid obesity
Define humidity and outline the importance of humidification

Respiratory – other
Describe the composition of ideal alveolar and mixed expired gases
Outline the non-ventilatory functions of the lungs
CICM - Explain the pathways and importance of the cough reflex L1

RESPIRATORY PHARMACOLOGY
Describe the pharmacology of anti-asthma drugs, including beta 2 agonists, corticosteroids, anticholinergics, leukotriene antagonists and theophylline
Outline the pharmacological management of bronchoconstriction in acute severe asthma. Include MoA and potential adverse effects: PAST QUESTION
Outline the pharmacology of drugs used to treat pulmonary hypertension including nitric oxide - ACUTE
Discuss oxygen therapy including methods of delivery, indications and contraindications, physiological and pathophysiological effects
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 + 12° ribs + costal cartilages 7-10, xifiternal 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 + ↑ intraabdo 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 → ↑f
- Accessory muscles: sternocleidomastoid + scalenes → elevate sternum + 1° 2 ribs respectively (↓)
- 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 → ↑intraabdominal 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 → ▼faccid 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 → ▼Vt
- 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 alveoli → 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
    - 1° 4 divisions of trachea
    - R main bronchi: 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

- **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 (4 proteins); 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

- **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
    - acidemia (↓pH): carotid bodies only
    - hypotension: ↓perfusion

- **Mechanoreceptors/ stretch receptors**
  - Stimulate apneustic centre (via VA) to ↓inspiratory volumes = Hering-Breuer reflex

#### 2. Respiratory centre

- Located in the medulla + pons

- **Medullary centre:**
  - 4 groups of neurones
  - **Respiratory pattern generation + coordination of voluntary + involuntary demands**
  - Located in reticular formation below floor of 4th ventricle:
    - **1. Dorsal resp group**
      - inspiration
      - Inspiratory UMN 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 $\Delta$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 $\Delta$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:

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

Effects of GA on the lungs
- airway devices:
  ○ Laryngospasm, bronchospasms, inadequate humidification | |
  ○ Loss of physiological PEEP | |
  ○ ↑WOB: due to Treistance 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, bronchospasms, 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 | |
Define compliance (static, dynamic and specific) and relate this to the elastic properties of the lung

Note on Laplace law:

What happens if there is no surfactant?

Surface tension
- surface tension = tendency of a fluid to △its surface area
  - related to attraction between particles in fluid, related to particles outside the fluid
  - described by Laplace’s Law: \( P = \frac{2T}{r} \) where \( P \) is pressure; \( T \) is surface tension; \( r \) is radius
- High surface tension causes 3 problems:
  - 1. \( r \)adius \( \rightarrow \) \( \frac{\Delta V}{\Delta P} \)compliance \( \rightarrow \) \( \frac{1}{\Delta P} \)work to expand alveoli
  - 2. Smaller alveoli empty into bigger alveoli \( \rightarrow \) \( r \)adius \( \rightarrow \) \( \frac{\Delta P}{\Delta V} \)transmural pressure to remain inflated
  - 3. Transudation of interstitial fluid: due to inward force of surface tension \( \rightarrow \) 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. \( \Delta \)surface alveolar tension
  2. stabilization of small alveoli:
  3. prevention of fluid transudation
- mechanism:
  - Surfactant = amphipathic
  - hydrophobic + hydrophilic end \( \rightarrow \) molecules align along air-liquid interface \( \rightarrow \) disrupting attractive bonds between water molecules \( \rightarrow \) surface tension
- Surface tension varies with the reciprocal of the radius of the alveolus
  - Greater effect during expiration (low surface area): 4alveolar radius \( \rightarrow \) surfactant molecules closer together \( \rightarrow \) \( \frac{1}{\Delta P} \)intermolecular repulsive forces \( \rightarrow \) further \( \Delta \)surface tension
  - As alveoli expand \( \rightarrow \) repulsion between DPPC molecules \( \Delta \) as they spread out

What happens if there is no surfactant?
- Lungs would be non-compliant \( \rightarrow \) 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 \( \rightarrow \) 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 = \( \frac{\Delta \text{volume}}{\Delta \text{pressure}} \)
- Inverse of elastance: force at which lung recoils for a given distension
- Respiratory compliance = function of lung and chest wall compliance: \( \frac{1}{C_L} = \frac{1}{C_{lu}} + \frac{1}{C_w} \)
Respiratory System Compliance:

1. Lung Compliance:
   - ∆Volume / ∆Transpulmonary 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:
   - ∆Volume / ∆Transthoracic 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:
   - ∆Volume per ∆pressure when there is no airflow
   - Measurement = slope of the lung pressure/volume curve
     - Results plotted on pressure-volume graph
   - ▲ intrapleural pressure: ▲ lung vol ➔ pressure-volume curve flat ➔ ▲ lung compliance
   - Normal intrapleural pressure (~5 to −10cmH2O): ▲ compliance at FRC

2. Dynamic Compliance:
   - Continuous pressure + volume 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:

<table>
<thead>
<tr>
<th>Lung Compliance</th>
<th>↑ Compliance</th>
<th>↓ Compliance</th>
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<tbody>
<tr>
<td>Aging</td>
<td>Lung size (e.g. neonates)</td>
<td>extremes of lung volume</td>
</tr>
<tr>
<td>Asthma</td>
<td>Surplus posture ➔ FRC</td>
<td>Pulmonary fibrosis; pneumothorax</td>
</tr>
<tr>
<td>COPD</td>
<td>Pneumonia/atelectasis</td>
<td>APO</td>
</tr>
<tr>
<td>Chest Wall Compliance</td>
<td>Collagen disorders</td>
<td>Pulmonary HTN</td>
</tr>
<tr>
<td>Obesity</td>
<td>Pregnancy</td>
<td>Kyphoscoliosis ➔ ↑ chest wall rigidity</td>
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<tr>
<td>Prone position</td>
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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 of 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
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
  - pro RR proportion of Vt, 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

**Resistance**
- airways resistance = resistance caused by air moving through the airways
  - Airway resistance = ∆P/ Q
    - ∆P = 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 5h generation → rapidly ↓s with each division thereafter due to ↑total cross sectional area

**Types of flow**
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 Hagen-Poiseille equation
  \[ R = \frac{8\eta L}{\pi r^4} \]
- Therefore resistance is:
  - proportional to viscosity of gas, length of tube
  - inversely proportional to radius
  - independent of density
- also proportional to velocity: \[ P = k x v \]
  - \( k \) = constant, \( v \) = velocity (flow rate)
- As length + viscosity remain constant \( \Delta r \) (airway caliber)
  - intramural radius: oedema, \( \tau \) mucous, wall hypertrophy
  - smooth muscle tone: bronchospasm (\( \tau \)), connective tissue loss, B2 agonist (\( \tau \))
  - external compression: tumour, haemorrhage, PTX, dynamic airways compression with forced expiration

