

I. ANATOMY OF THE RESPIRATORY SYSTEM

- (a) *To relate function of the upper airway to its structure.*
- (b) *To explain the structure of the chest wall and diaphragm and to relate these to respiratory mechanics.*

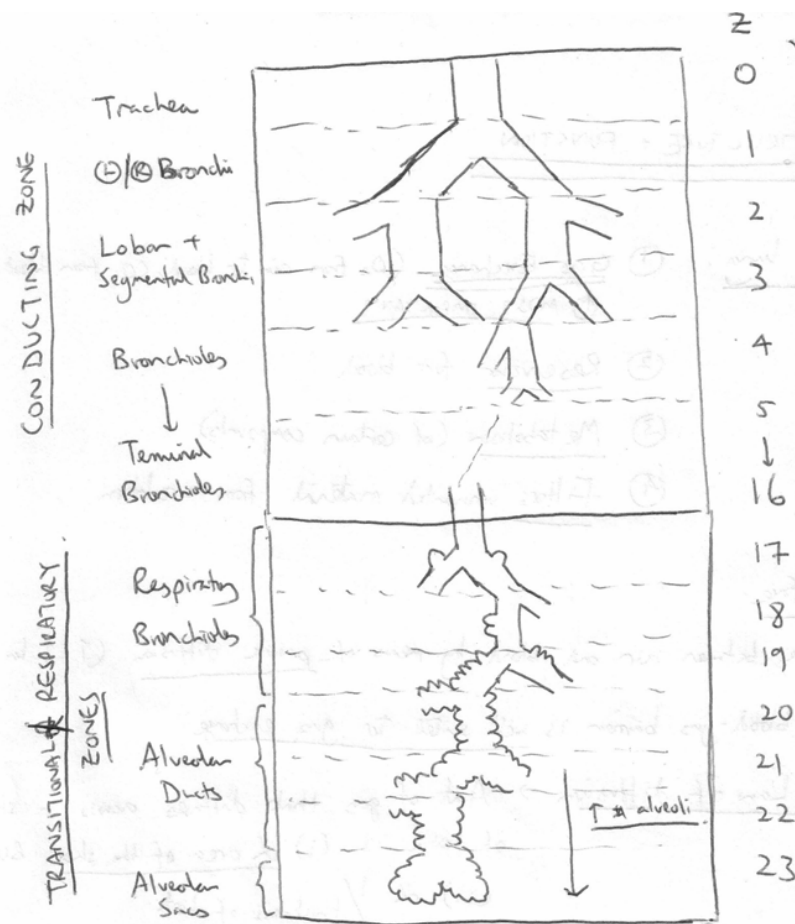
(I) Functional Anatomy of the Airways:

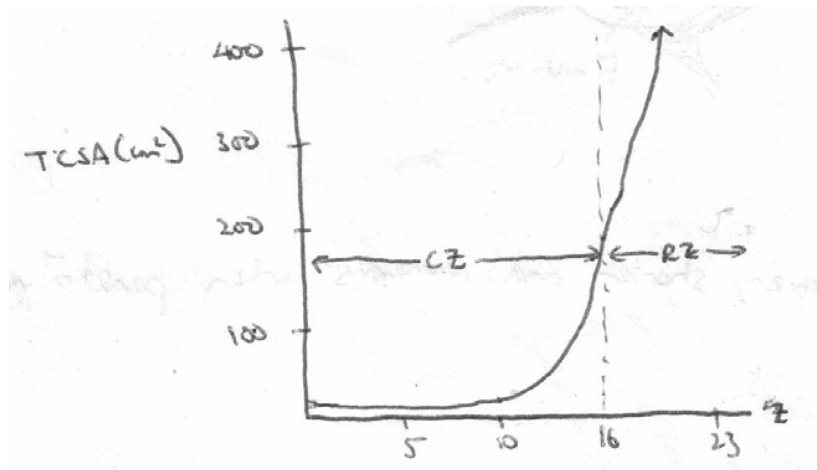
From the trachea, the AWs get (i) narrower, (ii) shorter and (iii) more numerous (with greater SA) when penetrating deeper into the lung

There are 2 functional zones of the AWs and lung that are differentiated on their ability to conduct gas exchange:

- (1) Conducting zone
 - These are AWs without alveoli – Thus, no gas exchange!
 - Extends from trachea (Z1) terminal bronchioles (Z16)
 - Volume ~ 150 mL (= Anatomical Dead Space)
 - Function – To conduct bulk air flow to and from the respiratory zone, and to warm/moisten inspired air
- (2) Respiratory zone
 - These are AWs with alveoli – Thus they exchange gas!
 - Includes – (i) Respiratory bronchioles (Z17-Z19) that contain alveoli in the walls, (ii) Alveolar ducts (Z20-22) and (iii) Alveolar sacs (Z23)
 - Volume ~3000 mL
 - Function – Gas exchange of O_2/CO_2 by means of diffusion

Important to note – “Pulmonary Lobule” or “Acinus” → an anatomical unit consisting of AWs and alveoli distal to a single terminal bronchiole





(II) Functional Anatomy of the Alveoli:

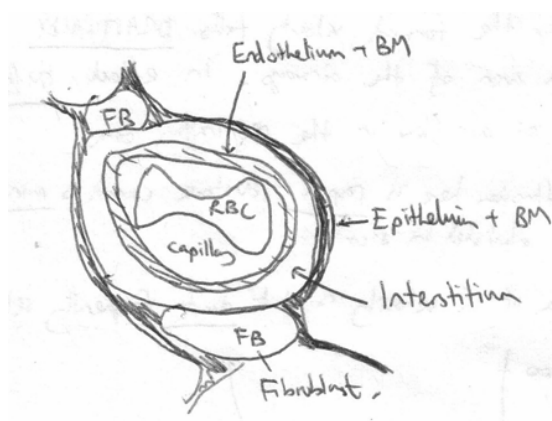
There are ~300 million alveoli that are engulfed by a rich capillary network → cumulative SA of all alveoli is ~85 m² with a volume of 4000 mL

Structure of alveoli:

- Polyhedral-shaped → 0.33 mm in diameter
- Each alveolar wall facing air is lined by Type I cells (one-cell-thick) → parts of alveolar wall consists of interstitial space that contain pulmonary capillaries
- Diffusion barrier that alveolar gas has to travel to pulmonary blood is short (0.3 μm only!) → consists of (i) Type I cell (epithelium), (ii) Basement membrane of type I cell, (iii) Basement membrane of pulmonary capillary endothelium, and (iv) Pulmonary capillary endothelium

Note – Pulmonary capillary endothelium is 0.1 μm thick; capillary diameter is 10 μm

- Alveoli are inherently unstable (I.e. collapse) given their small size and surface tension of their liquid-lining → this is offset by surfactant produced by Type II cells (round cells with large nuclei and cytoplasmic granules containing surfactant)



(III) Muscles of Respiratory:

Inspiration:

- ACTIVE process → requires contraction of respiratory muscles
- There are three sets of respiratory muscles:
 - (1) Diaphragm:
 - MOST important muscle in inspiration → vital role (75%) during TV breathing
 - Thin-dome-shaped sheet of muscle that inserts into the lower ribs → innervated by Phrenic nerve (C3-C5)
 - Contraction causes ↑ intrathoracic volume, which results in ↓ intrapleural pressures and net air flow into the lungs → this is achieved by two mechanisms:
 - (i) ↑ vertical thoracic dimension (moves 1 cm with TV breathing, but 10 cm with forced inspiration) by pushing abdominal contents down and forwards
 - (ii) ↑ transverse thoracic dimension by pushing ribs up and out
 - Other functions of this muscle include ↑ IAP for expulsive efforts (Ie. vomiting, defaecation and micturition)
 - (2) External intercostals muscles
 - Less important inspiratory muscle (cf. diaphragm) during TV breathing
 - Connect adjacent ribs in a downward and forward sloped arrangement → innervated by Intercostal nerves
 - Contraction causes ↑ lateral and AP thoracic diameters by pulling the ribs up and forwards ("Bucket-handle" movement) → ↑ intrathoracic volume
 - (3) Accessory muscles of inspiration:
 - Do NOT have a significant role during TV breathing – BUT they further ↑ intrathoracic volume when inspiratory volumes exceed TV breathing (Ie. VC breath) or during obstructed breathing (Ie. bronchospasm)
 - They include:
 - (a) Scalene muscle – Elevate 1st and 2nd ribs to ↑ AP diameter ("Pump-handle" movement) → innervated by Cervical nerve
 - (b) Sternomastoids – Elevate sternum to ↑ AP diameter ("Pump-handle" movement) → innervated by Accessory nerve
 - (c) Small muscles in neck and head – Lift the shoulder girdle to ↑ cross-sectional area of thorax

Expiration:

- Mainly a PASSIVE process → elastic properties of lung and chest wall allow them to return to their normal resting position after active expansion with inspiration (Ie. no muscular effort is required as they utilize the stored elastic potential energy gain during inspiration)
- BUT with forced expiration (Ie. tachypnoea or expiration below FRC, such as with exercise), accessory muscles of respiration are required – they include:
 - (1) Abdominal wall muscles
 - Includes – Rectus abdominus, internal/external obliques, transverses abdominus → innervated by nerves from T6-T12
 - Contraction causes ↑ IAP which raises the diaphragm → thus, ↓ intrathoracic volume
 - It also has a vital role in phonation, expulsive efforts and ↑ expiratory resistance
 - (2) Internal intercostals muscles
 - Connect adjacent ribs in an upward and backwards sloped arrangement → innervated by Intercostals nerves
 - Contraction pull ribs downwards and inwards → thus, ↓ intrthoracic volume

Important to note – Muscles of the upper airway:

- These muscles do NOT contribute directly to inspiration or expiration
→ BUT the resting tone of these muscles influence the patency and caliber of the upper airway
- These muscles include:
 - (1) Oral group of muscles and tongue muscle → ↓ AW resistance at oropharynx
 - (2) Alae nasi → Nostril flaring to reduce AW resistance at the nose
 - (3) Pharyngeal dilator muscles (genioglossus and geniohyoid – innervated by hypoglossal nerve) → relaxation of muscle (I.e. during GA or sleep) causes AW obstruction
 - (4) Posterior cricoarytenoids (innervated by recurrent laryngeal nerve via CN X) → abducts vocal cords to maintain patent upper AW and plays a role in phonation
 - (5) Thyroarytenoids (innervated by CN X) → adduction ↑ upper AW resistance but provides PEEP to prevent small AW closure

X. APPLIED RESPIRATORY PHYSIOLOGY

(a) ***To describe the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure.***

(I) Intermittent positive pressure ventilation (IPPV):

Overview of IPPV:

- Use of +ve intrathoracic pressures to ventilate lungs (cf. -ve intrathoracic pressures with normal breathing) → Nb. there is reversal of pleural and alveolar pressures b/t IPPV and normal breathing
- Consists of 2 phases:
 - (i) Inspiratory phase → +ve pressure is given through an airway from a ventilator to produce a given tidal volume
 - (ii) Expiratory phase → +ve pressure is released as the lungs deflate passively

Pulmonary effects of IPPV:

- Main pulmonary effect of IPPV → deliver +ve airway pressure to produce a given tidal volume in a patient who is under GA and paralysed with muscle relaxant
- The +ve ITP can also cause:
 - (1) ↑ V/Q mismatching → due to ↑ “dead space” ventilation 2° to ↑ P_{ALVEOLAR} (Ie. ↑ West zone 1)
 - (2) ↓ lung compliance → shift to less steep part of P-V curve
 - (3) ↓ AWR → due to +ve intrinsic airway pressures causing bronchial dilation
 - (4) ↑ PVR and RV afterload → due to extrinsic compression of pulmonary vessels
 - (5) FRC is variable:
 - FRC can ↑ → due to inadequate expiration time (Ie. gas trapping)
 - FRC can ↓ → due to low lung volume ventilation (close to RV and CC)
 - (6) Pulmonary barotrauma (Ie. PTX, pneumomediastinum, Etc.), esp if ↑ mean AW pressures, underlying lung disease, young age, and ↑ RR (Ie. intrinsic PEEP 2° to stacked breaths)

Cardiac effects of IPPV:

During inspiration → there is ↑ intrathoracic pressure (ITP) → causes following effects:

- (1) Initially, there is ↑ LV stroke volume and output due to ↑ LV preload → due to “squeezing” of blood from pulmonary circulation to the LA then LV as a result of ↑ ITP
- (2) Later, there is ↓ LV stroke volume and output due to ↓ LV preload → due to:
 - (i) ↓ venous return to the right heart → b/c ↑ ITP increases RA pressures, thus effectively ↓ the pressure gradient favouring systemic venous return to the RA
 - (ii) ↓ venous return to the left heart → b/c of ↓ RV output caused by ↑ RV afterload 2° to ↓ pulmonary vascular compliance and ↑ pulmonary vascular resistance brought on by ↑ ITP
 - (iii) Effects of “ventricular interdependence” → ↑ RV chamber size (caused by ↑ RVESV 2° to ↑ RV afterload) pushes the interventricular septum to the left, thus ↓ chamber volume of LV for a given filling pressure
 - (iv) “External splinting” → ↑ ITP reduces LV compliance to LV chamber filling
- (3) LV afterload ↓ (and thereby facilitating LV output) due to:
 - (i) ↑ pressure gradient from thorax to abdomen
 - (ii) ↓ transmural gradient → ↓ LV wall tension (as a result of “Law of LaPlace”, whereby wall tension is proportional to transmural pressure)

During expiration → there is ↓ ITP → causes the following effects:

- (1) Initially, there is ↓ LV stroke volume and output due to ↓ LV preload → due to sudden expansion of pulmonary vessels (Ie. ↑ pulmonary vascular capacitance and ↓ pulmonary vascular resistance 2° to ↓ ITP), which ↓ venous return to left side of heart
- (2) Later, LV preload, stroke volume and output return to pre-inspiratory levels as:

- (i) Venous return to the right heart resumes (as RAP normalises with ↓ ITP)
- (ii) Venous return to the left heart resumes (as RV afterload decreases with ↓ ITP) → permits blood from right heart to flow through pulmonary vessels into left heart

Effects of IPPV on LV output → highly variable:

- Normal LV function – IPPV causes ↓ LV output (I.e. ↓ C.O. and BP) b/c of ↓ LV preload
- Impaired LV function (Eg. CCF) or elderly – IPPV preserves or ↑ LV output (I.e. C.O. and BP unchanged or ↑) b/c of ↓ LV preload and ↓ LV afterload

Note – Thus, IPPV is beneficial in patients with ↓ LV function!

Important to note – Hypovolaemia, PEEP and high mean airway pressure exaggerate the fall in LV output (and C.O. and BP) with IPPV → this is b/c:

- Hypovolaemia is a/w ↓ CVP → thus, ↓ ability to offset the fall in venous return a/w IPPV
- PEEP/high mean airway pressures is a/w ↑ inspiratory pressures and ITP → thus, further effects on ↓ LV preload a/w IPPV

Other effects of IPPV:

- (i) ↓ RBF, ↓ GFR and U/O → due to ↓ C.O. and ↑ CVP
- (ii) ↑ ADH and AII levels
- (iii) ↓ HBF → due to ↓ C.O. and ↑ CVP
- (iv) ↑ ICP → due to ↑ CVP and ↓ venous return

(II) Positive-end expiratory pressure (PEEP):

Overview of PEEP:

- PEEP is +ve airway pressure at end-expiration → it is used to offset falls in FRC (a/w ↓ lung compliance, ↑ V/Q mismatching (esp shunting) and ↓ PaO₂) in patients who are spontaneously breathing or being mechanically ventilated

Pulmonary effects of PEEP:

The MAIN effect of PEEP is to ↑ transpulmonary distending pressures → ↑ lung volume (as per the P-V (or compliance) curve) → thus, ↑ FRC

In situations where PEEP is often use (I.e. GA, atelectasis, Etc.), there is a pre-existing ↓ FRC (which is a/w a heap of physiological sequelae) → thus PEEP increases and restores FRC which:

- (1) ↓ atelectasis and gas trapping → PEEP stabilises and expands partially collapsed alveoli and airway by ↑ FRC above “closing capacity” → shifts position on P-V curve above the “closing point” (I.e. inflection point) to steeper or more compliant part of curve
- (2) ↓ V/Q mismatching and ↑ PaO₂ → due to ↓ intrapulmonary shunt by – (i) ↓ atelectasis and gas trapping, and (ii) ↓ interstitial/alveolar oedema by redistributing extravascular lung water away from interstitial space (Nb. it does NOT reduce total lung water!)
- (3) ↑ lung compliance → shifts back to steep/compliant part of P-V curve
- (4) ↓ AWR → ↑ lung volume causes ↑ radial traction by lung parenchyma to open up airways, thus ↑ airway calibre
- (5) ↓ work of breathing → due to ↓ elastic work (I.e. ↑ lung compliance) and ↓ resistance work (I.e. ↓ AWR)

But in situations PEEP is excessive (I.e. > 20 cmH₂O), there can be:

- (1) ↑ V/Q mismatching → due to ↑ “dead space” ventilation 2° to ↑ P_{ALVEOLAR} (I.e. ↑ West zone 1)
- (2) ↓ lung compliance → shift to less steep part of P-V curve

- (3) ↓ AWR → due to +ve intrinsic airway pressures causing bronchial dilation
- (4) ↑ work of breathing → due to ↓ lung compliance
- (5) ↑ PVR and RV afterload → due to extrinsic compression of pulmonary vessels
- (6) Pulmonary barotrauma (Ie. PTX, pneumomediastinum, Etc.), esp if ↑ mean AW pressures, underlying lung disease, young age, and ↑ RR (Ie. intrinsic PEEP 2° to stacked breaths)

Cardiac effects of PEEP:

PEEP can ↓ C.O. due to ↑ intrathoracic pressures → causes ↓ LV SV (or preload) and output due to:

- (1) ↓ venous return to right heart → b/c ↑ ITP increases RA pressures, thus effectively ↓ the pressure gradient favouring systemic venous return to the RA
- (2) ↓ venous return to left heart → b/c of ↓ RV output caused by ↑ RV afterload 2° to ↓ pulmonary vascular compliance and ↑ pulmonary vascular resistance brought on by ↑ ITP
- (3) Effects of “ventricular interdependence” → ↑ RV chamber size (caused by ↑ RVESV 2° to ↑ RV afterload) pushes the interventricular septum to the left, thus ↓ chamber volume of LV for a given filling pressure
- (4) “External splinting” → ↑ ITP reduces LV compliance to LV chamber filling

Effect of PEEP on LV output → highly variable:

- Moderate levels of PEEP (< 15 cmH₂O) in patients with normal LV function have little impact on C.O. → of note, any ↓ C.O. can be negated by intravascular volume loading
- PEEP may ↑ C.O. in patients with poor LV function (Ie. elderly and CCF) due to:
 - (1) ↓ LV afterload due to – (i) ↑ pressure gradient from thorax to abdomen, and (ii) ↓ transmural gradient → ↓ LV wall tension (as a result of “Law of LaPlace”, whereby wall tension is proportional to transmural pressure)
 - (2) ↓ LV preload (due to above factors)

Important to note – Hypovolaemia, excessive PEEP (esp > 15 cmH₂O) and IPPV (esp high mean AW pressures) → exaggerate fall in LV output (and C.O. and BP) with PEEP → this can be offset by adequate intravascular volume loading

Other effects of PEEP:

- (i) ↓ RBF, ↓ GFR and U/O → due to ↓ C.O. and ↑ CVP
- (ii) ↑ ADH and AII levels
- (iii) ↓ HBF → due to ↓ C.O. and ↑ CVP
- (iv) ↑ ICP → due to ↑ CVP and ↓ venous return

(b) ***To explain the physiological effects of hypoxaemia, hyper and hypocapnoea, and carbon monoxide poisoning.***

(I) Hypoxaemia ($\text{PaO}_2 < 60 \text{ mmHg}$):

There are several causes of hypoxaemia (See notes in “Respiratory physiology – Ventilation-perfusion inequalities”)

The physiological effects of hypoxaemia are:

- $\uparrow$ local vasodilation to $\uparrow \text{O}_2$ delivery to tissues $\rightarrow$ causes $\downarrow$ SVR and $\downarrow$ BP
- Hypotension-induced stimulation of baroreceptors $\rightarrow$ causes SNS activation and catecholamine release $\rightarrow$ reflex $\uparrow$ HR and $\uparrow$ C.O.
- Stimulation of ventilation by peripheral chemoreceptors (when $\text{PaO}_2 < 50\text{-}60 \text{ mmHg}$)
- With severe hypoxaemia
 - o $\downarrow$ HR and BP $\rightarrow$ shock
 - o $\uparrow$ CBF (regardless of PaCO_2)
 - o In late stages $\rightarrow$ cardiac arrest, seizure, comas and death

(II) Hypercapnoea ($\text{PaCO}_2 > 44 \text{ mmHg}$):

Generally due to hypoventilation (and typically a/w hypoxaemia, which then exacerbates the physiological effects of hypercapnoea)

Hypercapnoea causes marked physiological effects b/c:

- (i) CO_2 crosses lipid barriers easily $\rightarrow$ enters all cells
- (ii) CO_2 rapidly reacts with H_2O $\rightarrow$ causes IC acidosis
- (iii) IC acidosis adversely impacts cellular enzymatic/metabolic processes

The physiological effects of hypercapnoea are:

- Stimulation of ventilation by peripheral and central chemoreceptors $\rightarrow \text{CO}_2$ is a powerful respiratory stimulation ($\uparrow$ MV by 2-3 L/min per mmHg rise in PaCO_2 above baseless)
- Direct depression of cardiac muscle and vascular SM (due to $\downarrow$ cellular influx of Ca^{2+}) $\rightarrow$ overshadowed by reflex SNS stimulation to compensate for $\downarrow$ C.O.
- Peripheral vasodilation $\rightarrow \downarrow$ SVR and $\uparrow$ regional BF
- $\uparrow$ CBF in proportion to PaCO_2 ($\uparrow$ CBF by 4% per mmHg rise in PaCO_2) $\rightarrow$ leads to $\uparrow$ ICP
- Right shift in OHDC $\rightarrow \downarrow \text{O}_2$ affinity by Hb and $\uparrow \text{O}_2$ unloading in peripheral tissues
- Pulmonary vasoconstriction $\rightarrow \text{CO}_2$ is potent pulmonary vasoconstrictor
- With severe hypercapnoea:
 - o SNS stimulation causes a hyperkinetic circulation $\rightarrow \uparrow$ C.O., $\uparrow$ BP and arrhythmias
 - o $\uparrow$ cardiac MRO_2 demand and $\downarrow$ cardiac blood supply
 - o Disorientation, confusion, headache and even unconsciousness (“ CO_2 necrosis”) at $\text{PaCO}_2 > 80 \text{ mmHg}$ $\rightarrow$ due to $\downarrow$ CSF pH
 - o Maximal stimulation of ventilation at PaCO_2 up to 100 mmHg (BUT ventilation $\downarrow$ or cases at $\text{PaCO}_2 > 100\text{-}120 \text{ mmHg}$)
 - o Hypoxia due to displacement of O_2 from alveoli (as per Alveolar gas equation)
 - o Respiratory acidosis $\rightarrow \uparrow \text{PaCO}_2$ overwhelms buffering capacity of blood
 - o $\uparrow$ serum K^+ and Ca^{2+} $\rightarrow$ due to extracellular shifts 2° to acidosis

(III) Hypocapnoea ($\text{PaCO}_2 < 36 \text{ mmHg}$)

Hypocapnoea is generally due to hyperventilation

The physiological effects are:

- $\downarrow$ C.O. and BP due to:

- (i) ↓ SNS activity
- (ii) ↓ pH which ↓ ionised Ca^{2+} → ↓ cardiac inotropy
- (iii) ↑ intrathoracic pressures with hyperventilation
- ↓ CBF in proportion to PaCO_2 (↓ CBF by 4% per mmHg ↓ in PaCO_2) → leads to ↓ ICP
- Respiratory depression due to ↓ stimulation of peripheral/central chemoreceptors (↓ MV by 2-3 L/min per mmHg ↓ in PaCO_2)
- Left shift in OHDC → ↑ O_2 affinity and ↑ O_2 loading in the lungs
- Respiratory alkalosis and ↓ serum K^+ and Ca^{2+} (due to intracellular shifts 2° to alkalosis)
- ↓ PaCO_2 to 20 mmHg will ↑ tissue O_2 consumption by 30% → ↑ demand for tissue perfusion and ↑ C.O.

(IV) CO poisoning:

- CO interferes with O_2 transport by combining with Hb by forming “carboxyhaemoglobin” → CO has 240x affinity at binding Hb cf. O_2 and has slow rate of dissociation from Hb
- This causes:
 - (i) Left shift in OHDC (interferes with O_2 unloading of O_2 due to ↑ O_2 affinity)
 - (ii) ↓ O_2 content of blood (despite normal PaO_2)
- Normally < 1% of Hb exists as CO-Hb (but can ↑ to 5% with smoking)
- CO poisoning occurs when % of CO-Hb is > 20%
 - Acute poisoning → causes ↑ C.O. to maintain O_2 flux to tissues
 - Chronic poisoning → polycythaemia to maintain O_2 content of blood

Note:

- CO-Hb > 30% → lactic metabolic acidosis and neural compromise (Eg. confusion, visual disturbances)
- > 50% → seizures, coma and death

(c) *To explain the effects of a change in posture on ventilatory function.*

Supine position:

- (1) ↓ FRC (by 500 mL) → due to cephalad movement of abdominal contents upwards on the diaphragm
- (2) ↑ tendency for AW closure if the FRC falls BELOW closing capacity (esp > 44 y.o.) → causes atelectasis/gas trapping → ↑ V/Q mismatch (as intrapulmonary shunting) → ↑ hypoxaemia
- (3) Gradients in ventilation and perfusion exist:
 - o When awake and spontaneously breathing → dependent (posterior) parts of lung have ↑ perfusion and ventilation (cf. non-dependent parts) due to effects of gravity
 - o With GA/paralysis and mechanical ventilation → non-dependent (anterior) parts of lungs have better ventilation (cf. dependent parts) while dependent parts remain well-perfused → this causes V/Q mismatching (esp when effects of GA compromise the effects of HPV, such that the imbalance in V/Q can no longer be resolved)
- (4) ↓ PVR → due to pulmonary venous congestion 2° to redistribution of venous blood into pulmonary circuit from extremities
- (5) ↓ lung compliance → due to ↓ FRC (I.e. shift away from the steep part of the pressure-volume curve) and ↑ thoracic venous pooling
- (6) ↑ airway resistance → due to ↓ airway calibre a/w ↓ lung volume
- (7) ↑ work of breathing → due to ↑ elastic work (as lung compliance is reduced at lower lung volumes), ↑ resistance work (as lung resistance increases at lower lung volumes) and ↑ work to open collapse airways and alveoli at their “Critical opening pressures”
- (8) ↑ regurgitation and aspiration risk (esp if under GA/paralysis)

Trendelenberg and lithotomy positions → similar to supine EXCEPT:

- (i) Marked ↓ lung volumes/capacities due to ↑ cephalad movement of abdominal contents upwards on diaphragm
- (ii) ↑ V/Q mismatching and hypoxaemia due to ↑ atelectasis (a/w ↓ FRC well below closing capacity)
- (iii) Significant ↑ regurgitation/aspiration risk

Lateral decubitus → similar to supine EXCEPT:

- (i) ↓ volume of dependent lung
- (ii) V/Q mismatching is even more pronounced if the non-dependent part of chest is opened, such as with thoracotomy (I.e. dependent parts are poorly ventilated but well-perfused; non-dependent parts are now both poorly ventilated and perfused)

Prone position:

- Minimal impact on FRC if positioned correctly (I.e. bollards across chest and pelvis, such that the abdomen is free; otherwise, FRC can be ↓ by abdominal and thoracic compression → minimises impact on lung compliance, AWR and work of breathing
- By ↓ pressure 2° to gravity on dorsal parts of the lung when supine:
 - o ↓ atelectasis in dependent parts and ↑ even distribution of ventilation
 - o Also ↑ homogenous distribution of perfusion → ↓ shunt and ↑ V/Q matching → ↑ oxygenation

Erect, head-up and reverse trendelenberg positions

- Lung volume ↑ towards FRC (as there is ↓ cephalad movement of abdominal contents upwards on the diaphragm) → results in:
 - o (i) ↓ atelectasis and gas trapping → due to FRC > CC
 - o (ii) ↓ V/Q mismatching and hypoxaemia due to intrapulmonary shunting 2° to atelectasis (but gravitational effects in V/Q distribution in the lung still exist, with the basal regions being better ventilated and perfused)
 - o (iii) ↓ AWR → due to ↑ airway calibre with ↑ lung volume

- (iv) ↑ lung compliance → due to ↑ FRC and ↓ thoracic venous pooling
- (v) ↓ work of breathing → due to ↓ elastic work (as lung compliance ↑ at higher lung volumes) and ↓ resistance work (as lung resistance ↓ at higher lung volumes)
- (vi) ↓ regurgitation/aspiration risk
- (vii) ↑ PVR → due to ↓ pulmonary venous congestion 2° to redistribution of venous blood away from pulmonary circuit into the extremities

(d) ***To define humidity and give an outline of the importance of humidification.***

Definition of humidity:

Absolute humidity:

- Defined as the mass of water vapour (g H₂O) present in a given volume of air (m³) → expressed as g H₂O/m³ or mg H₂O/L
- Varies between zero (dry air) and a maximum amount (humidity at saturation)
- Temperature-independent → EXCEPT when air is saturated with maximum amount of water vapour

Note – ↓ temperature causes ↓ absolute humidity of fully saturated air 2° to a ↓ in SVP → fully saturated air at 0 °C contains 4.8 mg/L; at 20 °C contains 17 mg/L; at 37 °C contains 44 mg/L

Relative humidity:

- Defined as the ratio of the mass of water vapour in a given volume of air (absolute humidity) to the mass required to fully saturate that volume of air at a given temperature (humidity at saturation) → expressed as %

$$\text{Relative humidity} = \frac{\text{Absolute humidity}}{\text{Humidity at saturation at that temperature}} \times 100\%$$

Aside: Since mass is directly proportional to # moles present, then as per “Ideal gas equation” (at a constant temperature) → Relative humidity = (actual vapour pressure of H₂O) / (saturated vapour pressure of H₂O)

- Temperature-dependent → this is b/c humidity at saturation varies with temperature (such that ↓ temperature causes ↓ absolute humidity of fully saturated air 2° to ↓ in SVP) → thus relative humidity ↑ with ↓ temperature

Note:

- Water content → defined as the total amount of water present per unit volume of gas (either water vapour and/or fine suspended droplets) → expressed as mg/L
- Dew point → defined as the temperature to which air must be cooled before water condenses from it (I.e. at dew point, vapour pressure of H₂O = SVP)

Importance of humidification:

The “conducting airways (or UAW)” is largely responsible for warming and humidifying air → thus, most heat and water exchange occur there:

- An obligatory loss of heat as energy is expended to evaporate water associated with “insensible loss of water” from the lungs → 400 mL of insensible water loss from the lungs requires 230 kcals/day of energy (as heat of vapourisation = 560 cal/g H₂O) → 12% of basal heat loss
- These requirements increase in dry or cold climates, or with exercise (due to ↑ RR)!

Gases used in operating theatres are at room temperature with little humidification (< 10 mg/L), and the use of ETT and high FGF bypasses normal conducting airway (or UAW) humidification system → thus, the “respiratory airways (or LAW)” is exposed to dry and dessicated air

The consequence of this is that the LAW are now responsible for warming and humidifying inspired gases → this causes:

- (1) Mucosal dehydration
- (2) Altered ciliary function

- (3) Inspissation of secretions
- (4) Atelectasis and V/Q mismatching (esp if underlying lung disease)
- (5) ↑ heat loss (5-10%) as the inspired gases are warmed and more H₂O needs to be added as vapour

This is prevented by providing the patient with warm and humidified inspired gases

(c) *To explain the importance of the cough reflex.*

“Coughing” → involuntary reflex mechanism that aims to remove foreign material from the upper respiratory tract before it reaches the lung

Reflex arc consists of:

- (1) Sensory (afferent) limb:
 - o Pulmonary (cough) receptors are located in the epithelium of respiratory tract → esp on posterior wall of trachea, pharynx and carina (less in distal airways, esp beyond respiratory bronchioles)
 - o Receptors are rapidly-adapting “irritant” receptors → sense various mechanical and chemical stimuli
 - o When activated → send impulse via “internal laryngeal nerve” (branch of “superior laryngeal nerve”) along CN X to the medulla of the brain
- (2) Central controller → note that there is NO cough centre in the brain!
- (3) Motor (efferent) limb:
 - o Cerebral cortex and medulla sends signs via CN X → superior laryngeal nerve → to glottis, external intercostal, diaphragm and other respiratory muscles

Mechanical process of coughing:

- (1) Diaphragm (innervated by phrenic n.) and external intercostal muscles (innervated by segmental IC n.) contract → generate large -ve intrapleural pressure → cause inflow of air into the lungs
- (2) Glottis closes and vocal cord contracts (innervated by recurrent laryngeal n.) → shut larynx
- (3) Abdominal muscles and expiratory muscles contract simultaneously against a relaxed diaphragm → generate a significant ↑ +ve intrapleural and airway pressure within lungs
- (4) Glottis and vocal cord opens → air from lung is released at a rapid velocity
- (5) Bronchi and non-cartilaginous portions of trachea collapse to form slits through which air is forced → clears out any irritant material attached to respiratory lining

Effectiveness of cough reflex is circumvented in various situations → results in ↓ effective clearance of airways of foreign material:

- (1) Respiratory muscle weakness → due to neuropathy, myopathy, effects of anaesthesia/muscle paralysis, prolonged inactivity/bed rest
- (2) Tracheostomy
- (3) Vocal cord pathology → due to SLN damage (esp swallowing foreign object, such as fish bone), effects of anaesthesia/muscle paralysis

(f) *To explain the effects of general anaesthesia on ventilatory function.*

- (1) ↓ minute ventilation
 - ↓ MV due to either (i) ↓ RR and/or (ii) ↓ TV
 - Caused by volatile agents, IV induction agents, opioids → depress chemoreceptors and respiratory muscle activity
- (2) ↓ ventilatory response
 - Volatile agents, IV induction agents, opioids all cause
 - o (i) ↓ rate of rise in MV due to hypercapnoea
 - o (ii) ↑ “apnoeic threshold”
 - o (iii) ↓ slope of CO₂ and O₂ response curve
 - o (iv) ↓ hypoxic respiratory drive (esp at 0.1 MAC of volatile)
- (3) ↓ FRC
 - All agents used in GA will ↓ FRC by 15-20% → this is more pronounced if patient is supine (further ↓ FRC by 20%) and if muscle relaxants are used
 - ↓ FRC with GA is due to:
 - o (i) Cephalad movement of the diaphragm (esp in dependent parts of diaphragm)
 - o (ii) Change in diaphragm shape
 - o (iii) Loss of tone by the diaphragmatic and other respiratory muscles (Eg. external intercostals) supporting lung volumes
- (4) ↓ compliance of respiratory system → due to ↓ FRC and use of muscle relaxants
- (5) Airway resistance is variable:
 - ↑ AWR → due to ↓ lung volumes, posterior displacement of tongue, laryngo- and bronchospasms, secretions/blood in airways, equipment issues (Ie. small ETT)
 - ↓ AWR → due to bronchodilating effects of volatiles
- (6) ↑ work of breathing
 - Due to ↓ compliance of respiratory system (and less commonly due to ↑ AWR)
 - This can be circumvented by controlled mechanical ventilation
- (7) ↓ pulmonary vascular resistance → due to inhibition of hypoxic pulmonary vasoconstriction (esp by volatiles)
- (8) ↑ hypoxaemia due to:
 - (i) ↑ V/Q mismatching
 - o Intrapulmonary shunting → due to atelectasis (small airway collapse) or impaired HPV (Ie. volatiles)
 - o Alveolar dead space → due to PEEP/IPPV, ↓ C.O., and hypotension
 - (ii) Hypoventilation
- (9) ↑ hypercapnoea due to hypoventilation
- (10) ↓ tissue metabolism → ↓ VO₂ (esp cerebral and cardiac O₂ consumption) and ↓ VCO₂
- (11) Impaired upper airway responses, mucous secretions and mucociliary responses

(g) *To explain the effects of pregnancy on ventilatory function.*

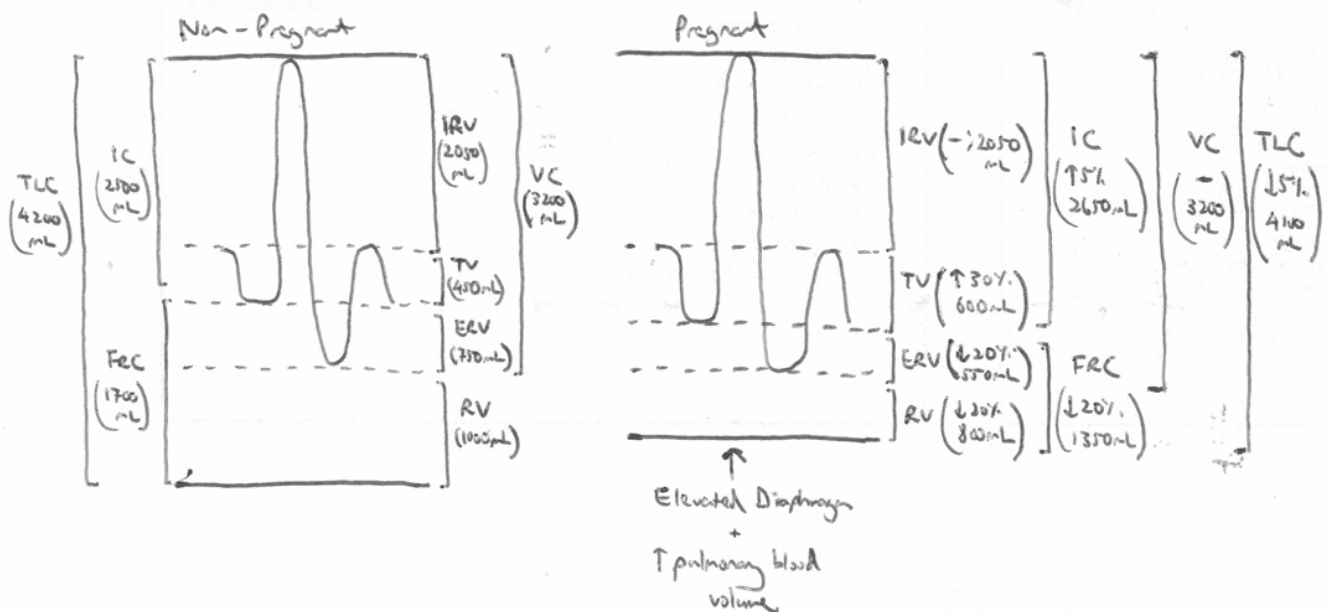
(1) Anatomical changes to thorax and airway:

- (i) Diaphragm displaced up 4 cm by gravid uterus → but contractility not markedly restricted
- (ii) ↑ AP and transverse diameter by 2-3 cm (so ↑ circumference by 5-7 cm) → due to “Relaxin” (from corpus luteum) that relaxes ligaments of ribs
- (iii) Upper respiratory tract (I.e. vocal cords, nasal mucosa) swollen → due to capillary engorgement

(2) Changes in lung volumes:

- Occur early in pregnancy and continue to change progressively during pregnancy (esp from 20/40) → normalize 2-5 days post-partum
- ↓ ERV and RV (incl FRC and TLC) → due to (i) elevated diaphragm (2° gravid uterus) and (ii) ↑ pulmonary blood volume

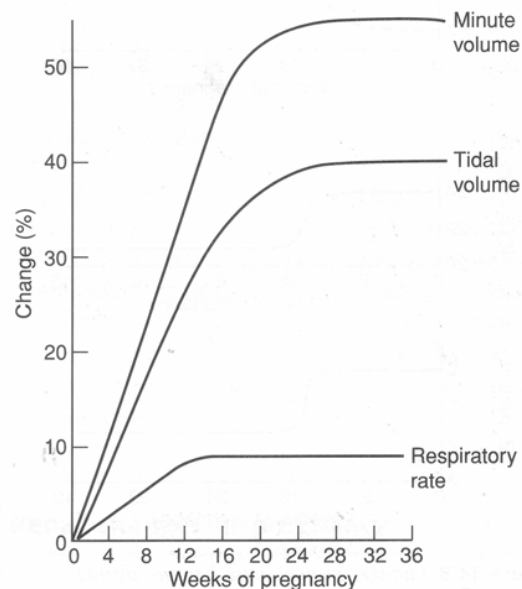
IRV (u/c; 2050 mL)	IC (↑ 5%; 2500 to 2650 mL)	VC (u/c; 3200 mL)	TLC (↓ 5%; 4200 to 4100 mL)
TV (↑ 30%; 450 to 600 mL)			
ERV (↓ 20%; 750 to 550 mL)	FRC (↓ 20%; 1700 to 1350 mL)		
RV (↓ 20%; 1000 to 800 mL)			



Note – FRC ↓ by 70% of sitting value when supine (due to effects of gravid uterus on diaphragm)

(3) ↑ minute and alveolar ventilation:

- ↑ early (esp after 10/40) and continues to ↑ gradually during pregnancy (↑ by 50-70% at term) → due to (i) ↑ TV (by 40% at term) and (ii) ↑ RR (by 15% at term)
- Caused by progesterone-mediated stimulation of medullary respiratory centres → ↑ sensitivity to PaCO₂ (left shift in CO₂ response curve)



- During labour – ↑ MV/AV further (by 160%) due to pain and ↑ MRO₂ a/w uterine contractions → can cause transient ↓ PaCO₂ (to 20 mmHg!)