Turbulent flow
- gas movement disorganized \( \rightarrow \) formation of eddies \( \rightarrow \) resistance
- occurs in large airways: nose, pharynx, larynx, trachea
- resistance in turbulent flow dependent on flow rate
- Factors that \( \rightarrow \) turbulent flow
  - density
  - minimal contribution from viscosity
  - \( \Delta \) with \( \Delta \) vessel radius; depends on degree of turbulence
  - RR: \( \tau \) gas velocity \( \rightarrow \) turbulent flow in large bronchi
  - upper airway obstruction \( \rightarrow \) \( \tau \) velocity around obstruction

Transitional flow
- occurs through most of the airways
- air flow = mixture of laminar + turbulent flow
- due to multiple bifurcations + \( \Delta \) 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 \( \rightarrow \) \( \tau \) flow rate
- Lung vol \( \rightarrow \) \( \tau \) 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: \( CC < FRC \) \( \rightarrow \) no airway closure during normal tidal breathing
- If \( CC > FRC \) \( \rightarrow \) dependent airway closure + gas trapping during normal tidal breathing \( \rightarrow \) V/Q mismatch. Causes:
  - \( \Delta \) FRC
  - \( \tau \) CC; \( \tau \) 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 \( \rightarrow \) expired \[ N2 \] during slow expiration measured with rapid N2 analyser \( \rightarrow \) plotted against vol of gas expired
  - 4 phases:
    - phase I: 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: \( \tau \) [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 = \(-7\)ml/kg or 10% of vital capacity
  - normal values:
    - 15-20% of VC
    - 10% of FRC in young adult
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

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

**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 (T 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 26.2** 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 parenchyma 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 + 1-2 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:
    o Ppl = Pel
    o PA = Patmospheric

Expiration
- Passive during quiet breathing: diaphragmatic relaxation + elastic recoil of the lung parenchyma to return the lung to FRC
- Thoracic vol 4s → Ppl falls to ~5cmH2O
- Elastic recoil of the lung causes it to collapse until PA = Patmospheric
  - Abdominal wall muscles (rectus abdominis, 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. VT: 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
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 ↓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

Physiological consequences of ↓FRC by 1L in adult (40-50% decrease)
- PEEP:
  - Emphysema: lung elastic tissue destroyed → ↓ inward elastic recoil
  - ↑age: ↑quantity of lung elastic tissue
  - asthma: air trapping + high intrinsic PEEP
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. ↓ PaO2

Changes to FRC that occur with anaesthesia
- FRC = vol of air in the lungs at the end of expiration when elastic recoil of lungs = outward force of chest wall + diaphragm tone
- FRC = ERV + RV (in erect pt = 30ml/kg → ~3000mls)

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. posture:
    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:
    i. 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:
       - \[ C_1V_1 = C_2V_2 \]
       - Before equilibration:
         - \[ C_1 = \text{initial concentration in spirometer} \]
         - \[ V_1 = \text{initial vol of spirometer} \]
       - After equilibration:
         - \[ \text{total vol} (V_2) = V_1 + \text{FRC} \]
         - \[ C_2 = \text{amount of He in spirometer (lower)} \]
         - \[ \text{He cannot diffuse across he alveolar capillary barrier to the amount of He before equilibration} \]
       - \[ C_1V_1 = C_2 (V_1 + \text{FRC}) \]
       - \[ C_1 = C_2 (V_1 + \text{FRC}) \]
       - \[ \text{FRC} = V_1 x (C_1-C_2) / C_2 \]

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: \[ P x V = \text{constant} \]
   - 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
3. Physiological

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 caliper: (bronchoconstriction ↓VDanat; bronchodilation ↑VDanat)
  - Age/ size
- Measurement: Fowlers method:
  - Inspiration of 100% O2 from RV → expired [N2] during slow expiration measure expired
  - 4 phases:
    - I: 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 + VDalv: VDalv can be calculated if VDphys (Bohr) + VDanat (fowlers) are known

3. Physiological
- VDphys = anatomical + alveolar dead space
- Normal value: 2-3ml/kg i.e. 30% of VT
- Calculated using Bohr equation
  - calculates the ratio of physiological dead space to tidal vol:
    - \[ \frac{V_D}{V_T} = \frac{Paco_2 - Pco_2}{Paco_2} \]
    - 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
- \[ PAO_2 = FiO_2 - \frac{(Paco_2 \times R)}{R} \]
- 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 → divides into lobar + segmental to supply each lobe + bronchopulmonary segment of the lung
- Pulmonary capillaries
  - Line walls of alveoli to form a mesh
  - Diameter: 7-10μm
  - 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:

<table>
<thead>
<tr>
<th>Systemic circulation</th>
<th>Pulmonary circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy:</strong> thick walled arteries – smooth muscle + elastic</td>
<td>2 pulmonary arteries; 4 pulmonary veins</td>
</tr>
<tr>
<td>Abundant autonomic (esp. SY) innervation</td>
<td>Thin walled capillaries</td>
</tr>
<tr>
<td>Highly regulated by ANS</td>
<td>Extensive ANS innervation, but less effect</td>
</tr>
<tr>
<td><strong>Function:</strong> 1. Offloads O2 / loads CO2</td>
<td>1. Loads O2 and unloads CO2</td>
</tr>
<tr>
<td>2. Acid/base</td>
<td>2. Acid/base via CO2</td>
</tr>
<tr>
<td>3. Metabolic: absorbs + delivers nutrients; toxins, drugs; excretes waste products</td>
<td>3. Filters blood</td>
</tr>
<tr>
<td>4. Produces factors for coagulation</td>
<td>4. Metabolic: activates AT1, inactivates bradykinin, takes up 5HT</td>
</tr>
<tr>
<td>Or…</td>
<td>Or…</td>
</tr>
<tr>
<td>Filtration</td>
<td>Filtration</td>
</tr>
<tr>
<td>Immune</td>
<td>Immune</td>
</tr>
<tr>
<td>Reservoir (blood)</td>
<td>Reservoir (blood)</td>
</tr>
<tr>
<td>Metabolic: ACE, alpha1-antitrysin</td>
<td>Metabolic: ACE, alpha1-antitrysin</td>
</tr>
<tr>
<td>Thermoregulation</td>
<td>Thermoregulation</td>
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<tr>
<td>Inhalational agents in</td>
<td>Inhalational agents in</td>
</tr>
<tr>
<td>Take up drugs</td>
<td>Take up drugs</td>
</tr>
<tr>
<td>Synthesis (surfactant)</td>
<td>Synthesis (surfactant)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pressure and flow</th>
<th>Systemic circulation</th>
<th>Pulmonary circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressures 4/8 MAP 100mmHg</td>
<td>25/8 MAP 15mmHg</td>
<td></td>
</tr>
<tr>
<td>Pressure drop inlet-outlet</td>
<td>Blood flow 5L/min (i.e. entire CO) achieved with MPAP 15mmHg</td>
<td></td>
</tr>
<tr>
<td>Atrial pressure</td>
<td>Right 2mmHg</td>
<td></td>
</tr>
<tr>
<td>Pressure drop inlet-outlet</td>
<td>Left 5mmHg</td>
<td></td>
</tr>
<tr>
<td>Major point of resistance</td>
<td>Evenly spread across pulmonary circulation</td>
<td></td>
</tr>
<tr>
<td>Blood flow</td>
<td>Continuous (windkessel)</td>
<td></td>
</tr>
<tr>
<td>Nature of flow</td>
<td>Pulsatile</td>
<td></td>
</tr>
<tr>
<td>Factors affecting flow and resistance</td>
<td>Determined primarily by arterioles affected by: 1. Hypoxia and hypercarbia (4PH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Resistance at high lung vol (compression of alveolar caps) + low lung vol (narrowing of extra-alveolar vessels)</td>
<td></td>
</tr>
</tbody>
</table>
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 \( \rightarrow \) thin walled vessels; optimal for gas exchange
      ii. \( \downarrow \) pressure \( \rightarrow \) likelihood of transudation into the alveoli (pulmonary oedema)
      iii. Pulmonary capillary pressures = hydrostatically dependent \( \rightarrow \) zones 1-4
   b. Pressures around pulmonary blood vessels
      i. Pulmonary capillaries surrounded by gas \( \rightarrow \) \( \downarrow \) support from endothelium \( \rightarrow \) 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 Ohm's law:
  - Pressure difference across vascular system = total flow \times\ text{vascular resistance}. Therefore
  - Vascular resistance = pressure difference / total flow. Therefore
    - \( \text{PVR} = \text{MPAP} - \text{PCWP} / \text{CO} = 2\text{mmHg/L/min} \)
    - \( \text{SVR} = (\text{MAP} - \text{mean RA pressure}) / \text{CO} = -20\text{mmHg/L/min} \)
  - Typical values
    - \( \text{MAP} = 100\text{mmHg} \)
    - Mean RA pressure = 2mmHg
    - \( \text{CO} = 5\text{L/min} \)
    - \( \text{MPAP} = 15\text{mmHg} \)
    - \( \text{PCWP} = 5\text{mmHg} \)