(4) ABG changes:

	Normal ABG	Pregnancy ABG	Important points
pH	7.40	7.42	- ↑ MV (esp at end of 1st TM → causes (i) ↓ PCO₂ and (ii) ↑ PO₂ → this creates favourable pressure gradients of O₂/CO₂ across placenta for exchange with foetus! - ↓ PCO₂ causes a respiratory alkalosis BUT Δ pH is compensated renally (by ↑ HCO₃⁻ excretion/↓ BE) → this prevents a shift in Hb ODC (despite ↓ PCO₂) BUT ↓ maternal buffering capacity - ABG changes normalize rapidly post-partum
PCO ₂ (mmHg)	40	30	
PO ₂ (mmHg)	95	105	
HCO ₃ ⁻ (mmol/L)	24	20	
BE (mmol/L)	0	-2	

(5) Changes in lung mechanics:

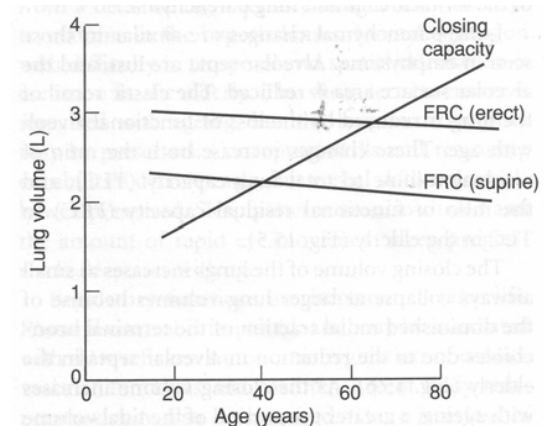
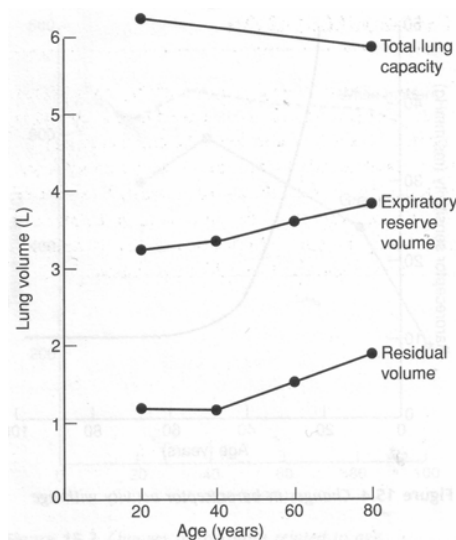
- (a) Work of breathing unchanged → due to balance b/t (i) Non-elastic forces (↓ AWR) and (ii) Elastic forces (↓ total compliance of respiratory system)
- (b) ↓ AW resistance (by 35%) and ↑ anatomical DS (by 45%) → due to progesterone-mediated large AW dilation
- (c) ↓ total compliance of respiratory system → due to ↓ CW compliance 2° to elevation of diaphragm by gravid uterus (Nb. lung compliance is unchanged)
- (d) F-V curves unchanged (while sitting)
- (e) AW closure (and atelectasis) when supine only → up to 50% ♀ have FRC < CC when supine (otherwise FRC remains > CC when sitting)

(6) ↑ tissue O₂ delivery to tissues:

- ↑ O₂ flux (by 10% at term) → due to (i) ↑ C.O. (main), (ii) ↑ PO₂, and (iii) ↑ tissue BF (a/w regional vasodilation) → despite limitations in CaCO₂ by (i) Anaemia of pregnancy, (ii) Right shift in Hb ODC (due to ↑ 2,3-DPG), and (iii) Hb being maximally saturated
- ↑ tissue MRO₂ during pregnancy (by 20% at term)

(h) *To explain the ventilatory changes accompanying the process of ageing.*

	Change with ageing	Reason
Lung volumes	TLC ↓ (10%)	↓ chest expansion 2° ↓ chest wall compliance and ↓ respiratory muscle function
	FRC unchanged (or slightly ↓)	↓ lung elastic recoil counteracts the fall in lung volume a/w ↑ chest wall rigidity
	VC ↓	↓ lung elastic recoil, ↓ chest wall compliance, ↓ respiratory muscle function
	TV ↓	As VC
	RV ↑	Dynamic AW compression (on expiration) and small AW closure during tidal breathing
	CC ↑ (at age 66, CC > FRC when erect)	Loss of elastic lung tissue → ↑ +ve P _{INTRAPLEURAL} → ↓ radial traction of terminal bronchioles → ↑ small AW collapse at larger lung volumes
	Maximum MV (30-40 L/min cf. 100 L/min in young adults)	Limitations in ↑ TV
Lung function	FEV1 ↓	Dynamic AW compression, ↓ expiratory muscle function
	FVC ↓	As VC
Gas exchange	↑ V/Q mismatching (esp ↓ V/Q ratio – shunt)	Gas trapping a/w small AW closure during tidal volume breathing
	↑ resting hypoxaemia (as “Resting PaO ₂ ” = 100 – (0.33 x age) mmHg)	↑ V/Q mismatching, ↓ alveolar surface area, ↑ alveolar capillary membrane thickness
	↑ A-a O ₂ gradient (as A-a gradient = (Age/4) + 4 mmHg)	As above
Lung mechanics	↓ lung and chest wall compliance	- Chest wall: ↑ thoracic cage rigidity (due to loss of elasticity), kyphoscoliosis, ↓ costovertebral joint mobility (due to calcification), and ↓ thoracic muscle mass - Lung: Loss of lung tissue → ↓ elastic recoil
	↑ AW resistance	Dynamic AW compression (on expiration)
	↑ work of breathing	↑ AW resistance
Control of respiration	- ↓ ventilatory response to CO₂/O₂ (25%) → ↓ hypoxic/hypercapnoeic drive - ↓ peripheral and central chemoreceptor sensitivity - ↓ ability of respiratory muscle to respond to change - ↓ exercise capacity due to limited respiratory reserve	
Others	- ↓ cough effectiveness due to ↓ reflex sensitivity and ↓ muscle strength - ↑ aspiration due to ↓ protective AW reflexes - ↑ sleep apnoea (esp males) due to loss of oropharyngeal tone	



(i) *To describe the differences in the respiratory system of the neonate compared with the adult.*

Anatomy	- Upper AW - o Large tongue and mandible angle (140° cf. 120° in adults) - o Narrow nasal passages (accounts for 50% of AWR) - o Obligate nasal breathing (cf. mouth breathing) → due to large tongue and mandible angle, and cephalad larynx → so nasal obstruction can precipitate respiratory distress! - Larynx - o Epiglottis is stiff, long, U-shaped and angled back 45° → so straight laryngoscope blade used for intubation - o Glottis is situated at C3/C4 level (cf. C6 in adults) and is angulated anteriorly → so backward pressure on larynx assists intubation - o Cricoid ring is the narrowest part of larynx → it enlarges during puberty so vocal cord in the narrowest part in adults - Lower AW - o Trachea is shorter (3-7 cm length) and smaller (6 mm diameter) - o Bronchi branch angle is similar to adults (30° R; 45° L) → risk of R endobronchial intubation remains - o Small peripheral AWs (< 2 mm diameter) → account for remaining 50% of AWR (cf. 20% in adults) - o ↓↓↓ bronchial muscle → so bronchospasms uncommon and bronchodilator drugs have minimal response - Chest wall - o Ribs more horizontal → limited AP expansion (lose pump handle mechanism) and transverse expansion (lose bucket handle mechanism) → thus, minimal thoracic component to ventilation and ↑ reliance on diaphragmatic breathing - o ↓ % type I muscle fibres (highly oxidative/slow contraction) in diaphragm (25% in neonate vs 55% in adults) and IC muscles (45% vs 65%) → ↑ risk of muscle fatigue
Lung volumes	- FRC (30 mL/kg) → same as adult (as FRC remains 40% of TLC) BUT ↓ stable and ↑ risk of atelectasis due to following reasons: - o (i) Significant ↓ in outward recoil of CW (as rib is cartilaginous and contains very little respiratory muscles) - o (ii) Mild ↓ inward recoil - TLC (75-80 mL/kg) → same as adult - VC (45 mL/kg) → lower cf. adult (60 mL/kg) - TV same as adult (7 mL/kg) - ↑ CC due to low elastic recoil of lungs → in fact, CC > FRC such that there is small AW closure during tidal ventilation → results in gas trapping and hypoxaemia
Minute ventilation	- MV = 140 mL/kg/min (2x adult) → required to cope with ↑ MRO₂ - ↑ MV generated by ↑↑ RR (30-40/min – cf. 12-15/min in adults) rather than ↑ TV (7 mL/kg – same as adult) → this minimises “work of breathing”
Lung mechanics	- Compliance - o Lung – ↑ from 1.5 to 6 mL/cmH₂O within 24 hrs post-birth. Specific compliance similar as in adult (0.05/cmH₂O) - o Chest wall – Very compliant due to soft rib cage (allows thorax compression to assist vaginal delivery) → BUT ↑ risk of respiratory failure due to sternal retraction and restricted diaphragm movement caused by AW obstruction - Airway resistance: - o AWR ↓ from 90 cmH₂O/L/sec to 25 cmH₂O/L/min after 24 hrs post-

	birth ○ Resistance of nasal passages = 50% AWR - End-expiratory $P_{\text{INTRAPLEURAL}} \sim 0$ (cf. -ve pressure in adults) - I:E ratio ~ 1 (cf. 1.5 in adults)
V/Q matching	- Significant V/Q mismatch ($V/Q = 0.4$) due to shunting caused by small AW closure/gas trapping during tidal ventilation $\rightarrow$ thus, neonate normally has a $\downarrow$ PaO_2 50-60 mmHg with A-a gradient of 30 mmHg - Dead space same as in adults (2.2 mL/kg), including physiological DS ($V_D/V_T = 0.3$)
Control of ventilation	- Respiratory control less developed (cf. adults) - Peripheral and central chemoreceptors are responsive: ○ CO_2 ventilatory response curve is shifted left cf. adult $\rightarrow$ so ventilation occurs at a $\downarrow$ level of PaCO_2 ○ O_2 ventilatory response $\rightarrow$ hypoxaemia causes a transient $\uparrow$ MV (2 mins only) post-birth $\rightarrow$ sustained $\uparrow$ MV response after 1 week ○ Nb. O_2/CO_2 ventilatory responses are depressed by hypothermia - Any $\uparrow$ in MV is achieved by $\uparrow$ TV (as RR is already $\uparrow$) - “Hering-Breuer reflex” (transient apnoea lasting 5 secs evoked by gradual lung inflation) and “Head’s paradoxical inflation reflex” ($\uparrow$ inspiratory effort evoked by partial inflation of lungs) are prominent - “Periodic respiration” is common and normal (pauses lasting 5-10 sec (up to 6 x per hr during sleep) $\rightarrow$ BUT “Apnoeic spells” are abnormal (pauses > 20 secs a/w bradycardia)
O_2 flux to tissues	$\uparrow$ O_2 flux to tissues due to: - (i) $\uparrow$ O_2 carrying capacity of blood cf. adult (by 1.25x) $\rightarrow$ due to: ○ $\uparrow$ [Hb] $\rightarrow$ 170-180 g/L ○ HbF ($\alpha_2\gamma_2$) $\rightarrow$ left shift in Hb O_2 dissociation curve 2° inability to bind 2,3-DPG (lacks β subunits) $\rightarrow$ $\uparrow$ O_2 affinity ($P_{50} = 19$ mmHg) ○ $\uparrow$ MV $\rightarrow$ $\uparrow$ pO_2 - (ii) $\uparrow$ C.O. (esp $\uparrow$ % to VRG)
MRO_2	- $\uparrow$ resting MRO_2 (6-8 mL/kg/min $\rightarrow$ 2x adult resting MRO_2) due to $\uparrow$ metabolic rate $\rightarrow$ matched by $\uparrow$ O_2 flux to tissues - MRO_2 varies with ambient temperature $\rightarrow$ MRO_2 is lowest within “thermoneutral zone” $\rightarrow$ it $\uparrow$ 2x for every $\downarrow 2^\circ\text{C}$
ABG	- Umbilical cord blood $\rightarrow$ combined respiratory and metabolic acidosis (pH 7.26, pO_2 20 mmHg, pCO_2 55 mmHg) - After birth $\rightarrow$ pH $\uparrow$ to 7.35 (within 2/52) then later to 7.40, pCO_2 $\downarrow$ to 32-36 mmHg initially then later $\uparrow$ to 40 mmHg, pO_2 $\uparrow$ to 50-60 mmHg

(j) *To outline the non-ventilatory functions of the lungs.*

The main function of the lung is its respiratory function, which is to provide gas exchange – Transfer O₂ from air to blood, and CO₂ from blood to air

The non-respiratory functions of the lung include:

- (1) Filtration:
 - o Of blood:
 - As the pulmonary vasculature receives all C.O., it is able to filter unwanted material from the circulation using its capillary bed (Ie. capillary is 7 µm, and thus able to filter particles larger > 10 µm)
 - Unwanted materials include:
 - Venous thromboemboli are trapped in the pulmonary circulation and broken down by intrinsic fibrinolytic activity of the lungs (Ie. heparin-containing mast cells within lung interstitium)
 - Microbes from the venous circulation are filtered, and prevented from entering the arterial circulation
 - o Of gas:
 - Filtering mechanisms and particle impaction in the upper AW (such as nasal hairs, mucous production, mucociliary escalator and AW reflexes such as coughing and sneezing) filter the majority of inspired particles
 - Sedimentation of smaller particles occurs in the terminal and respiratory bronchioles
- (2) Immunological:
 - o The smallest inspired particles reach the alveoli by diffusion – These are engulfed by Alveolar macrophages
 - o Secretory IgA helps fend off microbes in the respiratory tract
- (3) Reservoir:
 - o Of blood:
 - Lung can accommodate a blood volume of 450 mL (370 mL in pulmonary vasculature, 80 mL in pulmonary capillaries)
 - Accommodation of lung blood volume is caused by a rise in pulmonary artery pressure, which induces – (i) Recruitment (more vessels open up), and (ii) Distension (open vessels get bigger) of pulmonary capillary beds
 - Mobilisation of lung blood volume occurs with – (i) SNS stimulation, which constricts pulmonary vessels, and (ii) Raised intrathoracic pressures such as with straining (Nb. this can empty 50% of lung blood volume). This causes an increase in effective blood volume and a rise in C.O.
 - o Of gas:
 - The volume of air at FRC is practically an O₂ reservoir
 - Reservoir of gas facilitates transmission of air that permits vocalisation and coughing
- (4) Metabolism:
 - o (a) Metabolism of vasoactive substance
 - Activation of AI to AII (pulmonary capillary endothelium have the highest [ACE], which converts AI to AII)
 - Inactivation of bradykinin (pulmonary capillary ACE deactivates 80% of bradykinin)
 - Uptake and degradation of 5-HT (100%) and NAd (30%; via COMT and MAO)
 - Production of LTs (from phospholipids and arachidonic acid)
 - Enzymatic inactivation of PGE-1 and -2, PGF-2α
 - o (b) Protein synthesis (Ie. collagen and elastin to maintains lung structure)
 - o (c) CHO metabolism (Ie. mucopolysaccharides for mucous coating of AW's)
 - o (d) Removal of proteases (via α1-antitrypsin)

- (e) Production of surfactant (dipalmitoylphosphatidylcholine) by Type 2 pneumocytes – This decreases alveolar surface tension, which prevents:
 - Emptying (and collapse) of smaller alveoli into larger ones
 - Prevents transudation of water into alveolar space
- (f) Lung contributes 1-2% of basal O_2 consumption
- (5) Thermo- and water regulation:
 - The conducting airways (or UAW) is largely responsible for warming and humidifying air, therefore most heat and water exchange occur there
 - More specifically, an obligatory loss of heat as energy is expended to evaporate water associated with “insensible loss of water” from the lungs – 400 mL of insensible water loss from the lungs requires 230 kcals/day of energy (12% of basal heat loss)
 - These requirements increase in dry or cold climates, or with exercise (due to increased RR)
- (6) Acid-base balance:
 - Alters pH by altering the ratio of plasma HCO_3^- to PCO_2 (as part of the Henderson-Hasselbach equation) by controlling the extent of CO_2 excretion
- (7) Pharmacological:
 - Administration and elimination route for volatile agents and bronchodilators
 - Sequesters drugs (as “First pass uptake”), such as fentanyl (which it later releases into arterial circulation as a “2nd peak”), lignocaine and propofol

(k) *To outline the effects of common pulmonary pathology on respiratory function.*

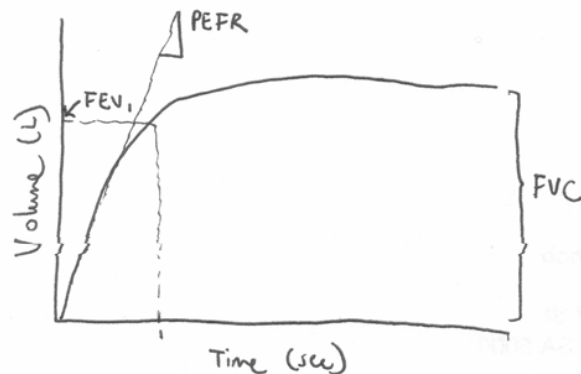
IX. CLINICAL PULMONARY FUNCTION TESTS

- (a) **To distinguish between obstructive and restrictive lung disorders using the family of curves measuring forced expiratory volume, peak expiratory flow rate and vital capacity.**

“Spirometry” → type of lung function test that can be used to distinguish b/t obstructive and restrictive lung disorders → involves use of a “dry spirometer” (vitalograph) that produces a curve of volume (in L) vs time (in sec)

Note – Dry spirometer (Vitalograph):

- Consists of a wedge-shaped bellow connected to a pen
- Expiration causes bellow expansion and movement of the pen → activates a motor that drives paper recorder to move at a fixed rate → tracing of changes in lung volume recorded over time

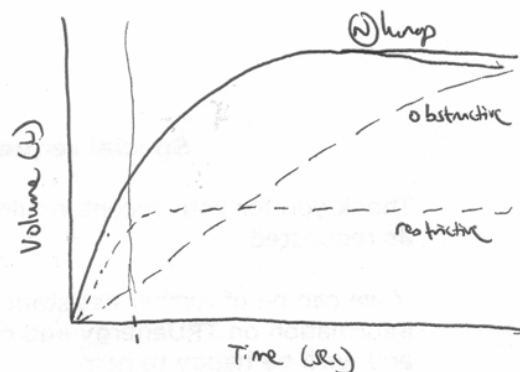


From the spirometry curve, one can obtain the following parameters:

- (1) FEV-1 → forced volume of gas exhaled in one second from full inspiration (or TLC)
- (2) FVC → total volume of exhaled forcibly from full inspiration (or TLC)
- (3) FEV-1/FVC ratio (normally 80%)
- (4) PEFR → maximal air flow rate during forced expiration from full inspiration (or TLC)
- (5) FEF 25-75% → mid-flow rate or forced expiratory flow occurring in the middle 50% of the patient's exhaled volume

Note – These parameters are compared to reference standards based upon gender, height, age, race to determine whether they are within normal limits

Spirometry curves vary with lung disease:



Obstructive lung disease (Eg. COPD, asthma)

		Reasons
FEV1	↓ (markedly)	- ↓ elastic recoil (due to loss of elastin with COPD) → ↓

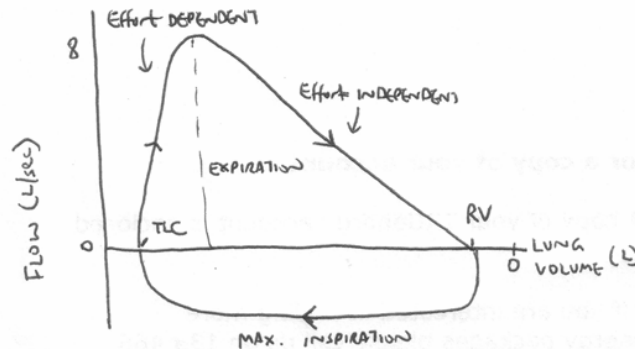
FVC	↓	driving pressure to generate expiratory air flow - ↑ AWR and atelectasis/small AW obstruction due to secretions, dynamic airway compression and bronchoconstriction → ↓ expiratory air flow
FEV1/FVC	< 80%	
PEFR	↓	
FEF 25-75%	↓	

Restrictive lung disease (Eg. ILLD, obesity)

		Reasons
FEV1	↓	- ↓ compliance of respiratory system or weakness in respiratory muscles → ↓ lung volume achieved from full inspiration and ↓ driving pressure to generate expiratory air flow - ↑ AWR due to dynamic airway compression (a/w ↓ lung volumes and ↓ lung compliance) → ↓ expiratory air flow
FVC	↓ (markedly)	
FEV1/FVC	> 80%	
PEFR	↓	
FEF 25-75%	↓	

(b) *To outline methods used for measuring mechanics of breathing, including flow-volume loops, and to interpret such results.*

“Flow-volume loop” – Obtained from a patient by forming a closed circuit with a pneumotachograph → patient maximally inspires to “total lung capacity” (TLC) then undertakes a maximal forced expiration to “residual volume” (RV) → plot of “Flow” (L/sec; y-axis) against “Volume” (L; x-axis) is made



Important to note – “Air flow rate” is determined by:

- (1) Driving pressure:
 - The pressure gradient generated between the alveolus and the mouth
 - This is influenced by:
 - (i) Muscular effort of respiratory muscles – Stronger muscle effort generates $\uparrow P_{\text{ALVEOLAR}}$ (and driving pressure gradient for air flow)
 - (ii) Size of inspired volume – Larger lung volumes generate more stored elastic potential energy, which can produce $\uparrow P_{\text{ALVEOLAR}}$ (and driving pressure gradient for air flow)
 - (iii) Lung compliance – Less compliant lungs are able to store more elastic potential energy when inflated (cf. highly compliant lungs), and thus produce $\uparrow P_{\text{ALVEOLAR}}$ (and driving pressure gradient for air flow)
- (2) Airway resistance:
 - $\downarrow$ AWR facilitates air flow by attenuating the degree of pressure drop within the airways → this occurs at higher lung volumes due to radial traction by lung interstitium, which $\uparrow$ airway calibre

$$\text{Air flow} = \frac{(P_{\text{ALVEOLAR}} - P_{\text{MOUTH}})}{\text{AW resistance}}$$

“Expiratory phase” of flow-volume loop with maximum forced expiration has 2 phases:

- (1) Effort-dependent process:
 - Occurs at the start of expiration at high lung volumes → part of curve where flow rate $\uparrow$ until maximum flow rate is attained
 - Expiratory flow rates (FR) in this phase are proportional to the +ve intrapleural pressures generated (I.e. expiratory effort), such that:
 - At maximal forced expiration → larger +ve $P_{\text{INTRAPLEURAL}}$ is generated to produce a maximal flow rate (FR_{MAX})
 - At submaximal forced expiration → smaller FR are achieved due to lower +ve intrapleural pressures generated
 - Apart from effort, expiratory flow rates are also influenced by:

- (i) Inspired lung volume – $\uparrow$ FR and FR_{MAX} are achieved at $\uparrow$ lung volumes due to $\uparrow$ stored elastic potential energy used to generate driving pressure
- (ii) Lung compliance – $\downarrow$ lung compliance (esp at high lung volumes) have $\uparrow$ stored elastic potential energy to generate $\uparrow$ driving pressure
- (iii) Airway resistance – $\downarrow$ AWR (esp at higher lung) generates $\uparrow$ FR and FR_{MAX} due to $\downarrow$ pressure drop encountered within the airways
- (2) Effort-independent process:
 - Occurs after maximum expiratory flow rates are achieved (at mid-to-low lung volumes)
 - Expiratory flow rates in this phase are independent of the +ve intrapleural pressures generated (I.e. expiratory effort)

This is caused by “Dynamic airways compression”:

- During forced expiration $\rightarrow$ there is $\uparrow$ in $P_{INTRAPLEURAL}$ to generate a driving pressure gradient and produce air flow
- BUT as gas flows from alveolus to mouth $\rightarrow$ there is $\downarrow$ P_{AIRWAY} as air moves away from alveolus, such that there will be a point where $P_{INTRAPLEURAL}$ will = $P_{AIRWAY} \rightarrow$ “Equal Pressure Point (EPP)”
- Airway past this point will be compressed as $P_{INTRAPLEURAL} > P_{AIRWAY} \rightarrow$ thus, at EPP, flow rate becomes dependent on driving pressure generated by $P_{ALVEOLAR} - P_{INTRAPLEURAL}$ difference (rather than $P_{ALVEOLAR} - P_{MOUTH}$ difference) $\rightarrow$ acts like a “Starling-Resistor mechanism”
- As forced expiration continues, lung volumes $\downarrow$ leading to $\downarrow$ driving pressure gradient ($P_{ALVEOLAR} - P_{INTRAPLEURAL}$ gradient) due to $\uparrow$ AWR and $\downarrow$ lung compliance a/w $\downarrow$ lung volumes $\rightarrow$ this causes EPP to move deeper into the lung towards the alveolus
- Air flow continues until AW closure at RV when $P_{ALVEOLAR} = P_{INTRAPLEURAL}$

- This air flow limitation can be exaggerated by:
 - (i) $\downarrow$ lung volumes (by $\downarrow$ stored elastic potential energy and $\uparrow$ AWR)
 - (ii) $\downarrow$ lung compliance (by $\downarrow$ stored elastic potential energy used to generate driving pressures)
 - (iii) $\uparrow$ AW resistance (by $\uparrow$ pressure drop within the airways, which $\downarrow$ driving pressures)

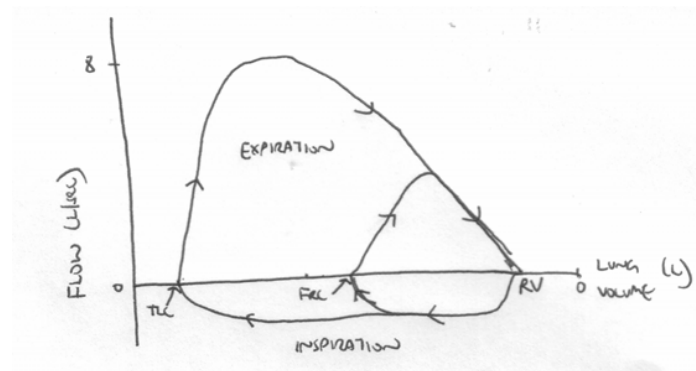
Flow-volume curves will vary depending on the inspired volume achieved prior to forced expiration:

(1) Flow-volume curve from TLC:

- In the effort-dependent part of the curve:
 - There is a rapid rate of $\uparrow$ in FR to a FR_{MAX} of ~ 8 L/sec $\rightarrow$ this is b/c at TLC, the $\uparrow$ lung volumes produce – (i) $\uparrow$ store of elastic potential energy to produce a large driving pressure gradient, and (iii) $\downarrow$ AWR, thus $\downarrow$ pressure drops in airway
- In the effort-independent part of the curve:
 - After FR_{MAX} is achieved, there is $\downarrow$ air flow rates with ongoing expiration due to the effects of “dynamic airway compression”
 - This is due to (i) $\downarrow$ lung volumes with expiration, which is associated with (ii) $\uparrow$ AWR (larger pressure drops) and (iii) $\downarrow$ lung compliance (less driving pressure)
 - Flow rates cease at RV when AW closure occurs

(2) Flow-volume curve from FRC:

- Similar as curve for TLC, EXCEPT is the nature of the effort-dependent part differs $\rightarrow$ there is (i) $\downarrow$ rate of rise in FR, and (ii) a $\downarrow$ maximal FR_{MAX} $\rightarrow$ this is b/c at this lower lung volume, there is:
 - (i) $\downarrow$ elastic potential energy is stored to generate driving pressure gradient
 - (ii) AWR is relatively $\uparrow$ (due to $\downarrow$ radial traction on AW to $\uparrow$ its calibre)
 - (iii) There is a lack in driving pressure gradient as $P_{ALVEOLAR} = P_{ATMOSPHERIC}$ at FRC
- The effort-independent part of the curve is the same as that when expiring from TLC



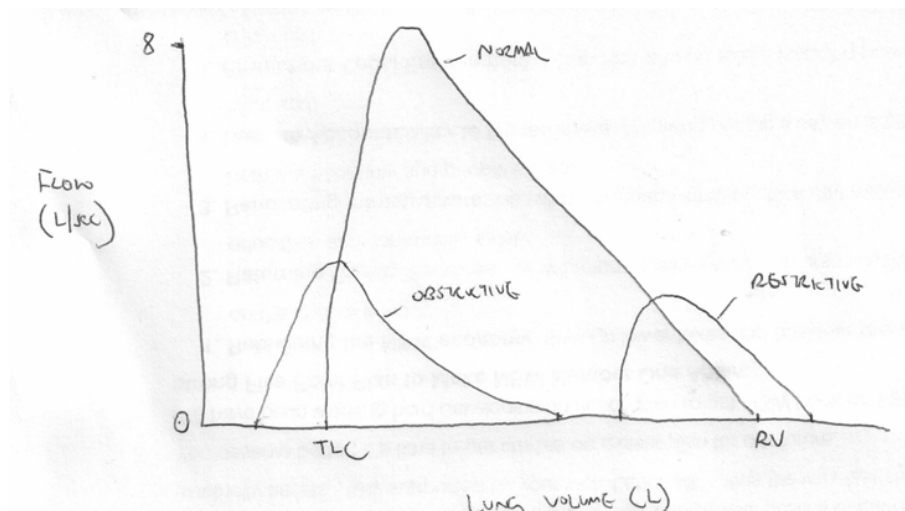
Flow-volume curves will also vary depending on underlying lung disease:

(1) Flow-volume curve for obstructive lung disease:

- Changes in lung volumes:
 - $\uparrow$ TLC and RV and $\downarrow$ VC $\rightarrow$ due to $\uparrow$ lung compliance (from parenchymal damage), which causes $\uparrow$ lung volumes and $\uparrow$ closing capacities (I.e. gas trapping)
- Changes to expiratory flow rates:
 - $\downarrow$ FR_{MAX} and $\downarrow$ steep rise in expiratory FR during effort-dependent part of the curve
 - $\downarrow$ steep and "scooped" appearance of flow curve in effort-independent part of the curve due to dynamic airway compression occurring at higher lung volumes
 - These changes are caused by:
 - (i) $\uparrow$ AWR caused by bronchial SM contraction, secretions, wall oedema, and reduced radial traction (from damaged lung parenchyma)
 - (ii) $\downarrow$ elastic potential energy is stored to generate driving pressure gradient (this is caused by $\uparrow$ lung compliance resulting from damaged lung parenchyma)

(2) Flow-volume curve for restrictive lung disease:

- Changes in lung volumes:
 - $\downarrow$ TLC and VC due to $\uparrow$ lung and/or CW compliance
 - $\downarrow$ RV due to lower closing capacity
- Changes in expiratory flow rates:
 - $\downarrow$ FR_{MAX} due to lower lung volumes (I.e. $\downarrow$ stored elastic potential energy)
 - Slope of expiratory FR during effort-dependent part of the curve is unchanged $\rightarrow$ BUT during the effort-independent part of the curve, FR is steeper (I.e. FR is $\uparrow$ cf. normal at a given lung volume) $\rightarrow$ this is due to (i) $\uparrow$ traction of fibrotic interstitium providing traction on AW (limits effect on dynamic airway compression), and (ii) $\uparrow$ lung elastic recoil

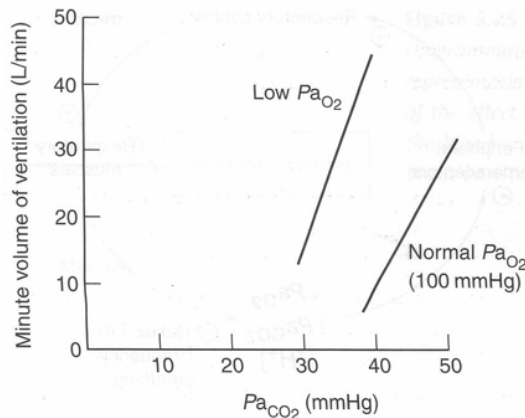


(c) *To describe the carbon dioxide and oxygen response curves and how these may be used to assess the control of breathing.*

CO₂ response curve:

Above PaCO₂ 40 mmHg:

- Minute ventilation is directly proportional to PaCO₂ → MV ↑ by 2-3 L/min per mmHg PaCO₂
- Hypoxaemia has a synergistic effect on hypercapnoeic-ventilatory drive such that ↓ PaO₂ causes an – (i) ↑ MV for a given PaCO₂, and (ii) ↑ Δ MV per Δ PaCO₂ (I.e. CO₂ response curve is shifted upwards and has a steeper slope)



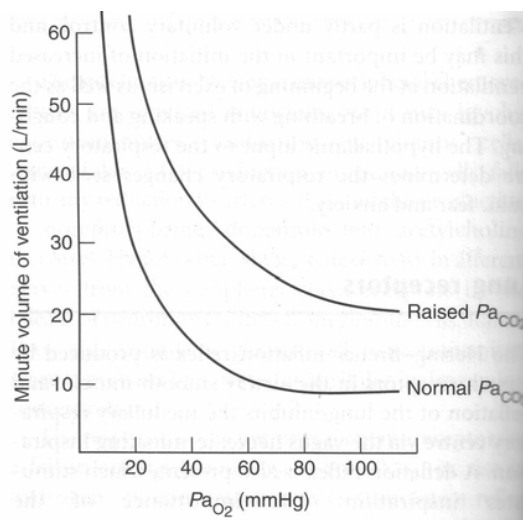
However, at PaCO₂ 70 mmHg → there is ↓ sensitivity of respiratory centres to PaCO₂ due to “CO₂ narcosis” → causes the CO₂ response curve to flatten after maximal MV is achieved at PaCO₂ 100 mmHg

Important to note – Ventilatory response to PaCO₂ ↓ with sleep, ↑ age, drugs (Eg. volatile agents, IV induction agents, opioids, Etc.)

O₂ response curve:

At normal PaCO₂, minute ventilation is inversely proportional to PaO₂ → sensitivity to PaO₂ begins at 500 mmHg and the ventilatory response to ↓ PaO₂ rises slowly until PaO₂ is < 50 mmHg, whereby MV ↑ drastically

There is a synergistic ↑ in ventilatory response in the presence of hypercapnoea and/or acidosis, whereby MV ↑ drastically when PaO₂ is < 100 mmHg



Important to note – “Hypoxic ventilatory drive” is useful under certain conditions:

- (1) Ascent to high altitudes
- (2) Patients with severe lung disease (involving chronic CO_2 retention) – Respiratory drive 2° to $\uparrow \text{PaCO}_2$ and $\downarrow \text{pH}$ are lost as brain ECF $[\text{H}^+]$ normalises rapidly (despite hypercapnoea) and renal compensation to acidosis occurs → as they are dependent on $\downarrow \text{PaO}_2$ for ventilatory drive, do NOT give them $\uparrow \text{FiO}_2$ or else apnoea will occur!

Important to note – Ventilatory response to $\text{PaO}_2 \downarrow$ with anaesthesia (esp volatile agents which depress it at 0.1 MAC)

(d) *To interpret and explain normal and abnormal blood gases.*

See notes on “Acid Base Physiology”

(e) *To outline the measurement of lung volumes including functional residual capacity and residual volume.*

See notes on “Respiratory Physiology – Pulmonary gas volumes and ventilation”

II. CONTROL OF VENTILATION

- (a) *To describe the medullary and pontine respiratory control centres and explain how the ventilatory pattern is generated and controlled.*
- (b) *To describe the chemical control of breathing via central and peripheral chemoreceptors, and indicate how this is altered in abnormal clinical states.*
- (c) *To describe the reflex control of ventilation.*

Overview of Ventilatory Control:

The main function of the lung is to exchange O_2/CO_2 between gas and blood, and in turn maintain a normal and strict PaO_2 and $PaCO_2$ DESPITE widely differing demands for O_2 uptake/ CO_2 output by the body

This level of control requires 3 basic elements:

- (1) Sensors – Detect changes in the body's internal or external environment and relays them to the central controller
- (2) Central controller – Coordinates inputs from sensors, integrates them, and sends impulses to the effectors to alter ventilation as appropriate
- (3) Effectors – Regulate breathing by bringing out necessary changes in ventilation

Note – This process is controlled by -ve feedback → changes in ventilation causes alterations in various physiological parameters that are detected by sensors, which in turn affects future changes in ventilation

(I) Central controller:

(1) Brainstem:

- “Respiratory centres” automate breathing by controlling minute ventilation (both RR and TV) → located in:
 - (a) Medulla (in reticular formation → beneath floor of 4th ventricle)
 - (i) Dorsal respiratory group (“inspiratory group”) – Generates periodic intrinsic impulses that forms the basic rhythm of ventilation (“Pacemaker rhythm”) → transmits signals to diaphragm for 2 seconds (producing a ramp-like inspiratory pattern), then ceases abruptly for 3 seconds to allow expiration to occur
 - (ii) Ventral respiratory group (“expiratory group”) – Usually silent during TV breathing (as expiration is passive), but ↑ activity with forced expiration
 - (b) Pons
 - (i) Pneumotaxic centre – “Fine tunes” respiratory rhythm by inhibiting DRG → causes ↓ inspiratory volume (but also ↓ inspiratory duration, which results in ↑ RR)
 - (ii) Apneustic centre – Acts to promote inspiration by stimulating DRG
- These centres receive input from other parts of the CNS – (i) Cortex, (ii) Limbic system, and (iii) Hypothalamic systems – in addition to input reception from the “sensors”

(2) Cortex → can override “automated” brainstem function if voluntary control of ventilation is needed (I.e. voluntary hyper- or hypoventilation)

(3) Limbic/Hypothalamic systems → influence “automated” brainstem ventilatory function by altering breathing patterns with changes in affective states (Eg. fear/anxiety) or pain

(II) Effectors:

- Muscles of respiration (Eg. diaphragm, IC, accessory and abdominal wall muscles) act in a coordinated manner through inputs from “central controllers” via α motor neurons

(III) Sensors:

(1) Chemoreceptors:

- (a) Central chemoreceptors (CCR):
 - o Located below the ventral surface of the medulla where they are bathed in brain ECF $\rightarrow$ CCR respond to Δ ECF $[H^+]$ whereby $\uparrow$ ECF $[H^+]$ stimulates $\uparrow$ ventilation
 - o ECF $[H^+]$ is influenced by:
 - (i) PCO_2 of blood – CO_2 in blood diffuses across BBB into CSF $\rightarrow$ combines with H_2O to form H_2CO_3 (via carbonic anhydrase), which dissociates into H^+ (and HCO_3^-) $\rightarrow \uparrow$ ECF $[H^+]$
 - (ii) Local blood flow – Cerebral vasodilation (Ie. due to $\uparrow PaCO_2$) causes $\uparrow$ CBF $\rightarrow \uparrow$ diffusion of CO_2 from blood into CSF $\rightarrow \uparrow$ ECF $[H^+]$
 - (iii) Local metabolism – $\uparrow$ cerebral metabolism causes $\uparrow$ ECF $[H^+]$