Determinants of PVR:
1. Pulmonary artery pressure
   a. \( \uparrow \text{MPAP} \rightarrow \downarrow \text{PVR} \) due to 2 mechanisms:
      i. Recruitment: \( \uparrow \text{pressure} \rightarrow \text{collapsed pulmonary capillaries reopened} \)
      ii. Distension: \( \uparrow \text{vascular pressure} \rightarrow \text{open capillaries further distended} \)

2. Lung volume
   a. Functionally: 2 different types of pulmonary blood vessels:
      i. Alveolar capillaries: little CT; \( \uparrow \text{alveolar pressure} \rightarrow \text{compression} \)
      ii. Extra-alveolar vessels: not exposed to alveolar pressure; can be pulled open by radial traction of surrounding parenchyma
   b. \( \Delta \text{shape of alveolar and extra-alveolar vessels account for \text{APVR at different lung volumes} } \)
      i. FRC: PVR lowest
      ii. \( \uparrow \text{lung vol:} \) \( \downarrow \text{PVR}\) \( \rightarrow \) blood flow resistance within alveolar capillaries (stretched \( + \) distorted); extra-alveolar vessels contribute little resistance to blood flow as \( \uparrow \text{lung vol} \rightarrow \uparrow \text{radial traction} \rightarrow \downarrow \text{resistance} \)
      iii. \( \downarrow \text{lung vol:} \) \( \uparrow \text{PVR} \) due to resistance to flow in extra-alveolar vessels (narrow)

3. HPV
   a. response to hypoxia \( \rightarrow \) acts to \( \downarrow V/Q \text{mismatch} \)
   b. \( \downarrow \text{Pao2} \rightarrow \text{vasoconstriction} \rightarrow \uparrow \text{local vascular resistance} \rightarrow \text{redirect blood flow to better ventilated alveoli} \)
   c. mediated by NO (potent arteriolar vasodilator released when PAO2 <70mmHg) + O2 sensitive K channels (stimulated by alveolar hypoxia) \( \rightarrow \) opening of Ca2+ channels \( \rightarrow \text{vasoconstriction} \)
   d. Examples of HPV:
      i. Foetal circulation
      ii. Pneumonia
      iii. High altitude
   e. Cardiogenic pulmonary oedema: due to gravity there is \( \uparrow \text{pressure at lung bases} \rightarrow \text{transudation} \rightarrow \text{HPV} \rightarrow \text{upper lobe diversion} \)
   f. Factors that modify HPV
      i. \( \uparrow \text{by:} \) acidosis, hypercapnia
      ii. \( \downarrow \text{by:} \) 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 \( \rightarrow \text{activate cGMP} \rightarrow \downarrow \text{intracellular Ca2+} \)

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

<table>
<thead>
<tr>
<th>Apex</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveoli in apex larger than base</td>
<td>Basal alveoli</td>
</tr>
<tr>
<td>- Traction from interstitium</td>
<td>- More compressed due to effect of gravity</td>
</tr>
<tr>
<td>- Maximally inflated</td>
<td>- Hardly inflated</td>
</tr>
<tr>
<td>- Pintrapl = -10cmH₂O</td>
<td>- Pintrapl = -2cmH₂O</td>
</tr>
<tr>
<td>- On flatter part of compliance curve – point A</td>
<td>- on steep part of compliance curve – point B</td>
</tr>
</tbody>
</table>

**During inhalation**
- Less expansion due to 4-compliance
  - -10cmH₂O → -13cmH₂O (flat compliance)
  - small Δvol → flow
- More expansion due to 4-compliance
  - -2cmH₂O → -5cmH₂O
  - Larger Δvol → flow i.e. better 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 ↑ 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
  - 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)**
Effect of V/Q mismatch on O2 transfer + CO2 elimination

A lung with V/Q inequality isn’t able to transfer as much 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

West’s 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 pressure

1. Zone 1 (apex): PA > Pa > Pv
   - Alveolar pressure > arterial pressure
   - Alveolus compresses capillary → no blood flow occurs
   - Ventilation but no perfusion = dead space; V/Q ratio
   - Occurs when:
     - Alveolar pressure high: PEEP
     - Arterial pressure low: shock, hypovolaemia
     - NB doesn’t exist in normal lungs as PAP

2. Zone 2: Pa > PA > Pv
   - Arterial pressure > alveolar pressure > venous pressure
   - Blood flow occurs intermittently during the cardiac cycle: systolic Pa > PA, but diastolic Pa is < PA
   - Alveolar pressure acts asStarling resistor
   - Flow is proportional to the Pa-PA gradient
     - When Pa falls below PA (e.g. diastole) then no blood flow occurs

3. Zone 3 (base): Pa > Pv > PA
   - Arterial pressure > venous pressure > alveolar pressure
   - Due to gravity
   - Blood flow contiguously throughout cardiac cycle
   - Flow is proportional to the Pa – Pv gradient

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%)

\[
\frac{Q_s}{Q_T} = \frac{C_o_2 - C_v O_2}{C_o_2 - C_t O_2}
\]

where \( Q_s \) = shunt blood flow;
\( Q_T \) = cardiac output
\( C_o_2 \) = pulmonary end capillary O2 content \( \Rightarrow \) assumed to be 100% saO2
\( C_t O_2 \) = arterial O2 content \( \Rightarrow \) calculated from ABG
\( C_v O_2 \) = mixed venous O2 content \( \Rightarrow \) 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 = vol of O2 in ventilated capillary + vol of O2 in shunt capillaries
   - written mathematically: \( QT \cdot CaO_2 = (QT – Qs) \cdot CcO_2 + Qs \cdot CvO_2 \)
   - rearranging gives: \( Qs \cdot (CcO_2 – CvO_2) = QT \cdot (CcO_2 – CaO_2) \)

   which gives the shunt equation:

Physiological consequences of a shunt:

1. Effect on CO2
   a. No CO2 can diffuse from shunted blood \( \Rightarrow \) CO2 might be expected to \( \uparrow \), however:
   b. In spont breathing pt \( \Rightarrow \) \( \uparrow \)PaCO2 \( \Rightarrow \) resp drive \( \Rightarrow \) alveolar ventilation = no \( \uparrow \) in \( PaCO_2 \) unless:
      i. Shunt fraction is large and
      ii. Pt unable to \( \uparrow \) alveolar ventilation to compensate

2. Effect on O2
   a. \( PaO_2 \) is \( \propto \) shunt fraction
   b. As shunted alveoli = ventilated but not perfused \( \Rightarrow \) true shunt is unresponsive to \( \uparrow \)FI02
   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 \( \propto \) perfusion
      ii. \( PaO_2 \) will \( \propto \) 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 \( TPAO2 \) \( \Rightarrow \) PaO2 will not improve
      ii. May get small \( \uparrow \) in \( PaO_2 \) 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 \( \Rightarrow \) inefficient gas exchange
  - Excessive ventilation \( \Rightarrow \) excessive work
  - Inadequate ventilation \( \Rightarrow \) inadequate gas exchange

Normal lung:

- Perfusion = 5L/min; alveolar ventilation = 4L/min \( \Rightarrow \) normal V/Q ratio = 0.8
- Considerable regional variation

Distribution of ventilation

- In erect pt at FRC: ventilation bases \( \propto \) apex due to gravity
  - Weight of lung parenchyma \( \Rightarrow \) 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 \( \Rightarrow \) Pintrapl by 3cmH2O throughout pleur
    - Inspiration: \( \Delta \) pressure \( \Rightarrow \) \( \Delta \) vol at base \( \Rightarrow \) basal alveoli compliance + ventilation
- 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 = 4pressure circulation \( \Rightarrow \) gravity has \( \uparrow \) effect pulmonary capillar
- Difference in pulmonary cap pressure between apex + base \( \Rightarrow \) equivalent to hydrostatic P exerted by column of blood
- Distance from apex to base = 30cm \( \Rightarrow \) 30cmH2O

V/Q ratios

- V and Q: bases \( \propto \) apex due to gravity
- Gravity has greater effect on perfusion than on ventilation
- V/Q ratio \( \propto \) from bottom to top of lungs
  - Base: V/Q ratio = 0.6 (perfusion > ventilation)
  - Apex: V/Q ratio \( \propto \) (ventilation > perfusion)
V/Q mismatch

- Occurs when V/Q ≠ 1
  - V/Q > 1 (dead space)
    - Causes: PE; RV SV (hypovolaemia, RV infarction, pericardial tamponade)
  - V/Q 0-1 (V/Q scatter)
    - perfuncted but not ventilated
      - Causes: pneumonia, atelectasis; ARDS; airway obstruction; COPD; one lung ventilation
    - Poorly V alveoli with normal Q have $PAO_2$: $FiO_2$ → $PAO_2$ → $PAO_2$-PaO2 gradient across alveolar-capillary barrier
  - V/Q = 0 (shunt)
    - Mixed venous blood entering systemic circulation without being oxygenated
      - $PaO_2$

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
  - Alveoli with $1/V/Q + 1/P_02$ → substantial $O_2$ concentration of blood leaving poorly ventilated alveoli.
  - Alveoli with a $V/Q$ and $P_02$ → produce only a small $\uparrow$ in O2 concentration
- CO2 elimination is less affected by V/Q mismatch
  - more linear relationship between PCO2 and $[CO_2]$ + importance of $PaCO_2$ in determining ventilatory drive
  - Any $\uparrow$PaCO2 $\Rightarrow$ in ventilation to normalize $PaCO_2$
  - A total ventilation $\Rightarrow$ elimination of CO2 from both well + poorly ventilated alveoli so $PaCO_2$ 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 $PO_2$ and pulmonary end capillary $PO_2$
- 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 $\Rightarrow$ 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
    - $Ventilation$: 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

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. $PO_2 = PB \times FiO_2$
   - b. $O2$ is 21% at sea level
   - c. $PO_2 = 760/mmHg \times 0.21 = 160/mmHg$
2. **Humidified tracheal gas**: 149mmHg
   - a. Gas humidified during inspiration
   - b. heated to 37°C with 100% relative humidity
   - c. $P_{O_2,inspir} \text{ at } 37°C = 47/mmHg$
   - d. Boyle’s Law:
     - i. $PO_2 = P_b - P_{SVP_{water}} \times FiO_2$
     - ii. $PO_2 = 0.21 \times (760 - 47)$
     - iii. $PO_2 = 150/mmHg$
3. **Alveolar gas**: 100mmHg
   - a. $P_aO_2$ mainly dependent on $FiO_2$, $PB$, and alveolar ventilation – as described by the AGE
   - b. $P_aO_2 = FiO_2 (P_b - P_{SVP_{water}}) - PaCO_2 / R$
   - c. Or $PAO_2 = P_aO_2 - PaCO_2 / R$
   - d. $P_aO_2 = 150 - 40 / 0.8$
   - e. $P_aO_2 = 100/mmHg$
4. **Arterial blood: normal $PaO_2 = 100/mmHg**
   - a. The difference in $PAO_2$ and $PaO_2$ = A-a gradient
   - b. A-a gradient = $PAO_2 - PaO_2 = (PaCO_2 / R) - PaO_2$
   - c. Step reduction in PO2 between alveolus and systemic arteries. Due to 3 factors:
     - i. Diffusion across alveolar-capillary barrier (if diffusion limited)
The diffusion of molecules across a semi-permeable membrane

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

Discuss diffusion capacity and its measurement

<table>
<thead>
<tr>
<th>Diffusion capacity is a measure of the rate at which a gas can diffuse across the blood gas barrier</th>
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<tbody>
<tr>
<td><strong>DL = V_{gas} / (P_1 - P_2)</strong></td>
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The diffusion of molecules across a semi-permeable membrane is governed by **5 factors**:

1. **Fick's law**: rate of diffusion is directly \( \propto \) 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

2. **Graham's law**: rate of diffusion is inversely \( \propto \) square root of MW