Note – ECF $[H^+]$ is NOT affected by blood $[H^+]$ or pH as BBB is impermeable to H^+

Important to note – Nature of CSF (or ECF) pH:

- (i) CSF has $\downarrow$ buffering capacity than blood (due to $\downarrow$ protein and HCO_3^- content) $\rightarrow$ so Δ CSF pH per $\Delta PaCO_2$ is GREATER than that of blood
- (ii) HCO_3^- is rapidly transported across BBB into CSF (unlike renal retention of HCO_3^- which is slow) $\rightarrow$ so prolonged Δ CSF pH is associated with more RAPID compensation than in blood

Consequence $\rightarrow$ patients that retain CO_2 2° to lung disease may have near normal CSF pH and abnormally low MV, DESPITE $\uparrow PaCO_2$ or $\downarrow$ blood pH

- (b) Peripheral chemoreceptors (PCR):
 - o There are two types of PCRs:
 - (i) “Carotid bodies” (more important) $\rightarrow$ at bifurcation point of common carotid arteries $\rightarrow$ supplied by CN IX
 - (ii) “Aortic bodies” (less important) $\rightarrow$ above and below the aortic arch $\rightarrow$ supplied by CN X

Note – PCRs are found in “Glomus cells” – Type I (rich in NAd, DA, ACh), and Type II (rich in capillary supply) $\rightarrow \downarrow PaO_2$, $\uparrow PaCO_2$ and/or $\downarrow$ pH causes $\downarrow$ IC [ATP] which leads to $\uparrow$ NT production and release $\rightarrow \uparrow$ AP firing rate of AB or CB afferent fibres

Note – CB and AB have $\uparrow\uparrow\uparrow$ blood flow (much in excess of their weight) so that their O_2 requirements are met by dissolved arterial O_2 (cf. venous O_2)

- o PCRs are activated by the following stimuli to $\uparrow$ ventilation:
 - (i) $\downarrow PaO_2$ – Sensed by PCRs in CB and AB $\rightarrow$ sensitivity begins at 500 mmHg, BUT the response $\uparrow$ drastically at $PO_2 < 50$ mmHg!
 - (ii) $\uparrow PaCO_2$ – Sensed by PCRs in CB and AB $\rightarrow$ response to $\uparrow PaCO_2$ is LESS pronounced cf. CCR response (Ie. $< 20\%$ of total response to $PaCO_2$), BUT is much FASTER cf. CCR response $\rightarrow$ so its role is to match ventilation to sudden Δ in $PaCO_2$ (Ie. fine-tuning)
 - (iii) $\downarrow$ blood pH – Sensed by PCRs in CB only

Important to note → PCR activity ↑ 1°ly due to hypoxaemia, by which this response is potentiated by hypercarbia and/or acidosis

(2) Lung receptors:

- (a) Pulmonary stretch receptors:
 - Present in AW smooth muscle → innervated by CN X
 - Responds to lung distension → triggers “Hering-Breuer inflation reflex”, whereby inflation of lung reflexly retards inspiratory muscle activity to cause ↓ RR 2° to ↑ expiratory time

Note – This reflex is largely INACTIVE unless TV > 1 L (Eg. exercise)

- (b) Irritant receptors:
 - Present in AW epithelial cells → innervated by CN X
 - Triggered by noxious gases (Eg. smoke, inhaled dusts, cold air); innervation via CN X (myelinated fibres) → causes (i) bronchoconstriction and (ii) ↑ RR
- (c) J(uxtacapillary)-receptors:
 - Present in alveolar wall close to capillaries → innervated by CN X
 - Responds to capillary engorgement & interstitial fluid in alveolar wall (Ie. LVF/CCF) → causes (i) ↑ RR but shallow TV, (ii) sensation of dyspnoea, and (iii) apnoea with intense stimulation

(3) Other receptors:

- (a) URT receptors (in nose, NP, larynx, trachea) → respond to mechanical and chemical stimuli to cause bronchoconstriction, sneezing/coughing reflexes, and laryngeal spasms
- (b) Joint/Muscle receptors → limb movement (Eg. exercise) can stimulate ventilation
- (c) Gamma-system (in muscle spindles) → muscle spindles sense muscle elongation, which can cause sensation of dyspnoea
- (d) Arterial baroreceptors (in AB and CB) → ↓ BP causes ↑ ventilation, while ↑ BP can cause ↓ ventilation (and even apnoea)
- (e) Nociceptors → pain causes apnoea initially, then stimulates ventilation
- (f) Thermoreceptors → ↑ temperature stimulates ventilation

Integrated responses and ventilatory control:

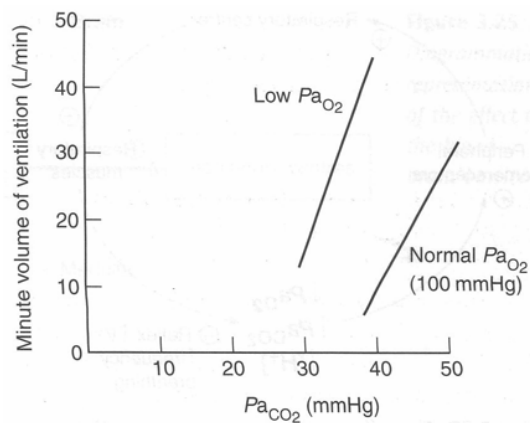
(1) Response to CO₂:

- PaCO₂ is the MOST important factor in ventilatory control → it is very tightly regulated such that PaCO₂ is kept at 40 +/- 3 mmHg

Note – Tight regulation of PaCO₂ is ↓ with – (i) Sleep, (ii) Age, (iii) Medications (Eg. Bz, opiates, anaesthetic agents), and (iv) Lung disease

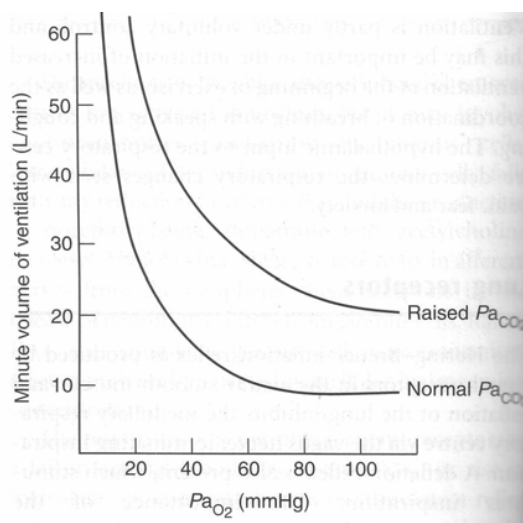
- PaCO₂ is sensed by:
 - (i) CCR (below ventral surface of medulla) – Respond indirectly to Δ in PaCO₂ by Δ in brain ECF [H⁺] → produce significant ventilatory response to ↑ PaCO₂ (80% of total response to PaCO₂)
 - (ii) PCR (in CB and AB) – Respond directly to Δ in PaCO₂ → produce less pronounced ventilatory response to ↑ PaCO₂ (20% of total response) BUT rate of response to Δ in PaCO₂ is very fast → allows fine-tuning of ventilation on breath-to-breath Δ in PaCO₂
- Effect of PaCO₂ on ventilation:
 - Minute ventilation is directly proportional to PaCO₂ → MV ↑ by 2-3 L/min per mmHg PaCO₂

- Hypoxaemia has a synergistic effect on hypercapnoeic-ventilatory drive such that $\downarrow \text{PaO}_2$ causes an – (i) $\uparrow \text{MV}$ for a given PaCO_2 , and (ii) $\uparrow \Delta \text{MV}$ per ΔPaCO_2



(2) Response to O_2 :

- PaO_2 plays a SMALL role in ventilatory control
- PaO_2 is sensed by PCR in CB and AB
- Effect of PaO_2 on ventilation:
 - At normal PaCO_2 , the sensitivity of the receptor to PaO_2 begins at 500 mmHg and the ventilatory response to $\downarrow \text{PaO}_2$ rises slowly until PaO_2 is < 50 mmHg, whereby $\text{MV} \uparrow$ drastically
 - There is a synergistic $\uparrow$ in ventilatory response in the presence of hypercapnoea and/or acidosis, whereby $\text{MV} \uparrow$ drastically when PaO_2 is < 100 mmHg

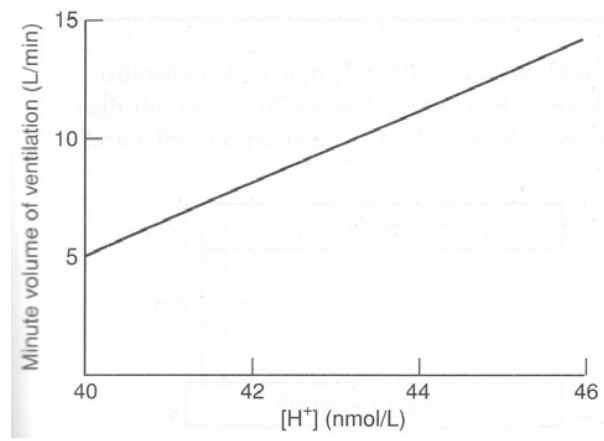


Important to note – “Hypoxic ventilatory drive” is useful under certain conditions:

- (1) Ascent to high altitudes
- (2) Patients with severe lung disease (involving chronic CO_2 retention) – Respiratory drive 2° to $\uparrow \text{PaCO}_2$ and $\downarrow \text{pH}$ are lost as brain ECF $[\text{H}^+]$ normalises rapidly (despite hypercapnoea) and renal compensation to acidosis occurs $\rightarrow$ as they are dependent on $\downarrow \text{PaO}_2$ for ventilatory drive, do NOT give them $\uparrow \text{FiO}_2$ or else apnoea will occur!

(3) Response to pH:

- pH plays a small role in ventilatory control
- pH is sensed by PCR in CB only (and also by CCR if Δ in blood pH is significant, despite BBB being largely impermeable to H^+) $\rightarrow$ such that $\downarrow \text{pH}$ stimulates ventilation



(d) *To describe the ventilatory response to exercise.*

Ventilatory response to exercise:

With exercise, ventilation $\uparrow$ promptly to closely match $\uparrow$ O_2 uptake and CO_2 output $\rightarrow$ BUT no satisfactory mechanism exists:

- (1) $PaCO_2$ – Does NOT $\uparrow$ with exercise (in fact it $\downarrow$ with severe exercise!)
- (2) PaO_2 – $\uparrow$ slightly with exercise (in fact it only $\downarrow$ with severe exercise!)
- (3) Oscillations in $PaO_2/PaCO_2$ – Periodic nature of ventilation in exercise causes fluctuations in $PaO_2/PaCO_2$ (EVEN though mean $PaO_2/PaCO_2$ remain stable)
- (4) $\downarrow$ CCR sensitivity to CO_2 – This allows $\uparrow$ ventilation despite $\downarrow$ $PaCO_2$ with severe exercise
- (5) pH – ONLY $\downarrow$ with severe exercise (2° lactic acidosis)
- (6) Joint/muscle receptors & Gamma-system – Limb movement stimulates ventilation ONLY in the first few seconds of exercise
- (7) $\uparrow$ body temperature can stimulate ventilation
- (8) $\uparrow$ impulses from the motor cortex may directly stimulate ventilation

(e) *To explain the consequences of increased altitude on respiratory function.*

Ventilatory response to increased altitude:

Important to note – $\uparrow$ altitude causes hypoxaemia b/c barometric pressure $\downarrow$ with $\uparrow$ altitude (but FiO_2 remains at 21%) $\rightarrow$ this $\downarrow$ PiO_2 which in turn causes $\downarrow$ PAO_2 (which can be calculated using the “Alveolar gas equation”) and $\downarrow$ PaO_2

There are three phases:

- (1) Altitude-induced hypoxaemia ($\downarrow$ PaO_2) stimulates PCR (in CB and AB) $\rightarrow$ $\uparrow$ MV significantly
- (2) This $\uparrow$ MV then $\downarrow$ PaCO_2 $\rightarrow$ this indirectly $\downarrow$ brain ECF $[\text{H}^+]$ which $\downarrow$ CCR stimulation (in medulla) $\rightarrow$ effectively limits any further $\uparrow$ MV due to hypoxaemia
- (3) Over several days, brain ECF $[\text{H}^+]$ returns to normal (despite $\downarrow$ PaCO_2) as HCO_3^- rapidly equilibrates across the BBB b/t blood and CSF $\rightarrow$ hypoxic ventilatory drive is restored which allows further $\uparrow$ MV to occur

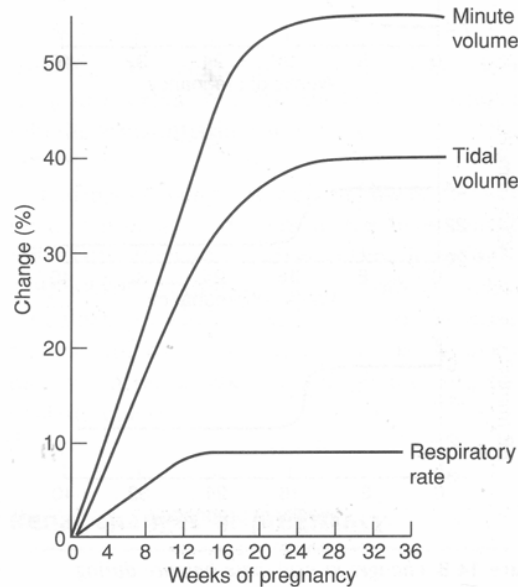
Important to note – It takes several days for maximal ventilatory response to occur $\rightarrow$ there is up to 5x $\uparrow$ MV $\rightarrow$ cause $\uparrow$ PaO_2 and $\downarrow$ PaCO_2

(f) *To explain the consequences of pregnancy on ventilation.*

Ventilatory response to pregnancy:

Pregnancy causes $\uparrow$ minute and alveolar ventilation:

- $\uparrow$ early (esp after 10/40) and continues to $\uparrow$ gradually during pregnancy ($\uparrow$ by 50-70% at term) $\rightarrow$ due to (i) $\uparrow$ TV (by 40% at term) and (ii) $\uparrow$ RR (by 15% at term)
- Caused by progesterone-mediated stimulation of medullary respiratory centres $\rightarrow \uparrow$ sensitivity to PaCO_2 (left shift in CO_2 response curve)



During labour $\rightarrow \uparrow$ MV/AV further (by 160%) due to pain and $\uparrow$ MRO_2 a/w uterine contractions $\rightarrow$ can cause transient $\downarrow$ PaCO_2 (to 20 mmHg!)

(g) *To describe and explain the effects of anaesthesia on ventilatory control.*

Ventilatory response to anaesthetic agents:

Typical anaesthetic agents (Eg. volatile anaesthetic agents, barbiturates and opioids):

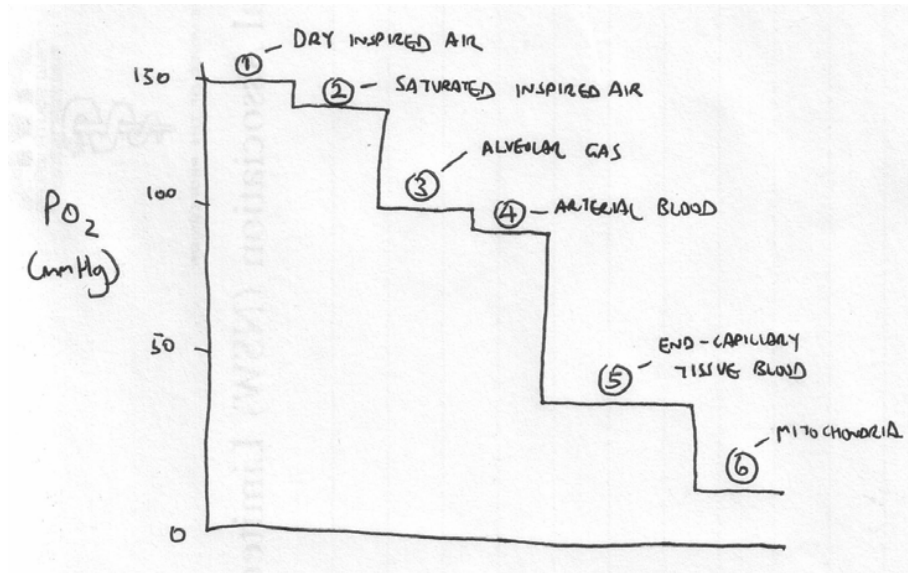
- (1) Depress ventilatory drive to hypercapnia, hypoxaemia and acidosis
- (2) ↓ rate of rise in minute ventilation with hypercapnia
- (3) ↑ “apnoeic threshold” (PaCO_2 at which spontaneous breathing resumes after hyperventilation)

V. DIFFUSIVE TRANSFER OF RESPIRATORY GASES

(a) *To describe and explain the oxygen cascade.*

“Oxygen cascade” is the sequence of stepwise decreases in PO_2 as O_2 moves from inspired gas to the site of consumption within cell (mainly the mitochondria)

Oxygen cascade (assuming room air):



- (1) Dry inspired air:

$$\begin{aligned}
 PO_2 \text{ of dry inspired air (at room air)} &= FIO_2 \times [P_{\text{BAROMETRIC}} - P_{\text{H}_2\text{O VAPOUR @ } 37^\circ\text{C}}] \\
 &= 0.21 \times [760 \text{ mmHg} - 0 \text{ mmHg}] \\
 &= \mathbf{159 \text{ mmHg}}
 \end{aligned}$$

- (2) Saturated inspired air:

- o Dry inspired air is humidified at body temperature (37 °C) within the airways

$$\begin{aligned}
 PO_2 \text{ of saturated inspired air (at room air)} &= FIO_2 \times [P_{\text{BAROMETRIC}} - P_{\text{H}_2\text{O VAPOUR @ } 37^\circ\text{C}}] \\
 &= 0.21 \times [760 \text{ mmHg} - 47 \text{ mmHg}] \\
 &= \mathbf{149 \text{ mmHg}}
 \end{aligned}$$

- (3) Alveolar gas:

- o Exchange of gases (O_2/CO_2) occur in the alveoli such that PAO_2 is determined by:
 - (i) Rate of O_2 transfer from inspired air into alveoli (MAJOR role) – This is influenced by the degree of alveolar ventilation (Nb. this affects $PaCO_2$ in the alveolar gas equation)
 - (ii) Rate of O_2 transfer from alveoli into pulmonary capillary blood – This is influenced by tissue O_2 consumption [VO_2], which varies little at rest (Nb. this affects “R” in alveolar gas equation)
 - (iii) Partial pressure of O_2 of inspired gas (PIO_2) – This is influenced by the $P_{\text{BAROMETRIC}}$ and FIO_2
- o As a result, “Alveolar gas equation” is used to calculate PAO_2 :

$$\begin{aligned}
 PAO_2 \text{ (at room air)} &= PIO_2 - (PaCO_2/R) + F \\
 &= 149 - (40 \text{ mmHg}/0.8) + 0.2 \\
 &= \mathbf{100 \text{ mmHg}}
 \end{aligned}$$

Nb. $F = PACO_2 \times FIO_2 \times (1-R/R)$

“F” is a correction factor ($\sim 2 \text{ mmHg}$ at room air), and is only an issue when breathing higher FIO_2

- (4) Arterial blood:
 - Venous admixture from (i) True shunts and (ii) Lung units with $V/Q < 1$ added to end-capillary blood causes a fall in PaO_2 , thereby resulting in an alveolar-arterial PO_2 gradient of 5-10 mmHg

$$PaO_2 \text{ (at room air)} = PAO_2 - 5 \text{ mmHg} = \mathbf{95 \text{ mmHg}}$$

- (5) Tissue end-capillary blood:
 - Diffusion of O_2 into cells causes PO_2 at end-capillary (assuming breathing at room air) is **40 mmHg**
- (6) Mitochondria:
 - O_2 is consumed within the cell mainly by mitochondrial oxidative phosphorylation
 - PO_2 is highly variable (1-20 mmHg) due to variations in:
 - (i) Mitochondrial O_2 consumption
 - (ii) Diffusion distance to mitochondria
 - (iii) Mean capillary O_2 tension
 - “Pasteur point”:
 - Critical PO_2 at which aerobic metabolism (I.e. oxidative phosphorylation) can occur. Below this, anaerobic metabolism proceeds
 - This PO_2 at which this happens is $\sim 1 \text{ mmHg}$ – It is very low as Cytochrome oxidase (terminal enzyme in ETC) has a very high O_2 affinity