**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 \( \propto \) solubility of the gas, and inversely \( \propto \) square root of MW
    - Surface area: alveoli have TSA \( \rightarrow \) allows max exposure of blood to gas within alveoli
    - Membrane thickness: rate of diffusion inversely \( \propto \) membrane thickness
    - MW of gas: CO2 and O2 are small, uncharged molecules
    - Solubility: CO2 20x more soluble than O2 in blood \( \rightarrow \) much faster rate of transfer
  - **Concentration gradient**
    - Molecules will diffuse down concentration gradient
    - Cone 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
3. **Surface area**: (directly \( \propto \)) Affected by:
   - Parenchymal volume: body size, pathology; V/Q mismatch; pulmonary blood volume; posture

4. **Membrane thickness**: (inversely \( \propto \))

5. **Solubility**: (directly \( \propto \))

**Measurement of diffusing capacity**

- CO
  - Diffusion limited
  - Normal blood concentration is nearly zero
  - \( DL = \frac{V_{\text{gas}}}{(P_1-P_2)} \)
  - Vital capacity breath of 0.3% CO \( \rightarrow \) held for 10s then exhaled \( \rightarrow \) 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 \( \downarrow \) in:
  - Thickened alveolar-capillary barrier: interstitial lung disease
  - \( \downarrow \) surface area: emphysema, PE, lobectomy/pneumonectomy

- Factors that \( \uparrow \) diffusion capacity
  - Exercise (due to pulmonary vasodilation and alveolar recruitment)
  - Blood-gas barrier area: lung size, alveolar recruitment, capillary distension
Diffusion through tissues is described by Fick’s law

- **Fick’s law of diffusion**
  - $\Delta P = \text{pressure gradient across membrane}$
  - $A = \text{area of membrane}$
  - $S = \text{solubility of substance}$
  - $T = \text{thickness of membrane}$
  - $MW = \text{molecular weight of substance}$

The rate of diffusion of a gas through a tissue is:

- **directly $\propto$**:
  - surface area of the barrier
  - solubility of the gas
  - concentration gradient (partial pressure difference)

- **inversely $\propto$**:
  - 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
    - $\downarrow$diffusion rate will not $\downarrow$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**
  - Pulmonary fibrosis: thickening of alveolar-capillary barrier → $\downarrow$rate of diffusion
  - Exercise: $\downarrow$CO → $\downarrow$RBC transit time
  - Altitude: $\downarrow$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 $\propto$ 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 (= Hufner’s 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 = Hufner’s 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

Determinant 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
- 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 – 2nd 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
    - 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 ↓ 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:
  - In arterial blood, O2 sats are usually >97%. This corresponds to a PO2 of 100mmHg and 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
  - 4 affinity of O2 for Hb → O2 easily offloaded (i.e. for a given PO2, SaO2 is lower)
  - Causes: ↑PCO2; acidosis; ↑2, 3, DPG; exercise; ↑temp; HbS
  -Bohr effect: a CO2 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
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 mitochondria
- non-polar
- small molecule
- able to diffuse across membranes
- Blood muscle transport CO₂ from site of production (active tissue) to site of elimination (lungs)

Role of Hb
- main O₂ carrying compound
- Bohr effect: 4pH or 7PaCO₂ → 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 t
   - 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
     - CI shift: maintains electroneutrality (Hamburger effect): mediated by CI/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

**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 7CO₂ 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 curve 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 to CO₂ content ↑s due to fraction of dissolved CO₂

**How is the Haldane effect related to the Bohr effect?**
- **Bohr effect**: 4pH or 7PaCO₂ shifts P50 of Hb to 4PO₂ values i.e. shifts OHC to right ⇒ Hb having a 4O₂ 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 4s (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**
- ↑TPR
- cerebral vasodilatation
- placental vasodilatation

**Effects of hypercapnia**
- cerebral vasoconstriction
- ↑ICP
- ↑CNS SY outflow
Oxygen

- CO2 is produced in the mitochondria during the citric acid cycle as a product of aerobic metabolism
  - Entry of substrate (CHO, FFA, ketone, aa) 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

CO2:

- 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%)

Measurement

Spriometry 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)
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 → expiratory volume-time graph
- 2 parameters measured: FEV1 and FVC. These are compared with predicted values based on normal pts matched for age, gender, height

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 bronchodilator
      → improvement in FEV1 of 400ml = 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 20 to dynamic airways compression)
  - dynamic airways compression
    - starting resistor mechanism
    - during forced expiration → lung vol/ airway (4intra-airway pressure)
    - when intrapleural pressure > airway pressure → airway compression → calibre of airways
    - 4calibre → 4resistance (Hagan-Poiseuille)
- Normal curve:
  - Max inspiration to 80ml/kg (TLC)
  - At TLC → minimal airways resistance due to radial traction on airways
  - Max driving pressure due to 4elastic 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 4calibre of airways
- ↓PEFR due to 4airways resistance at any vol
- concave loop: compression of major airways with premature airways closure + rapid 4flow rate; fast then slow alveolar emptying
- FEV1/FVC <0.7
- ↑RV due to gas trapping

Restrictive 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
**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: ↓PEFR; 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 ↓
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 of 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)
  - ↓PVR 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*

1. Effect of drugs on resp system
   - Volatile anaesthetic agents
     - Dose dependent effects on resp system
     - ↑RR, but with ↓VT
Respiratory Anatomical and Physiological Effects

- **IV anaesthetic agents**
  - Initial resp stimulation: following induction of anaesthesia → resp stimulation → ↑VT and ↑RR
  - Subsequent resp depression: ↓VT and apnoea
  - Depression of protective airway reflexes

- **Opioids**
  - Depression of respiratory centre → ↓RR + blunting of response to hypercapnoea
  - Antitrussive
  - Histamine release
  - Chest wall rigidity

- **Benzos**
  - Depression of resp centre → ↓RR and blunting of response to hypercapnoea
  - Antitussive
  - Histamine release
  - Chest wall rigidity

- **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 Treasistance 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:
  o i) hypoxaemic hypoxia
  o ii) anaemic hypoxia
    • impaired O2 delivery due to low Hb
      • CO poisoning
  o iii) ischaemic hypoxia
    • due to impaired CO resulting in impaired O2 delivery
  o 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
  o Hypoventilation
    • Leads to ↓PAO2 → ↓O2 partial pressure gradient across alveolar-capillary barrier → ↓PaO2
    • Leads to ↑PaCO2 (VA and PaCO2 are inversely related)
  o Diffusion limitation
    • ↓alveolar surface area
    • ↑alveolar capillary barrier thickness: pulmonary fibrosis; ARDS
    • NB diffusion limitation is rarely a cause of hypoxaemia
  o Shunt
    • Physiological: anatomical; functional
    • Pathological: intracardial; large communicating vessels; intrapulmonary shunts
    • V/Q mismatch

Effects

- Respiratory:
Physiological causes of early post-operative hypoxaemia

- Hypoxaemia = presence of abnormally low PaO2 levels in arterial blood
  - differs form hypoxia, which is O2 deficiency at the tissues
  - Hypoxia 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 ↑his response
    - May have residual NMB
  - Low inspired FiO2 for patient needs
    - ↑VO2 will require ↑DO2 to maintain PaO2
    - 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