(b) *To explain the capillary exchange of oxygen and carbon dioxide, and the relationship of erythrocyte transit to oxygen and carbon dioxide transfer.*

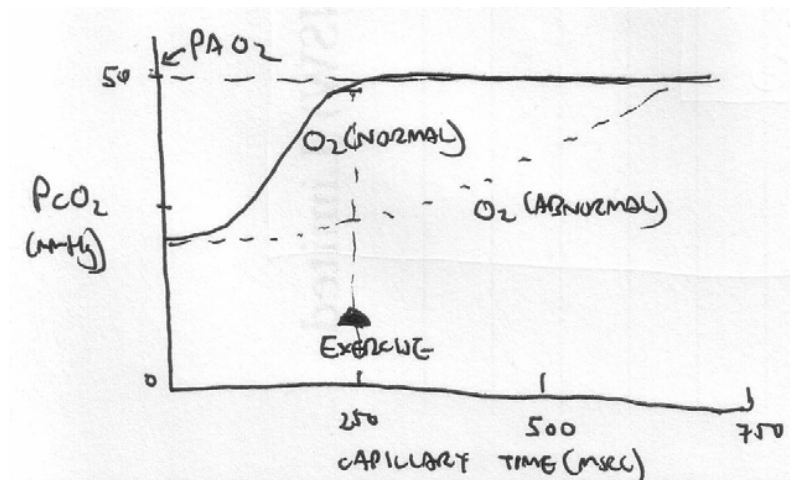
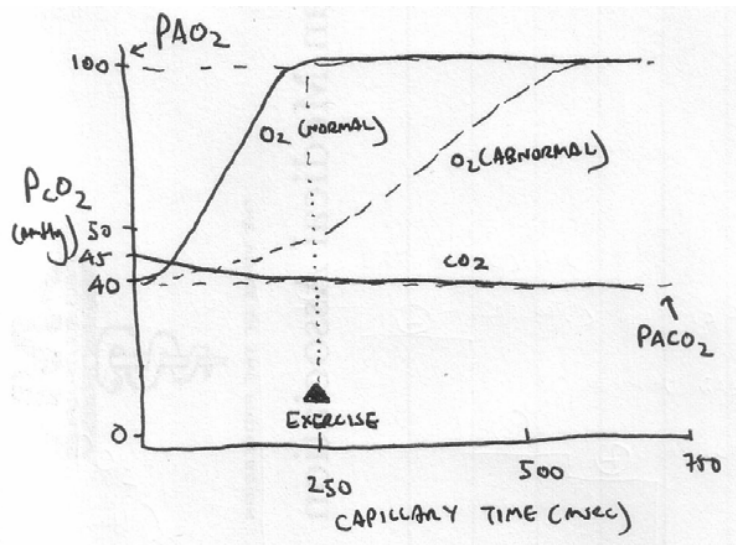
Capillary exchange of oxygen and carbon dioxide:

- Oxygen:
 - In healthy lung at rest, O₂ transfer is perfusion-limited:
 - O₂ has a high blood-gas barrier solubility due to its high pressure gradient (PvO₂ 40 mmHg and PAO₂ 100 mmHg, giving a gradient of 60 mmHg)
 - O₂ has a high blood solubility due to the flat upper position it has on the ODC (I.e. Hb is nearly saturated), thus the majority of O₂ is dissolved in plasma instead and PcO₂ rises quickly
 - As a result, PO₂ of the alveoli and capillary equilibrate within 250 msec (or 1/3rd pulmonary transit time) and no further O₂ transfer can occur until more blood flow happens
 - In diseased lungs, O₂ transfer is diffusion-limited:
 - O₂ diffusion is impeded as blood-gas solubility of O₂ is lowered
 - This causes the rate of rise in PcO₂ to be attenuated, thus preventing it from reaching equilibrium with PAO₂ by end-capillary
 - At high altitudes, O₂ transfer remains perfusion-limited in healthy lungs:
 - O₂ has a lower blood-gas solubility due to a smaller pressure gradient (as PIO₂ and PAO₂ are reduced to 50 mmHg, and PvO₂ is reduced to 30 mmHg, such that P_{GRADIENT} is now only 20 mmHg)
 - O₂ solubility in blood is also decreased as PvO₂ sits in the lower and steeper part of the ODC (I.e. Hb in blood binds more O₂ than is dissolved in blood), hence PcO₂ rises much slower
 - Despite these changes, equilibrium between PAO₂ and PcO₂ is still achieved by end-capillary, hence gas transfer is perfusion-limited in healthy lungs
 - If blood-gas solubility of O₂ is lowered with lung disease, the rate of rise in PcO₂ is attenuated such that equilibrium with PAO₂ will not occur by end-capillary, thus O₂ transfer becomes diffusion-limited
- Carbon dioxide:
 - CO₂ rapidly crosses the blood-gas barrier due to its high blood-gas barrier solubility such that the P_{CO2} in the alveolus rises rapidly and equilibrates with P_{CO2} in capillary blood within 250 msec (or 1/3rd pulmonary capillary transit time)
 - As a result, there is no further CO₂ transfer UNTIL more minute ventilation is achieved – Thus, CO₂ gas transfer is limited by the level of minute ventilation (I.e. it is NOT by diffusion)

Effect on oxygen and carbon dioxide transfer with increased cardiac output:

- With increased cardiac output, there is:
 - (i) Alveolar recruitment (increased lung SA for gas diffusion to occur; or increased blood-gas barrier solubility)
 - (ii) Reduced pulmonary capillary transit time by RBC (reduced from 750 msec to 250 msec; or increased blood solubility)
- Implications on oxygen transfer:
 - In healthy lungs, O₂ transfer remains perfusion-limited despite increased C.O. – Despite a fall pulmonary capillary transit time to 250 msec, PO₂ of the alveoli and capillary are still able to equilibrate, and thus no further O₂ transfer can occur until more blood flow happens
 - In elite athletes, O₂ transfer becomes diffusion-limited with increased C.O. – C.O. can increase vastly such that pulmonary capillary transit time is < 250 msec (such that gas is more soluble in blood than blood-gas barrier), thus preventing equilibration between PAO₂ and PcO₂ by end-capillary

- At high altitudes (for both healthy and diseased lungs), O_2 transfer becomes diffusion-limited with increased C.O. – Pulmonary capillary transit time falls to 250 msec, which prevents equilibration between PAO_2 and PcO_2 by end-capillary
- Implications on carbon dioxide transfer:
 - With increased C.O., CO_2 transfer remains limited by minute ventilation as equilibration between $PACO_2$ and $PcCO_2$ still occurs by end-capillary despite an attenuation of pulmonary capillary transit time to 250 msec



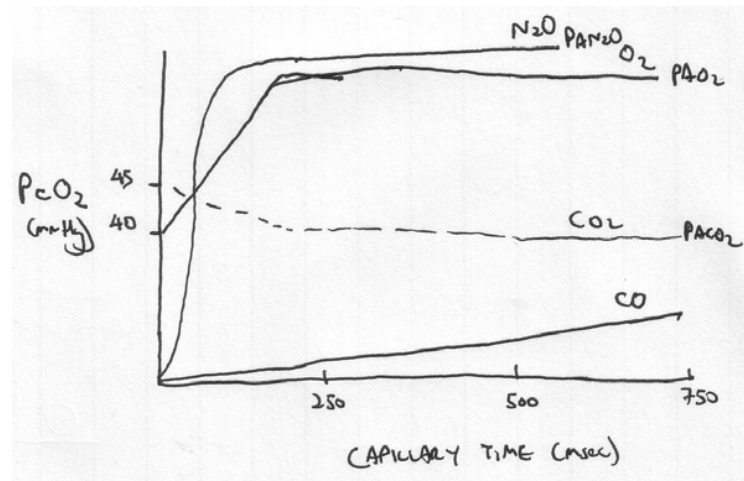
(d) *To explain perfusion-limited and diffusion-limited transfer of gases.*

Perfusion limitation in gas transfer:

- Rate of gas transfer between alveolus and capillary is dependent on the amount of blood flow through the alveolar capillary
- Mechanism:
 - o Limitations in blood flow cause equilibrium between the partial pressure of gas in the capillary and partial pressure of gas in the alveoli to be achieved BEFORE blood finishes passing through the pulmonary capillaries, and as a result no more gas transfer can occur along the length of the capillary
 - o However, with perfusion-limited gases, the rate at which this equilibrium occurs is dependent on the amount of blood flowing in the pulmonary capillaries – In other words, increasing blood flow will reduce the rate of achieving equilibrium, and thereby facilitate gas transfer along the length of the capillary
- Example: N₂O
 - o Due to its high blood-gas barrier solubility, N₂O crosses the blood-gas barrier. However, due to its low solubility in blood, it does not combine readily with Hb or dissolve in blood
 - o As a result, the rate of rise in P_{N₂O} in capillary blood is rapid such that it equilibrates with P_{N₂O} in alveoli within 100 msec (or 10% along pulmonary capillary system) – There is no further N₂O transfer UNTIL more blood passes through the capillary system (thus, perfusion-limited)

Diffusion limitation in gas transfer:

- Rate of gas transfer between alveolus and capillary is dependent on the diffusion property of the blood-gas barrier
- Mechanism:
 - o Limitations in diffusion of gas across the blood-gas barrier cause the partial pressures of gas in the capillary and in the alveoli to NOT equilibrate before blood leaves the pulmonary capillaries. As a result, gas transfer continues (and is NOT complete) at end-pulmonary capillary
 - o With diffusion-limited gases, the rate at which the partial pressure of gas in the capillary rises is independent of pulmonary capillary blood flow – As a result, increasing blood flow does not facilitate gas transfer, and hence gas-transfer is not perfusion-limited (or in other words, it is diffusion-limited)
- Example: CO
 - o CO has a very high solubility in blood (I.e. much higher than its solubility in the blood-gas barrier) because it binds very avidly with Hb in blood such that little is dissolved in plasma
 - o As a result, PaCO rises only slightly such that at the end-capillary transit a significant alveolus-blood [] gradient remains (I.e. equilibration of PACO and PcCO is incomplete) – There is still ongoing diffusion of CO across the blood-gas barrier at this point, which suggests that CO transfer is diffusion-limited



Determining whether gas transfer is diffusion- or perfusion-limited:

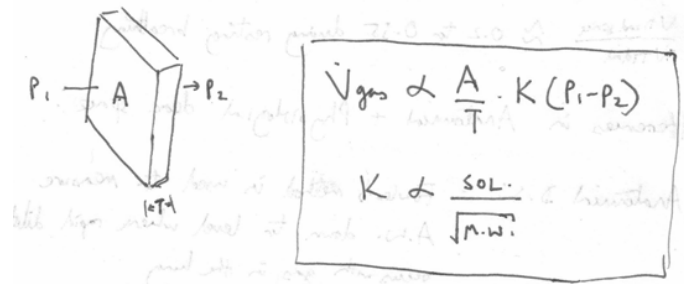
- Whether a gas is diffusion or perfusion limited is dependent on its:
 - (1) Solubility of gas in the blood-gas barrier – According to Fick's law of diffusion, this is mainly influenced by:
 - (a) Pressure gradient
 - (b) Solubility of the gas in the barrier
 - Nb. The remaining variables are generally fixed (Eg. MWT, thickness and surface area of blood-gas barrier)
 - (2) Solubility of gas in blood – This is influenced by:
 - (a) Transit time of blood through alveoli (Eg. cardiac output)
 - (b) Gas's affinity for Hb
 - (c) Gas's solubility in plasma

<i>Gas transfer</i>	<i>Blood solubility</i>	<i>Blood-gas solubility</i>
Perfusion-limited	Low	Low
Perfusion-limited	Low	High
Perfusion-limited	High	High
Diffusion-limited	High	Low

(d) *To define diffusion capacity and its measurement.*

Blood-gas barrier:

- The blood-gas barrier of each of these units comprises of:
 - (i) Alveolar wall
 - (ii) Interstitial space
 - (iii) Pulmonary capillary endothelium
- The barrier is 0.3 μm thick and has an alveolar surface area of 50-100 m^2
- Transfer of gas across this barrier (from the alveolus to the pulmonary capillary) occurs by diffusion, which is governed by "Fick's Law":



- (1) Diffusion is proportional to:
 - (a) Surface area of barrier (B-G barrier is 50-100 m^2)
 - (b) Pressure gradient across the barrier
 - (c) Diffusion constant, which is "Solubility of gas" divided by the "Square root of MWT"
- (2) Diffusion is inversely proportional to thickness (B-G barrier is 0.3 μm)

Definition of "Diffusion capacity of the lung" (D_L):

- Describes the diffusion properties of the lungs as it takes into account the:
 - (1) Surface area of the barrier
 - (2) Thickness of the barrier
 - (3) Solubility coefficient of the gas (molecular weight and solubility of gas in the barrier)
- Based on these properties, it determines the lung's ability to transfer gas (I.e. whether gas is diffusion-limited or not)

Measurement of "Diffusion capacity of the lung":

- Since CO is diffusion limited, it is the gas of choice when measuring the diffusion properties of the lung during pulmonary function tests:

$$V_{\text{GAS}} = \frac{A \cdot K}{T} (P_1 - P_2) \quad ; \text{whereby } D_L = (A \cdot K) / T$$

$$\text{So, } V_{\text{GAS}} = D_L (P_1 - P_2)$$

$$\text{For CO, } D_L = \frac{V_{\text{CO}}}{(P_A \text{CO} - P_{\text{CAP}} \text{CO})}$$

But as noted above $P_{\text{CAP}} \text{CO}$ is very small (almost zero), thus:

$$D_L \text{CO} = \frac{V_{\text{CO}}}{P_A \text{CO}}$$

- The normal value of D_LCO is “25 mL CO transferred/minute/mmHg of PACO” (Nb. this can increase 2-3X with exercise due to recruitment/distension of pulmonary capillary beds)
- D_LCO is measured using the “Single Breath Method”:
 - Dilute mixture of CO is inspired, followed by a 10-second breathhold
 - Inspired and expired [CO] are then measured with an infrared analyser, and the rate of disappearance of CO from alveolar gas during breathhold is calculated to give D_LCO

(c) *To describe the physiological factors that alter diffusion capacity.*

The uptake of gas in the lungs (and hence diffusion of gas) occurs in two steps:

- (1) Diffusion of gas across the B-G barrier [D_M]
 - Determined by Fick's law of diffusion (Ie. influenced by thickness, surface area, molecular weight, solubility and pressure gradient)
 - Includes plasma and RBC interior
- (2) Reaction of gas with Hb within the capillary system [$\theta \cdot V_C$]
 - Determined by product of:
 - (i) Volume of capillary blood (V_C)
 - (ii) Rate of gas (in mL/min) that combines with a mL of blood per mmHg of gas (θ)
 - For gases that bind to Hb (Eg. CO and O₂), the diffusion rate of gas from alveoli to capillary blood is determined by the extent and rate of binding to Hb – This is because binding to Hb maintains the pressure gradient for diffusion (Ie. it prevents equilibration between alveolar and capillary blood partial pressures of gas)

The overall resistance of the diffusion barrier can be expressed as a function of the resistance of the (i) blood-gas barrier, and (ii) reaction of gas with Hb within the capillary system:

$$(1/D_L) = (1/D_M) + (1/[\theta \cdot V_C])$$

Thus, the factors that alter D_L include:

- (1) Diffusion of gas across the B-G barrier (D_M)
 - Factors that decrease D_M (Eg. reduced surface area, increased thickness, reduced pressure gradient, increased molecular weight of gas, decreased solubility of gas in barrier) will decreased D_L
- (2) Volume of capillary blood (V_C)
 - Factors that impair capillary blood flow (Eg. reduced CO) will decrease D_L
- (3) Rate of gas that combines with blood (θ)
 - Factors that reduce the rate at which gas combines with blood (Eg. breathing a mixture of another gas that competes with Hb; O₂ vs CO) will cause D_L to fall

VII. GAS TRANSPORT IN THE BLOOD

- (a) *To describe the carriage of oxygen in blood.*
- (b) *To explain the oxyhaemoglobin dissociation curve and factors that may alter it such as carbon dioxide, temperature, carbon dioxide and hydrogen ion concentration and 2,3-diphosphoglycerate.*
- (c) *To describe the carbon dioxide carriage in blood including the Haldane effect, and the chloride shift.*
- (d) *To explain the carbon dioxide dissociation curve and its clinical implications.*
- (e) *To describe the oxygen and carbon dioxide stores in the body.*

(I) O₂ Carriage in Blood:

O₂ is carried in blood in 2 forms:

- (1) Dissolved O₂
 - o Obeys “Henry’s Law” → concentration of gas dissolved in a liquid is proportional to its partial pressure [$C_x = K \times P_x$], whereby $K = 0.003 \text{ mL O}_2/100 \text{ mL blood}/1 \text{ mmHg O}_2$

Important to note – This is a very inefficient means of O₂ carriage → assuming normal PaO₂ = 100 mmHg, blood carries only 0.3 mL O₂/100 mL in dissolved form

- (2) O₂ combined with haemoglobin
 - o Amount of O₂ bound to Hb depends on:
 - (i) “O₂ Capacity of Hb” → maximum amount of O₂ that can bind to Hb (I.e. all binding sites on Hb are occupied)

$$\text{O}_2 \text{ capacity of Hb} = [\text{Hb}] \times (k)$$

Where:

- [Hb] = [] of Hb in g/dL
- k = “Hufner’s number”, which is the amount of O₂ that can combine with 1 g Hb when fully saturated

Note – 1 g of Hb can carry up to 1.39 mL O₂, BUT “k” is only 1.34 mL O₂/g Hb → this is b/c there are Hb variants (Eg. COHb, MetHb, Etc.) that cannot combine with O₂

- (ii) “O₂ Saturation of Hb” (SO₂) → percentage of available binding sites on Hb with O₂ attached

$$\text{SO}_2 = \frac{(\text{Actual content of O}_2 \text{ combined with Hb})}{(\text{Maximal O}_2 \text{ capacity of Hb})} \times 100 \%$$

Note – Blood contains up to 4 Hb species (oxyHb, deoxyHb, met-Hb and CO-Hb), BUT only oxyHb is able to carry O₂ → as a result, there are 2 types of “Hb O₂ saturations”:

- (i) Functional saturation – Traditional consideration of Hb O₂ saturation as defined above

$$\text{Function saturation} = \frac{[\text{HbO}_2]}{([\text{HbO}_2] + [\text{deoxy Hb}])} \times 100\%$$

- (ii) Fractional saturation – Considers Hb O₂ saturation in context of total [Hb] (rather than maximal O₂ capacity of Hb as oxy- and deoxyHb only) → more appropriate in calculating O₂ content in blood bound to Hb, and more clinically relevant (esp if large amts of met-Hb and CO-Hb are present)

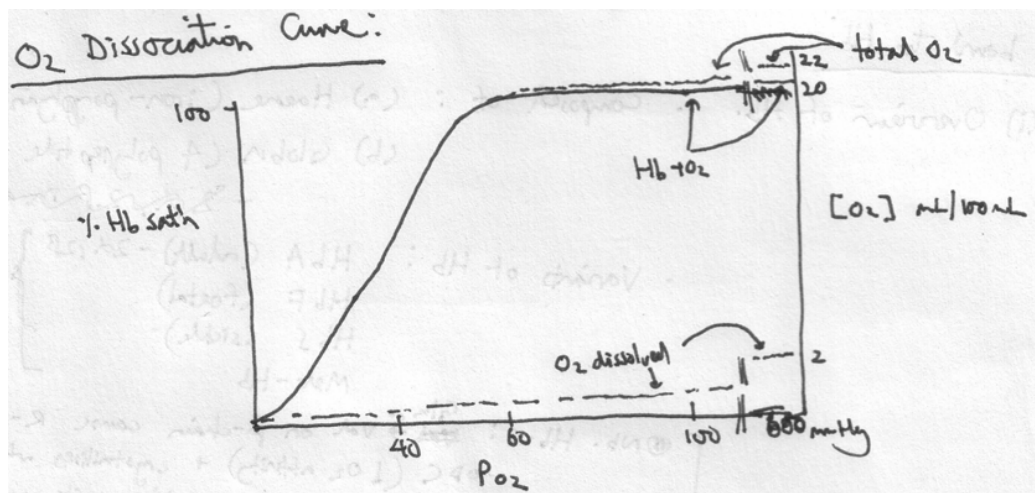
$$\text{Fractional saturation} = \frac{[\text{HbO}_2]}{(\text{Total [Hb]})} \times 100\%$$