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑PaCO2</td>
<td>↑Cerebral vasodilation → ↑CBF → ↑ICP</td>
<td>- Peripheral vasodilation</td>
</tr>
<tr>
<td></td>
<td>↑CNS depression when &gt;100-150mmHg</td>
<td>- SY stimulation: ↑HR</td>
</tr>
<tr>
<td></td>
<td>Autonomic: ↑SY outflow; ↑sensitivity to PSY tone via ↓AChE activity in acidosi</td>
<td>- Myocardial depression (intracellular acidosis)</td>
</tr>
<tr>
<td></td>
<td>to PSY tone via ↓AChE activity in acidosis</td>
<td>- Arrhythmogenic</td>
</tr>
<tr>
<td></td>
<td>↑respiratory drive</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>↑Pulmonary vasoconstriction</td>
<td>Renal: chronic hypercapnia → renal compensation by</td>
</tr>
<tr>
<td></td>
<td>↑ R shift of OHDC</td>
<td>retention of HCO3</td>
</tr>
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<td></td>
<td></td>
<td>Endocrine: SY response to ↑s BSL and ↑K</td>
</tr>
</tbody>
</table>

| CO poisoning | Cerebral vasocstriction → 4ICP | Myocardial depression |
| Sub set of anemic hypoxia | ↓neutral excitability at low PaCO2 | Intracellular alkalosis |
| Headache + confusion | Resp depression | - 210x affinity for Hb than O2 |
| Weakness, dizziness, N+V | ↓L shift of OHDC | - CO rapidly displaces O2 from Hb |
| Convulsions, coma, death | | - ↓O2 carrying capacity of blood |
| - No ↑ in resp drive since PaO2 unchanged | | - L shift OHDC |
| - ↓O2 carrying capacity | | - ↓O2 concentration at a given PaO2 → ↓DO2 |
| hypoxaemia | | |

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

Acclimatisation:
- Respiratory
  - Hyperventilation
    - ↓PaO2 compensated by ↑minute ventilation
    - most important feature of acclimatisation
    - limits of compensation reached on 100% O2 at 13 700m
    - Mechanism
### Hypoxic (\(\Delta\)PaO\(_2\)) stimulation of peripheral chemoreceptors
- Resulting \(\Delta\)PaCO\(_2\) + alkalosis →
- Compensation is limited by resp alkalosis = Braking effect
  - The resp alkalosis stimulates compensatory movement of HCO\(_3\) out of CSF + renal excretion HCO\(_3\)

- 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 polycythaemia, fatigue, severe hypoxaemia

### Hyperbaric
- ↑ambient pressure
- 2-3 atmospheres absolute (i.e. 1-2 atmospheres above normal atmospheric pressure)
- ↑partial pressure of gases (TO2 carried in blood rather than bound to Hb)
  - Boyle’s and Dalton’s 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, ↑PaO\(_2\), ↑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 unavaiilable 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 ↓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/m\(^3\)

### Importance of humidification:
- Optimal function requires relative humidity >75%
- 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
Outline the non-ventilatory functions of the lungs

**Filtration (blood/gas)**
- Blood: receives all CO; venous embolic filtering; microbe filtering
- Airway: particulate matter filtration: impaction/ sedimentation; nasal hairs, mucus 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

**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 alpha1 antitrypsin
- 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

**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 I: 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
**RESPIRATORY ANATOMY AND PHYSIOLOGY**

**B2 agonist – e.g. salbutamol**

<table>
<thead>
<tr>
<th>Chem</th>
<th>Synthetic sympathomimetic amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses</td>
<td>Asthma / COPD / Preterm labour</td>
</tr>
<tr>
<td>Pres</td>
<td>2/4/8mg tablets aerosol 100mcg/puff</td>
</tr>
<tr>
<td>Action</td>
<td>Beta-adrenergic agonist (B2&gt;B1)</td>
</tr>
<tr>
<td>CNS</td>
<td>High doses beta-1 actions → +ve inotrope + chronotropic effects</td>
</tr>
<tr>
<td>CVS</td>
<td>High doses beta-1 actions → +ve inotrope + chronotropic effects</td>
</tr>
<tr>
<td>Resp</td>
<td>Bronchodilation → TPEFR + FEV1 Interferes with HPV</td>
</tr>
<tr>
<td>AS</td>
<td>Uterine relaxation: 40me gravid uterus; 10% crosses placenta</td>
</tr>
<tr>
<td>Other</td>
<td>4plasma [K+] by shift of ion into cells Tplasma [FFAs] + glucose stimulates insulin release</td>
</tr>
<tr>
<td>Toxicity/SE</td>
<td>Anxiety, insomnia, tremor, sweating, palpitations, ketosis, lactic acidosis, hypoK, postural hypotension, N+V</td>
</tr>
<tr>
<td>Route/</td>
<td>Inhaled: 5mg nebs q4hr; MDI 6-12 puffs q6hr or 1-2 puffs</td>
</tr>
<tr>
<td>Onset</td>
<td>5-15mins</td>
</tr>
<tr>
<td>Duration</td>
<td>Up to 4hrs</td>
</tr>
<tr>
<td>A</td>
<td>10% of inhaled dose reaches bronchial tree</td>
</tr>
<tr>
<td>D</td>
<td>8-60% protein bound</td>
</tr>
<tr>
<td>M</td>
<td>Liver; major metabolite salbutamol 4-O-sulfate</td>
</tr>
<tr>
<td>E</td>
<td>30% unchanged in urine; remainder in faeces + sulfate derivative in urine clearance 28L/hr elimination ½ life 3-5hrs</td>
</tr>
<tr>
<td>Special points</td>
<td>Potentiate NDNMBs</td>
</tr>
</tbody>
</table>

**Antimuscarinic e.g. ipratropium**

| Chem | Synthetic quaternary ammonium compound / Derivative of atropine |
| Uses | Asthma / COPD / Derivative of atropine |
| Pres | Solution containing 0.25mg/ml for nebulization MDC delivering 200microg/dose (18microg of which is available to patient) |
| Action | Competitive inhibition of cholinergic Rs on bronchial smooth muscle → blocking bronchoconstrictor action of VA efferent impulses |
| CNS | Large doses: +gastric secretion/ salvia |
| Route/| Inhaled via nebs 100-500microg q4hr or 1-2 puffs |
| Onset | Variable; peak plasma time 1-2hr |
| Duration | Variable |

**Theophylline**

| Chem | methylxanthine derivative/ methylxanthines |
| Uses | Asthma / COPD |
| Pres | Capsule IV |
| Action | Non selectively inhibit phosphodiesterase → cAMP hydrolysis → Tintracellular cAMP → smooth muscle relaxation |
| CNS | Nil – unable to cross BBB |
| Route/| IV: inhibits HPV |
| Onset | Variable; peak plasma time 1-2hr |
| Duration | Variable |