Aside – Pulse oximeters measure neither functional nor fractional saturation → Hb O₂ saturation measured depends on calibration used for a given brand (I.e. measured value may lean towards one or the other of these two saturations)

- So, amount of O_2 combined to Hb = (O_2 capacity of Hb) x (SO_2)
 $= [Hb] \times (k) \times (SO_2)$
 $= [Hb] \times (1.34 \text{ mL } O_2/\text{g Hb}) \times (SO_2)$

Important to note – This is a very efficient means of O_2 carriage → assuming Hb = 15 g/dL and it is 100% saturated with O_2 , blood can 20.8 mL O_2 /100 mL

The MAJORITY of O_2 transported in blood is combined with Hb (99 %), while only 1% of O_2 is transported in blood dissolved



The “Total O_2 Concentration in Blood” is the sum of both (i) dissolved O_2 and (ii) O_2 combined with Hb:

$$\text{Total } O_2 [] \text{ in blood} = [\text{Amt of } O_2 \text{ dissolved in blood}] + [\text{Amt of } O_2 \text{ combined to Hb in blood}]$$

$$= [(0.003 \text{ mL } O_2/100 \text{ mL}) \times (P_{O_2})] + [(1.34 \text{ mL } O_2/\text{g Hb}) \times [Hb] \times SO_2]$$

Important to note: O_2 content of arterial blood (CaO_2) = 20 mL/dL
 O_2 content of MVB (CvO_2) = 15 mL/dL

Blood has a SIGNIFICANT reserve of O_2 for any $\uparrow$ in tissue requirements → following O_2 delivery to tissues, only 5 mL O_2 /100 mL blood is actually used by tissues (despite a 60 mmHg $\downarrow$ in P_{O_2}) and CvO_2 is high at 15 mL/dL

(II) **Oxygen Flux:**

“Oxygen flux” – Amount of O₂ delivered to peripheral tissues per minute (Ie. total body O₂ delivery)
→ ~ 1000 mL O₂/minute in healthy young adult at rest

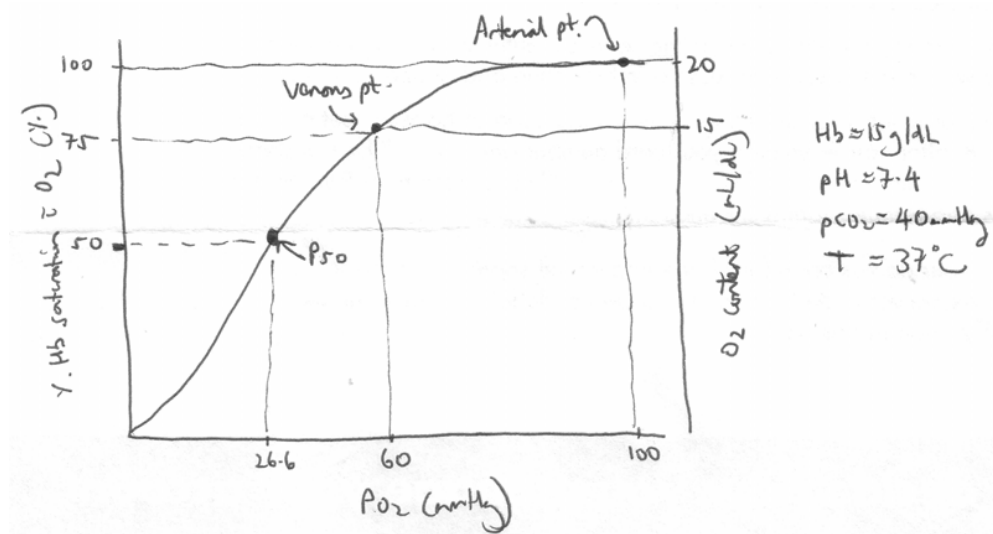
It is calculated as follows:

$$\begin{aligned} \text{O}_2 \text{ flux} &= (\text{Total O}_2 \text{ content of blood}) \times (\text{C.O.}) \\ &= [(0.003 \times 100 \text{ mmHg}) + (15 \text{ g/dL} \times 0.99 \times 1.34)] \times (50 \text{ dL/min}) = 1000 \text{ mL O}_2/\text{min} \end{aligned}$$

Important to note – In a resting state, the body’s tissues extract 250 mL O₂/min such that 750 mL O₂/min return to the right heart

Important to note – Oxygen uptake by the lungs matches the body’s tissues consumption → at resting state, lungs take up 250 mL O₂/min (as the body’s tissues extract 250 mL O₂/min)

(III) Oxygen Haemoglobin Dissociation Curve:



There are 3 important points on the oxygen haemoglobin dissociation curve (OHDC):

- (i) Arterial point:
 - o Represents arterial blood → PO_2 100 mmHg, O_2 content 20 mL/100mL blood and SaO_2 97.5%
- (ii) Mixed venous point:
 - o Represents mixed venous blood → PO_2 40 mmHg, O_2 content 15 mL/100mL blood, and SaO_2 75%
- (iii) P50:
 - o Partial pressure of O_2 at which an Hb is 50% saturated → P50 of Hb = 26.6 mmHg
 - o It is an index of O_2 affinity of Hb:
 - ↑ P50 (associated with right shift in ODHC) → ↓ O_2 affinity by Hb
 - ↓ P50 (associated with left shift in ODHC) → ↑ O_2 affinity by Hb
 - o P50 lies on the steepest part of the OHDC → most sensitive point for detecting shift in the curve, thus useful in comparing position of other OHDCs under varying conditions (Eg. CO_2 , pH, temperature, Etc.)

The shape of the OHDC is “sigmoidal”:

- This is due to its multimeric structure, which permits “+ve cooperative binding” b/t Hb and O_2 , whereby reaction of O_2 with each of the 4 subunits of Hb occur sequentially with each reaction facilitating the next → results in ↑ O_2 affinity with ↑ O_2 binding

Note – Hb exists in 2 states:

- Tense (T) – Deoxygenated Hb has ↓ O_2 affinity as globin molecules stuck together
- Relaxed (R) – Oxygenated Hb has ↑ O_2 affinity as globin molecules released from each other exposing ↑ O_2 bind sites

- This has the following implications:
 - o (i) Flat upper portion (> 60 mmHg)
 - Acts as to “buffer” Hb saturation and arterial O_2 content against significant ↓ in PAO_2 (Ie. PAO_2 can ↓ to 80 mmHg yet Hb SaO_2 and CaO_2 remain at 96% and 18 mL O_2 /100 mL, respectively)
 - o (ii) Steep lower portion (< 60 mmHg)

- Large quantities of O_2 can be unloaded from Hb to peripheral tissues without a significant $\downarrow$ in capillary blood PO_2
- Hb can be rapidly saturated in the pulmonary circulation without a significant $\uparrow$ in PO_2
- Maintains O_2 diffusion gradient from capillary blood to cell (despite $\uparrow O_2$ extraction)

Position of OHDC can be shifted by several factors:

Important to note – OHDC shift is measured by P50 (see above):

- (i) RIGHT shift $\rightarrow \uparrow P_{50}$, which implies $\downarrow O_2$ affinity by Hb and $\uparrow O_2$ unloading from Hb
- (ii) LEFT shift $\rightarrow \downarrow P_{50}$, which implies $\uparrow O_2$ affinity by Hb and $\downarrow O_2$ unloading from Hb

- (1) $H^+ - [H^+]$ causes a RIGHT shift; $\downarrow [H^+]$ causes a LEFT shift
- (2) $P_{CO_2} - \uparrow P_{CO_2}$ causes a RIGHT shift; $\downarrow P_{CO_2}$ causes a LEFT shift

“Bohr Effect” $\rightarrow CO_2$ loading assists O_2 unloading from Hb

Mechanism – Due to a secondary effect on $[H^+]$ $\rightarrow CO_2$ forms H^+ via H_2CO_3 , which then competes with O_2 for Hb $\rightarrow$ effectively causes $\downarrow O_2$ affinity

- (3) Temperature – $\uparrow$ temperature causes a RIGHT shift; $\downarrow$ temperature causes a LEFT shift
- (4) 2,3-DPG – $\uparrow [2,3-DPG]$ causes a RIGHT shift; $\downarrow [2,3-DPG]$ causes a LEFT shift

Note – 2,3-diphosphoglycerate (2,3-DPG) is a side-shunt product of RBC glycolysis that binds with β -chain of Hb to $\downarrow$ its affinity for $O_2 \rightarrow$ its levels are $\uparrow$ with chronic hypoxia, anaemia, exercise, high altitudes; $\downarrow$ with blood storage

- (5) CO – Causes a LEFT shift (blocks O_2 unloading) $\rightarrow$ BUT it also has 240x greater affinity for Hb than O_2 (I.e. saturates Hb at a LOWER partial pressure than O_2), thus, impairing O_2 carriage in blood (I.e. $\downarrow O_2$ content)
- (6) Hb type – Hb-S and Met-Hb cause a RIGHT shift; Hb-F causes a LEFT shift

(IV) CO₂ Carriage in Blood:

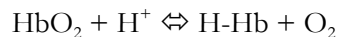
CO₂ is carried in blood in 3 forms:

- (1) Dissolved CO₂
 - o Obeys “Henry’s Law” (like O₂), whereby the amount of CO₂ dissolved is proportional to (i) PCO₂ in blood, and (ii) Solubility of CO₂ in blood (CO₂ is 20X more soluble than O₂)
 - o CO₂ can be dissolved in plasma or RBC
- (2) As HCO₃⁻
 - o CO₂ is converted within the RBC to HCO₃⁻ as follows:

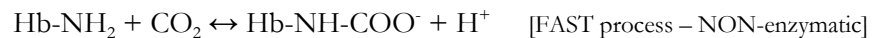


Note – Carbonic anhydrase is present in RBC only (NOT in plasma!)

- o “Chloride shift” occurs (Hamburger effect) – HCO₃⁻ diffuses out of RBC into plasma BUT H⁺ does not (as membrane impermeable to cations) → so to maintain electrical neutrality Cl⁻ shifts intracellularly
- o Intracellular H⁺ is buffered by binding to basic imidazole groups on histidine moieties in deoxygenated Hb (or Reduced Hb):



- (3) As Carbamino compound
 - o CO₂ rapidly and spontaneously combines with terminal NH₂ (amine) groups and NH₂ side-chains of arginine/lysine moieties in blood proteins



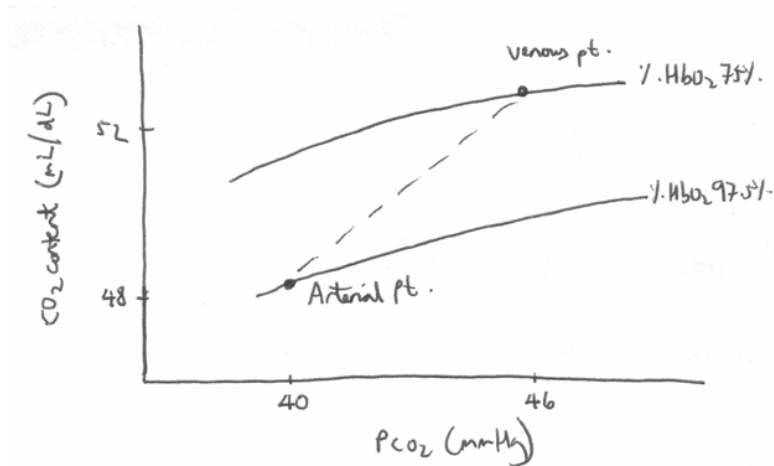
- o Hb is MORE important than plasma proteins in forming carbamino compounds b/c:
 - (i) More Hb present cf. plasma proteins (15 g/dL vs 7 g/dL)
 - (ii) Hb is tetramer → each globin has a terminal NH₂ group so Hb has 4 potential binding sites for CO₂ (cf. albumin has only 1)
 - (iii) Formation of carbamino compounds ↑ greatly as Hb deoxygenated (I.e. Haldane effect)

The % contribution to the total amount of CO₂ carried in blood in each form depends on the type of blood:

Form of CO ₂ carriage	Arterial blood (%)	Arterial-venous difference (%)
Dissolved CO ₂	5	10
As HCO ₃ ⁻	90	60
As carbamino compound	5	30

Important to note: CO₂ content of arterial blood (CaCO₂) = 48 mL/dL
CO₂ content of MVB (CvCO₂) = 52 mL/dL

(V) Carbon Dioxide Dissociation Curve:



There are 2 important points on the carbon dioxide dissociation curve (CO₂ DC):

- (i) Arterial point → represents arterial blood (PCO₂ 40 mmHg and CO₂ content 48 mL/dL)
- (ii) Mixed venous point → represents MVB (PCO₂ 46 mmHg, CO₂ content 52 mL/dL)

The CO₂ DC has the following characteristics that are distinct from the OHDC:

- (1) CO₂ DC curve is more LINEAR cf. OHDC
- (2) CO₂ DC curve is more STEEP cf. OHDC
 - o Δ in 1 mmHg CO₂ causes a ↑ Δ in CO₂ content (while a 1 mmHg Δ in O₂ causes a smaller Δ in O₂ content) → so a higher pressure change is needed to load/unload O₂ than CO₂
 - o This explains the greater PO₂ arterial-mixed venous difference (~60 mmHg) than PCO₂ arterial-mixed venous difference (~5 mmHg)
- (3) The lower the % HbO₂, the larger the CO₂ content of blood for a given PCO₂ → due to “Haldane effect”

“Haldane Effect” → blood has ↑ ability to carry CO₂ when Hb gives up binding to O₂

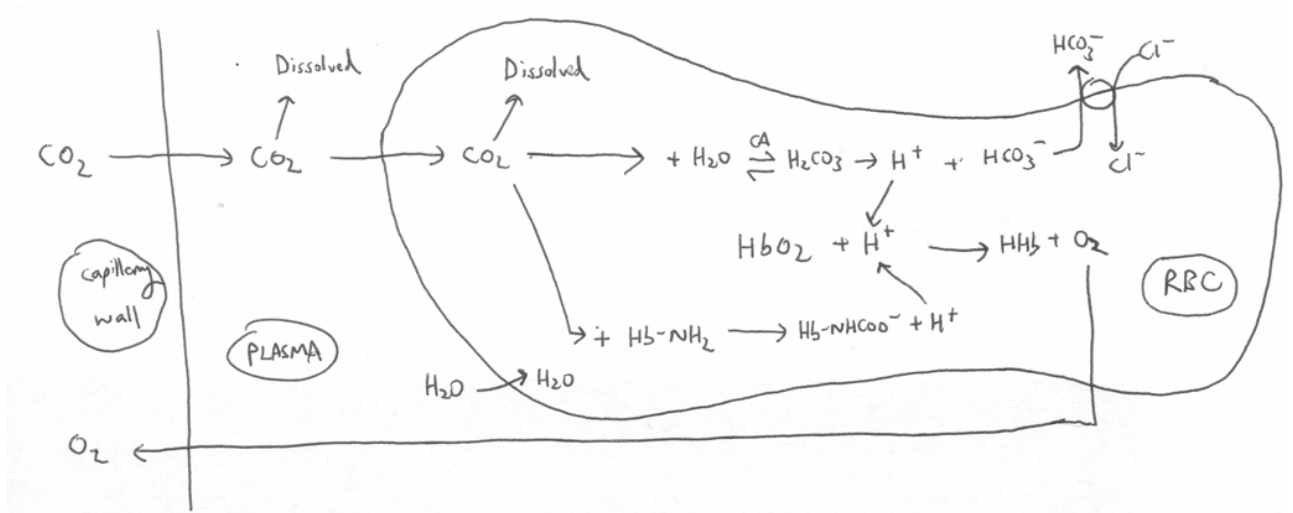
Mechanism:

- (i) Deoxygenated (or reduced) Hb is 2-3x more effective than oxy-Hb in forming carbamino compounds → MAJOR factor (70%)
- (ii) Deoxygenated (or reduced) Hb is a better buffer than oxy-Hb (as it is less acidic), so more H⁺ produced from H₂CO₃ dissociation is bound, thus facilitating CO₂ carriage as HCO₃⁻ → minor factor (30%)

Implication: Allows MVB to carry more CO₂ than arterial blood at a given PCO₂ (I.e. MVB carries 52 mL CO₂/dL at PCO₂ of 46 mmHg, while arterial blood would need a PCO₂ of 55 mmHg to carry the same amount of CO₂)

(VI) Schematic of CO₂/O₂ Loading in Systemic Capillary:

In systemic capillaries, CO₂ is loaded and O₂ is unloaded as follows:



The reverse processes of the schematic occur in the lung capillaries, where CO₂ is unloaded and O₂ is loaded

Important to note – RBC osmolality and volume changes in arterial and venous blood:

- CO₂ uptake in peripheral tissues by blood increases the osmolality of RBC (I.e. ↑ ions and Hb-bound compounds) and more H₂O enters intracellularly → thus, red cell has ↑ volume in venous blood
- CO₂ is unloaded in the lungs, which decreases RBC osmolality (I.e. ↓ ions and Hb-bound compounds) and H₂O enters extracellularly → thus, red cell has ↓ volume in arterial blood

(VII) Oxygen and Carbon Dioxide Stores in the Body:

O₂ stores in the body:

Body has 1500 mL O₂ stores (at room air):

- (1) O₂ in lungs (most important) → FRC has 480 mL of O₂
- (2) O₂ bound to haem-containing compounds (esp Hb and Mb)

Note – Haem proteins (esp Mb) have very high affinity for O₂ → restrict ability of these O₂ stores to give up O₂ into solution for tissues to use

- (3) O₂ dissolved in body fluids

Importance of O₂ body stores:

- Apnoea (I.e. following induction of anaesthesia) leads to impairment of normal O₂ flux → so existing O₂ body stores become vital for ongoing cellular aerobic metabolism (otherwise, hypoxia and cell deaths ensues when O₂ stores are depleted)
- As a result, “Preoxygenation” (an anaesthetic technique where a patient breathes 100% O₂ for several minutes prior to induction of GA) plays an important role in ↑ O₂ store in patients lung to prevent hypoxaemia (and tissue hypoxia) during apnoea a/w intubation

Mechanism – Pre-oxygenation involves the process of “Denitrogenation” → displaces N₂ from FRC and replaces it with O₂:

- Apnoea at room air (FiO₂ 0.21) at FRC (2300 mL) means O₂ store in lungs is 480 mL → metabolic activity of tissues (VO₂ 250 mL/min) means this store is depleted in 90-120 secs
- Apnoea following “preoxygenation” (FiO₂ 1.0) at FRC means O₂ store in lungs is significant → delays depletion of O₂ lung stores only after 4-5 minutes of apnoea

CO₂ stores in the body:

Body has a very large CO₂ store (120 L) → mainly in form of dissolved CO₂ and HCO₃⁻

These forms of CO₂ are stored in – (i) rapid-, (ii) intermediate- and (iii) slow-equilibrium compartments → where the latter two compartments have very large capacities → this means any change in CO₂ production vs elimination results in a very delayed change in CO₂ stores (I.e. equilibration takes 20-30 mins cf. 4-5 mins with O₂ stores)

(VIII) Summary of Gas Exchange in the Lungs and Peripheral Tissues:

Pulmonary gas exchange and gas transfer in the circulation:

Pulmonary exchange of gas → with each minute of alveolar ventilation (~4-5 L/min):

- 840 mL of O₂ and ~0 CO₂ are inspired
- Pulmonary circulation (5 L/min) removes 250 mL of O₂ (for tissue use) and delivers 200 mL of CO₂ (from tissue metabolism)
- So 590 mL of O₂ and 200 mL of CO₂ are expired

Oxygen:

- Every minute, venous blood entering the pulmonary circulation (~5 L/min) contains 750 mL of O₂ (15 mL of O₂/100 mL)
- In the pulmonary capillaries, 250 mL O₂ is taken up every minute to give 1000 mL of O₂ in arterial blood (20 mL of O₂/100 mL) going to tissue every minute
- In tissue, 250 mL O₂ is consumed every minute (this can increase with further tissue metabolism), leaving 750 mL O₂ in venous blood each minute