**Aminophylline**

| Chem | Ethylenediamine salt of theophylline (methylated xanthine derivative) |
| Uses | Asthma / COPD / Heart failure |
| Pres | Tablets: 100/225/350mg Suppositories Clear solution for injection: 25mg/ml aminophylline |
| Action | inhibits Mg2+ dependent phosphodiesterase (responsible for degradation of cAMP) → Tintracellular cAMP |
| CNS | Nil – unable to cross BBB |
| Route/| IV: inhibits HPV |
| Onset | Variable; peak plasma time 1-2hr |
| Duration | Variable |

**Leukotriene antagonist – e.g. montelukast**

| Chem | Synthetic quaternary ammonium compound / Derivative of atropine |
| Uses | Asthma / COPD / Heart failure |
| Pres | Tablets: 10mg |
| Action | Bronchodilation blocks binding of leukotriene D4 to its receptor |
| CNS | Blocks inflammatory contribution to asthma |

**Uses**

- Asthma / COPD / Preterm labour
- Asthma / COPD
- Asthma / COPD / Heart failure
- Asthma/ allergic rhinitis

**Pres**

- 2/4/8mg tablets aerosol 100mcg/puff dry powder for inhalation 200/400microg solution for nebulization 2.5/5mg/ml clear, colourless solution for injection 1mg/ml salbutamol sulphate
- Solution containing 0.25mg/ml for nebulization MDC 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 Tintracellular [cAMP] | MDC delivering 200microg/dose (18microg of which is available to patient)

**CNS**

- High doses beta-1 actions → +ve inotrope + chronic effects
- Lower doses B2 predominate → ↓PVR → ↓DBP 10-20mmHg

**CVS**

- Inh: Nil IV: ↑HR, ↑BP, TCO, ↓CVP

**Resp**

- Bronchodilation → ↑PEFR + FEV1 Interferes with HPV

**AS**

- Large doses: ↓gastric secretion/ saliva

**Other**

- 4plasma [K+] by shift of ion into cells Tplasma [FFAs] + glucose stimulates insulin release

**Toxicity/SE**

- Anxiety, insomnia, tremor, sweating, palpitations, ketosis, lactic acidosis, hypoK, postural hypotension, N+V

**Route/|**

- Inhaled: 5mg nebs q4hr; MDI 6-12 puffs PO
- Inhaled via nebs 100-500microg q4hr or 1-2 puffs

**Onset**

- 5-15mins

**Duration**

- Up to 4hrs

**A**

- 10% of inhaled dose reaches bronchial tree

**D**

- 8-60% protein bound

**M**

- Liver; major metabolite salbutamol 4-O-sulfate

**E**

- 30% unchanged in urine; remainder in faeces + sulfate derivative in urine clearance 28L/hr elimination ½ life 3-5hrs

**Special points**

- Potentiate NDNMBs

**Uses**

- Asthma / COPD / Preterm labour
- Asthma / COPD
- Asthma / COPD / Heart failure
- Asthma/ allergic rhinitis
<table>
<thead>
<tr>
<th>Hydrocortisone</th>
<th>Prednisone</th>
<th>Methylprednisolone</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Glucocorticosteroid</td>
<td>Synthetic glucocorticosteroid</td>
<td>Synthetic glucocorticosteroid</td>
</tr>
<tr>
<td>Pres</td>
<td>Tablets: 10/20mg Vials: white lyophilized powder diluted in water → 100mg of hydrocortisone sodium succinate Topical creams</td>
<td>Tablets: 1/2.5/5/20mg Solution for injection 25mg/ml prednisolone acetate drops</td>
<td>Tablets 0.5/2mg oral solution IV dexamethasone sodium phosphate 3.8mg/ml Topical creams</td>
</tr>
<tr>
<td>Relative dose equivalent</td>
<td>100mg</td>
<td>25mg</td>
<td>20mg</td>
</tr>
<tr>
<td>Route/ dose</td>
<td>IV: 100-500mg 6-8hrly PO: 10-20mg/day</td>
<td>PO: 5-60mg/day PO: IV/ IM</td>
<td>PO: 1-9mg IV:</td>
</tr>
<tr>
<td>Onset</td>
<td>&lt;2hrs</td>
<td>IV: 5min / PO: 1hr</td>
<td>PO: 1-2hr IV: &lt;5min</td>
</tr>
<tr>
<td>Duration</td>
<td>8hrs</td>
<td>18-36hr</td>
<td>PO:36hr IM: 1-4weeks</td>
</tr>
<tr>
<td>A</td>
<td>PO: bioavailabilty 50%</td>
<td></td>
<td>70% protein bound; high uptake in liver, kidney, adrenals</td>
</tr>
<tr>
<td>D</td>
<td>Reversibly bound to albumin (20%) + specific corticosteroid binding globulin (70%)</td>
<td>Reversibly bound to albumin (20%) and specific corticosteroid binding globulin (70%)</td>
<td>Vd 1L/kg</td>
</tr>
<tr>
<td>Low conc: 90% proteinbound</td>
<td></td>
<td>Low conc: 90% protein bound</td>
<td>Liver</td>
</tr>
<tr>
<td>High conc: 60% protein bound</td>
<td></td>
<td>High conc: 60% protein bound</td>
<td></td>
</tr>
<tr>
<td>Vd 0.3-0.5L/kg according to dose</td>
<td></td>
<td>Vd 0.3-0.7L/kg according to dose</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>M</td>
<td>To tetrahydrocortisone</td>
<td>Hydroxylation → conjugation</td>
<td>Urine</td>
</tr>
<tr>
<td>E</td>
<td>Clearance dose dependent: 150-250ml/min Elimination ½ life 2hrs</td>
<td>11-14% unchanged in urine clearance dose dependent: 170-200ml/min elimination ½ life 2-5hrs</td>
<td>Urine Elimination ½ life 3hr Glucocorticoids antagonize effects of anticholinesterase drugs</td>
</tr>
<tr>
<td>Special points</td>
<td>½ as potent as predisolone</td>
<td>Prednisone and predisolone are metabolically interchangeable (only latter is active)</td>
<td>PO 1-9mg</td>
</tr>
<tr>
<td>Relative mineralocorticoid effect</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- **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 lipocortins
  - Act on HPA axis at receptors on plasma membrane
  - Antiallergic, antitoxic, antishock, antipycritic, 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dose/ route</th>
<th>MoA</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemental o2</td>
<td>↑ FiO2</td>
<td>Inh</td>
<td>↑ FiO2 → ↑ alveolar O2 in areas undergoing gas exchange</td>
<td>removal of HPV to non-ventilated units → ↑ shunt → ↓ O2 content of blood</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>Non-specific α/β</td>
<td>1mg neb; 1mg IMI</td>
<td>β2 agonist GPCR → ↑ adenylyl cyclase → ↑ cAMP → ↑ Ca2+ → ↑ bronchial smooth muscle tone + ↑ mucous production → ↑ airways resistance</td>
<td></td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Selective β2 agonist (β2-β1)</td>
<td>Dose: 1mg neb; 1mg IMI</td>
<td>non selective β agonist: GPCR → ↑ adenylyl cyclase → ↑ cAMP → ↑ Ca2+ → ↑ bronchial smooth muscle tone + ↑ secretions</td>
<td>β1: ↑ THR, palpitation β2: stimulation of skeletal muscle → tremor/ sweat/ postural hypotension removal of HPV ↑ K via intracellular shift N+V ↑ BSL</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Anticholinergic</td>
<td>500ug neb</td>
<td>Competitive inhibition of nAChR (M3) on bronchial smooth muscle → GPCR → blockade → ↑ phospholipase C → ↓ DAG, IP3, ↑ Ca2+ ↑ bronchoconstriction effect of VA stimulation Inhibit Ach ↑ mediator release from mast cells</td>
<td>Minimal Unpleasant taste</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory</td>
<td>Pred 1mg/kg Hydrocort 100-300mg TDS</td>
<td>Bind to intracellular Rs to augment gene transcription/ translation inflammatory mediators: ↑ phospholipase A2 production → ↓ arachidonic acid → ↓ PG/ leukotrienes/ IL production/ ↑ capillary leak → oedema</td>
<td>↑ BSL (↑ gluconeogenesis) Adrenal suppression: inhibition of HPA Loss of subcut CT ↓ platelet aggregation ↓ arachidonic acid ↑ TXA2</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Phosphodiesterase</td>
<td>PO: 900mg divided IV: 5mg/kg bolus → 0.5mg/kg/hr</td>
<td>↓ breakdown of cAMP → ↑ cAMP → ↑ Ca2+ → ↓ bronchial relaxation Antagonises adenosine effect on mast cells</td>
<td>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</td>
</tr>
<tr>
<td>Volatile anaesthetics</td>
<td>Non-adrenergic Non-cholinergic</td>
<td>Titrated</td>
<td>↑ smooth muscle tone</td>
<td></td>
</tr>
<tr>
<td>Heliox</td>
<td>Density + specific gravity than air/ O2 WOB: improves oxygenation</td>
<td>↑ inspired O2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MG2+</td>
<td>Ca2+ channel blockade</td>
<td>20mmol IV</td>
<td>Smooth muscle relaxation → CCB → ↓ Ba2+</td>
<td>Sedation/ hypocalcaemia</td>
</tr>
</tbody>
</table>

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
<table>
<thead>
<tr>
<th>Nitric oxide</th>
<th>Prostacyclin e.g. iloprost</th>
<th>Endothelin R antagonist e.g. bosentan</th>
<th>Phosphodiesterase type 5 inh. e.g. sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>NO</td>
<td>Pulmonary HTN</td>
<td>Pulmonary artery HTN</td>
</tr>
<tr>
<td></td>
<td>Inorganic gas Produced by L-arginine</td>
<td>Endothelin HTN</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Uses</td>
<td>Selective pulmonary vasodilator in pulmonary HTN ARDS</td>
<td>Pulmonary artery HTN</td>
<td>Pulmonary artery HTN</td>
</tr>
<tr>
<td></td>
<td>Severe R sided HF</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Pres</td>
<td>aluminium cylinders containing NO + nitrogen (pure NO is toxic + corrosive)</td>
<td>Ampule containing 10 microg/ml or 20 microg/ml</td>
<td>Tablets 62.5mg/ 125mg</td>
</tr>
<tr>
<td>Action</td>
<td>NO produced in vivo by NO synthase 00&lt; diffuses into vascular smooth muscle layer → stimulates ↑expression of guanylate cyclase → ↑ production of cGMP → ↑ smooth muscle relaxation + platelet aggregation + angiogenesis</td>
<td>Synthetic analogue to prostaglandin PGI2 relaxation of vascular smooth muscle by stimulating production of cAMP + inhibit growth of smooth muscle cells</td>
<td>Endothelin-1 has direct vasoconstrictor effect, stimulates proliferation of vascular smooth muscle, fibrosis, and inflammation Competitive antagonist of endothelin-1 → inhibition of vasoconstriction</td>
</tr>
<tr>
<td>CNS</td>
<td>NO ↑ CBF Physiological role as a NT within ANS + CNS</td>
<td>Platelet inhibitor</td>
<td>↓ BP</td>
</tr>
<tr>
<td>CVs</td>
<td>Inhibits platelet aggregation + adhesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resp</td>
<td>preferentially dilates vessels of well perfused alveoli → improvement in V/Q matching inhibits HPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Insulin release modulated by NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity/SE</td>
<td>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</td>
<td>Jaw pain, cramp; sudden or abrupt withdrawal → rebound pulmonary HTN; caution in bleeding ↑ALT/AST; hepatotoxicity 4Hb resp infection, headache, oedema, flushing</td>
<td>Headache, flushing, dyspepsia, insomnia</td>
</tr>
<tr>
<td>Route/dose</td>
<td>Inhalation; 5-20ppm</td>
<td>IV/ subcut: teprostinil Inhaled: iloprost 2.5 microg → 5 microg → q2h</td>
<td>PO: 62.5mg BD then ↑ to 125mg BD</td>
</tr>
<tr>
<td>Onset</td>
<td>Peak serum time &lt;5min</td>
<td>Peak plasma time 3-5hr</td>
<td>&lt;60mins</td>
</tr>
<tr>
<td>Duration</td>
<td>30-60min</td>
<td>24hr</td>
<td>2-4hr</td>
</tr>
<tr>
<td>A</td>
<td>Highly lipid soluble Diffuses freely across CMs</td>
<td>60% protein bound</td>
<td>50% bioavailability bioavailability 40%</td>
</tr>
<tr>
<td>D</td>
<td>Vd 0.8L/kg</td>
<td>98% protein bound / VD 18L</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Combines with oxy-Hb → methaemoglobin + nitrate</td>
<td>Beta-oxidation of carboxyl side chain Metabolite: tetranor-iloprost (inactive)</td>
<td>Liver via CYP3A4 and 2C9 into 3 metabolites</td>
</tr>
<tr>
<td>E</td>
<td>70% excreted as nitrate in urine &lt;48hrs ½ life &gt;5s</td>
<td>½ life 20-30min urine (70%); faeces (10%)</td>
<td>½ life 8hrs/ total clearance 4L/hr Faeces</td>
</tr>
<tr>
<td>Special points</td>
<td>Delivering with FiO2 not recommended → combines with NO to form toxic NO2 Abrupt cessation can cause profound ↓PAP + ↑PAP ?downregulation of endogenous NO or guanylate cyclase activity Must monitor [nitrogen dioxide] during treatment Cl in neonates know to have circulation dependent on R to L shunt</td>
<td>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</td>
<td>contraindicated in pts taking nitrates → profound hypotension; headache</td>
</tr>
</tbody>
</table>
Discuss oxygen therapy including methods of delivery, indications and contraindications, physiological and pathophysiological effects

<table>
<thead>
<tr>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chem</strong></td>
</tr>
<tr>
<td><strong>Uses</strong></td>
</tr>
<tr>
<td><strong>Pres</strong></td>
</tr>
</tbody>
</table>
| **Action** | - Essential role is in the process of oxidative phosphorylation → energy required for cellular function  
- Elemental O₂ is combined with H ions via mitochondrial 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**