Carbon dioxide:

- Every minute, arterial blood entering tissues contains 2400 mL of CO₂ (48 mL of CO₂/100 mL)
- 200 mL CO₂ is added in tissues every minute, giving 2600 mL of CO₂ in mixed venous blood each minute (52 mL of CO₂/100 mL)
- 2600 mL CO₂ enter the lungs each minute, where 200 mL of CO₂ is expired, leaving back to 2400 mL CO₂ in arterial blood

Gas Exchange at the tissues and lung:

O₂/CO₂ exchange between (i) pulmonary capillary blood and lungs, and (ii) systemic capillary blood and tissues obeys "FICK'S LAW of Diffusion"

Blood-lung gas exchange:

- O₂ exchange:
 - o MVB has SaO₂ 75% and PO₂ 40 mmHg → thus exposure to ↑ alveolar PO₂ (105 mmHg) causes O₂ to diffuse ↓ its [] gradient
 - o O₂ then dissolves in plasma, then combines with Hb
 - o PO₂ of pulmonary capillary blood remains < PAO₂ until Hb and plasma are fully saturated with O₂
- CO₂ exchange:
 - o PCO₂ of MVB is 45 mmHg, which is < PACO₂ (40 mmHg) → causes CO₂ to diffuse ↓ its [] gradient
 - o Of note, this effectively facilitates O₂ loading (due to Bohr Effect)

Blood-tissue gas exchange:

- O₂ exchange:
 - o Tissue PO₂ is > PaO₂, thus O₂ diffuses ↓ its [] gradient (I.e. draws O₂ from plasma, then draws it from Hb)
 - o O₂ unloading is also facilitated by tissue temperature, 2,3-DPG, pH and CO₂
 - o O₂ exchange continues until there is adequate O₂ for metabolism – In effect, ~ 5 mL O₂ per 100 mL blood is spent by tissue, requiring PO₂ drop from 100 to 40 mmHg
- CO₂ exchange:

- CO_2 is made in mitochondria, and it diffuses down pressure gradient and enters blood in its 3 forms
- CO_2 loading in blood is facilitated by deoxygenation of Hb (Haldane's effect)

(IX) Role of Haemoglobin in O₂ and CO₂ Carriage:

Location of Hb: RBC (contains 200-300 million Hb molecules)

Structure of Hb:

- Globular metalloprotein complex (MW 65 kDa) with contains 4x subunits
- Each subunit contains:
 - o (i) Haem group → iron (in ferrous or Fe²⁺ state) within protoporphyrin ring
 - o (ii) Globin → polypeptide chains

Functions of Hb:

- (1) O₂ transport in blood → Hb can bind up to 4 molecules of O₂, with each subunit able to bind 1 molecule of O₂ reversibly (Hb + O₂ ↔ HbO₂)

Important to note:

- Multimeric structure → allows “+ve cooperative binding” (↑ O₂ affinity with ↑ O₂ binding) → gives “sigmoidal” Hb O₂ dissociation curve:
 - o Tense (T) – Deoxygenated Hb has ↓ O₂ affinity as globin molecules stuck together
 - o Relaxed (R) – Oxygenated Hb has ↑ O₂ affinity as globin molecules released from each other exposing ↑ O₂ bind sites
- P₅₀ = 26 mmHg (relative R shift in O₂ dissociation curve → ↓ O₂ affinity)
- Cooperative binding affected by:
 - o pH and pCO₂ (↑ O₂ affinity with ↓ pH and ↑ pCO₂ – Bohr effect)
 - o Temperature (↑ O₂ affinity with ↑ temp.)
 - o 2,3-DPG (↑ O₂ affinity with ↑ 2,3-DPG)

These allows ↑ O₂ loading in lungs (↑ pH, ↓ pCO₂ → ↑ O₂ affinity) and ↑ O₂ delivery in tissues (↑ temp, 2,3-DPG, pCO₂, ↓ pH → ↓ O₂ affinity)

- (2) CO₂ transport in blood → CO₂ bound to N-terminal of globin (as carbamino-Hb)
- (3) Buffering role in blood → Basic histidine moieties of globin buffer H⁺
- (4) Iron storage → Iron in haem forms 65-70% of total iron stores

Variants of Hb → mainly characterised by the structure of the globin chains:

- HbA (adult Hb) is α₂β₂ → 96-98% of adult Hb content
- HbA2 is α₂δ₂ → forms 1-3% of adult Hb content
- HbF (foetal Hb) is α₂γ₂ → forms 1% of adult Hb content

Note – HbF OHDC has a left shift → it possess γ-chains (instead of β-chains), which are unable to bind avidly to 2,3-DPG → thus ↑ O₂ affinity (P₅₀ = 18 mmHg)

Others Hb variants to note:

- Met-Hb → iron in haem is oxidised to Fe³⁺ (ferric) state due to MetHb reductase deficiency or oxidizing agents (Eg. SNP, prilocaine, sulphonamides, Etc.)
- Hb-S → “Sickle-cell” variant due to abnormal a.a. substitution on β-chain (substitute Glu with Val on 6th a.a. position)

Aside: Myoglobin

Location: Skeletal muscle (esp involved in sustained contractions; Ie. anti-gravity) and cardiac muscle

Structure:

- Globular metalloprotein complex (MWT 17 kDa) → 1 subunit that contains (i) Haem and (ii) Globin (like Hb)
- No Mb variants as only single polypeptide type

Functions:

- (1) O₂ store in muscle tissue → provides O₂ supply in muscles with sustained contractions where contractions ↓ blood supply

Important to note:

- Single subunit that binds O₂ reversibly ($\text{Mb} + \text{O}_2 \leftrightarrow \text{MbO}_2$) → Mb can bind only 1 O₂
- No “cooperative binding” (O₂ affinity not influenced by O₂ binding) → gives “rectangular hyperbola” Mb O₂ dissociation curve
- P₅₀ = 2.75 mmHg (relative L shift in O₂ dissociation curve → much ↑ O₂ affinity) → P₅₀ of Mb is very low is such that (i) it can extract O₂ from Hb (P₅₀ = 26.6 mmHg), and (ii) it is able to unload O₂ to the mitochondria for [O]
phosphorylation to occur
- O₂ binding not affected by pH, pCO₂, temperature, 2,3-DPG

- (2) Iron storage/metabolism → Fe²⁺ in haem

(X) **Cyanosis:**

“Cyanosis” → blue-purple discolouration of skin and mucous membranes that occurs when capillary blood has reduced (or deoxygenated) Hb > 5 g/dL due to ↓ oxygenation of blood

Note – Cyanosis occurs when [Met-Hb] is 1.5 g/dL in capillary blood!
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Since cyanosis depends on ABSOLUTE levels of reduced (or deoxygenated) Hb, patients with polycythaemia (and reduced oxygenation) are more susceptible to cyanosis than anaemic patients with reduced oxygenation

III. MECHANICS OF BREATHING

(a) *To describe the inspiratory and expiratory process involving the chest wall, diaphragm, pleura and lung parenchyma.*

Important to note – The lung is very elastic/compliant and little AW pressure is needed to establish airflow → TV breathing (500 mL) involves fluctuations of 1-3 cm H₂O of alveolar pressure with airflows of 0.5-1 L/sec

At rest (Pre-inspiration):

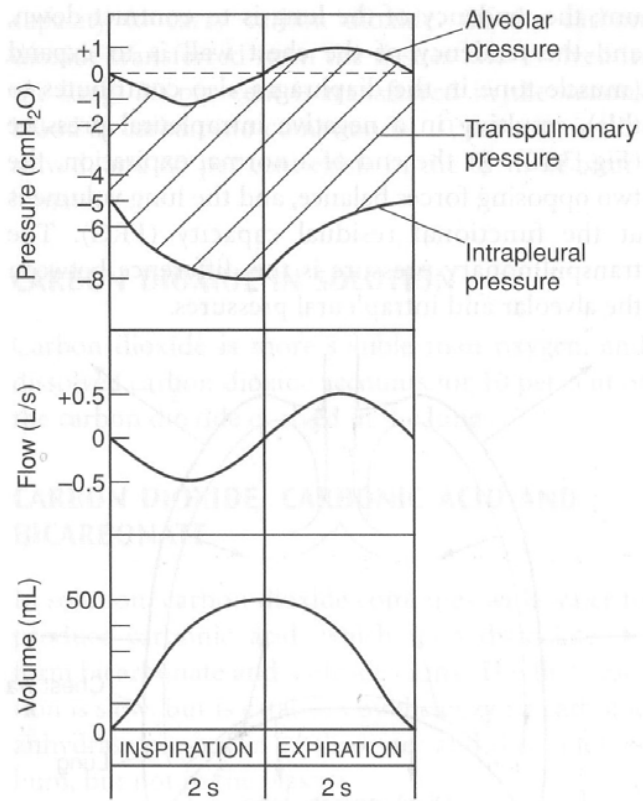
- At the end of expiration of a normal TV breath (I.e. at FRC), the elastic forces of the lung and the chest wall are at equilibrium (I.e. elastic forces that cause the lung to collapse inwards are EQUAL the elastic forces that cause the chest wall to spring out)
- $P_{\text{INTRAPLEURAL}} = -5 \text{ cm H}_2\text{O}$ due to the elastic recoil of the lung (which is caused by surface tension of alveolar fluid, and elastin/collage framework of the lung)
- P_{ALVEOLAR} and P_{MOUTH} are both the same as $P_{\text{ATMOSPHERIC}}$, which is equal to zero
- Since “Transpulmonary pressure” = $P_{\text{ALVEOLAR}} - P_{\text{INTRAPLEURAL}}$, then $P_{\text{TRANSPULMONARY}} = +5 \text{ cmH}_2\text{O}$
- Since there is no pressure drop along the airway (from mouth to the alveolus), the net flow of air is 0 L/sec

During inspiration:

- Inspiration is an active process requiring contraction of respiratory muscles to expand the lung and chest wall
- Lung expansion causes increased elastic recoil of the lung, which produces a fall in $P_{\text{INTRAPLEURAL}}$ to less than -5 cmH₂O
- This causes P_{ALVEOLAR} to also fall, thus establishing a pressure gradient along the airway (usually to a maximum of -1 cmH₂O at mid-inspiration)
- This pressure gradient creates an inward inspiratory flow (maximum of -0.5 L/sec at mid-inspiration) and causes lung volume to increase towards TV
- At end-inspiration, $P_{\text{INTRAPLEURAL}}$ falls as low as -8 cmH₂O. A delayed rise in $P_{\text{TRANSPULMONARY}}$ up to +8 cmH₂O eventually causes P_{ALVEOLAR} to return to 0 cmH₂O. The lack of pressure gradient along the airway at this point causes airflow to cease. The lung volume achieved at this point is TV (500 mL)

During expiration:

- Expiration is a passive process that depends on the release of energy stored in the expanded elastic tissues of the lungs. However, with more forceful breathing, expiratory muscles are activated
- Passive collapse of the lung due to elastic recoil causes a rise in $P_{\text{INTRAPLEURAL}}$ to greater than -8 cmH₂O
- This causes P_{ALVEOLAR} to also rise, thus establishing a pressure gradient along the airway (usually to a maximum of +1 cmH₂O at mid-expiration)
- This pressure gradient creates an outward expiratory flow (maximum of -0.5 L/sec at mid-expiration) and causes lung volume to decrease back towards FRC
- At end-expiration, $P_{\text{INTRAPLEURAL}}$ returns to -5 cmH₂O. A delayed return in $P_{\text{TRANSPULMONARY}}$ to +5 cmH₂O eventually causes P_{ALVEOLAR} to return to 0 cmH₂O. The lack of pressure gradient along the airway at that point causes airflow to cease. The lung volume at this point returns to FRC



- (b) *To define compliance (static, dynamic and specific) and relate this to the elastic properties of the lung.*

Definition of compliance:

- Compliance is defined as the volume change per unit pressure (I.e. slope of P-V curve). It is measured in mL/cmH₂O

$$C = \Delta V / \Delta P$$

Types of compliance:

- (1) Specific compliance:
 - Compliance is dependent on the size of the lung (Eg. compliance is larger in bigger people due to their larger lung size)
 - As a result, to account for this compliance can be standardised by dividing compliance by lung volume (I.e. compliance per unit volume of lung):

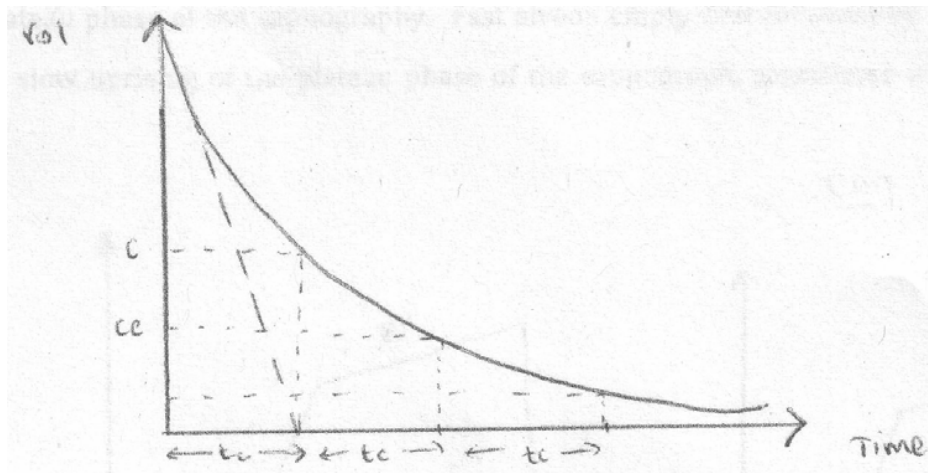
$$\text{Specific compliance} = \frac{\text{Static compliance}}{\text{FRC}}$$

- In children and adults, it is $\sim 0.05 \text{ cmH}_2\text{O}^{-1}$
- (2) Static compliance:
 - Compliance measured at true equilibrium, such as where there is absence of air flow in and out of the lungs (I.e. breathholding)
 - Measured as follows:
 - Patient inspiring and expiring in series of given volume (Eg. few 100 mLs) and measuring P_{INTRAPLEURAL} (which is estimated by an oesophageal manometer)
 - At each step, lung volume is held for > 10 secs (to allow fast and slow alveoli to equilibrate) while keeping the glottis open
 - Different P-V curves (lung volume vs P_{INTRAPLEURAL}) are produced during inspiration and expiration (different due to “hysteresis”) to determine the slope of the curve (which is compliance)
- (3) Dynamic compliance:
 - Compliance measured during normal breathing (I.e. no breathholding)
 - Measured as follows:
 - While taking a normal breath:
 - Transpulmonary pressure (alveolar-intrapleural pressure gradient) is measured using a mouthpiece (for P_{ALVEOLAR}) and an oesophageal manometer (for P_{INTRAPLEURAL})
 - Lung volumes (as absolute values above RV or % VC) is measured using a spirometer
 - P-V loop (lung volume vs P_{TRANSPULMONARY}) is produced
 - Compliance is determined using points of no airflow (I.e. end-inspiration and end-expiration) – This is calculated by dividing the tidal volume by the differences in P_{TRANSPULMONARY} at end-inspiration and end-expiration
 - Dynamic compliance is always LOWER than static compliance:
 - This is because “fast lung units” (which are less compliant) are preferentially ventilated when measuring dynamic compliance, while “slow lung units” (which are more compliant) are not
 - This difference is magnified in lung disease that produces more “slow lung units” (due to increased AWR or compliance), which are not accounted for with dynamic compliance

- (c) *To explain the concepts of time constants and relate these to “fast” and “slow” alveoli.*

Definition of time constant:

- “Time constant” describes the rate of change of an exponential process (I.e. air flow into a lung unit)
- It is defined as the time at which the process would have been complete had the initial rate of change continued (or alternatively, the time required for an exponential process to reach 63% of its final change)
- This exponential process is 95% complete after 3x “time constants”



Overview of lung time constant:

- “Lung time constant” describes the time taken for a lung unit to be filled or emptied with gas. It is determined by – (i) Airway resistance (cmH₂O/L/sec), and (ii) Lung unit compliance (mL/cmH₂O)

$$\tau_{\text{LUNG}} = R_{\text{AIRWAY}} \cdot C_{\text{LUNG}}$$

- After 3x “lung time constants”, 95% of lung unit filling or emptying with gas occurs – This generally happens within 0.6s (assuming a “time constant” of 0.2s for a lung units with a AWR of 2 cm H₂O/L/s and lung compliance of 100 mL/cm H₂O)
- Lung units can have varying lung time constants:
 - (1) Alveoli with long “lung time constant” (aka. “Slow” alveoli):
 - These lung units take longer to fill (and empty) due to slower movement of air in (and out) of the alveolus. As a result, they continue to fill at end-expiration due to redistribution of volume from “fast” alveoli (Pendulluft or swinging air phenomenon), and are thus well-ventilated
 - Caused by either – (a) High AW resistance (> 2 cmH₂O/L/s), and/or (b) High lung compliance (> 100 mL/cmH₂O)
 - These lung units occur physiologically (Eg. highly compliant alveoli at dependent parts of the lung) or pathologically (Eg. COPD/asthma due to high compliance and resistance)
 - (2) Alveoli with short “lung time constant” (aka. “Fast” alveoli):
 - These lung units fill up (and empty) quickly due to rapid movement of air in and out of the alveolus. As a result, they rapidly fill up completely with gas during inspiration (while the rest of the lungs are still filling up with inspired gas), and are thus poorly-ventilated
 - Caused by either – (a) Low AW resistance (< 2 cmH₂O/L/s), and/or (b) Low lung compliance (< 100 mL/cmH₂O)

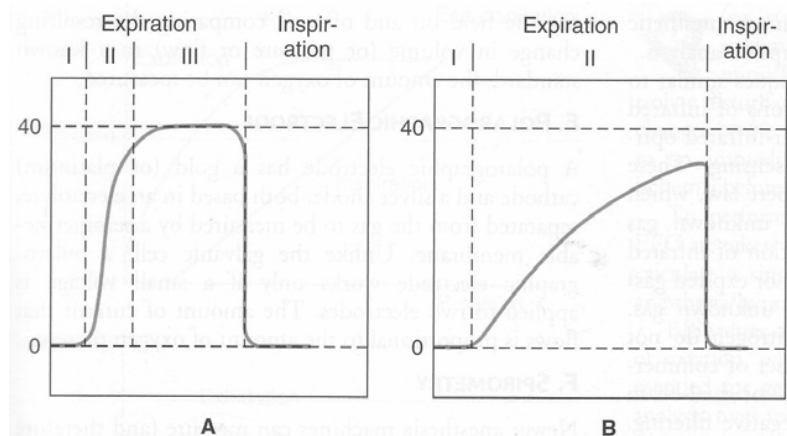
- These lung units occur physiologically (Eg. less compliant alveoli at non-dependent parts of the lung) or pathologically (Eg. pulmonary fibrosis due to poor compliance)

Effect on varying lung constants on ventilation:

- Lung units with different time constants can occur physiologically (Eg. apical vs basal alveoli), but are more pronounced in diseased lung (Eg. COPD) – The outcome of this are regional variations in ventilation can occur, leading to V/Q mismatch
- Mechanism:
 - Inspired gas will continue to redistribute within parts of the lung with varying time constants, even after gas flow at the mouth has ceased due to the Pendulluft or swinging air phenomenon (Ie. “Slow alveoli” fill very slowly during inspiration and even continue to fill at end-expiration using gas redistributed from adjoining “fast alveoli”)
 - As RR increases, regional variations in ventilation and V/Q mismatching occurs – This is because faster breathing causes the Pendulluft phenomenon (or redistribution of gas from “fast” to “slow” alveoli) to be hindered as a consequence of the slow filling/emptying nature of “slow” alveoli. As a result, these lung units become poorly ventilated (as they receive a smaller proportion of the TV breath) and shunting occurs
 - Of note, with higher RR, the lung appears less compliant as the highly compliant “slow alveoli” are eliminated from partaking in ventilation

Measuring the effects of heterogeneity in lung time constants:

- The plateau phase of capnography (phase III) can be used to illustrate the presence of lung units with varying time constants
- For instance, a lung with a heterogeneity in lung time constants (Eg. with COPD) produces a slow uprising of phase III occurs due to “differential emptying” caused by “fast alveoli” emptying CO₂ first followed by “slow alveoli”

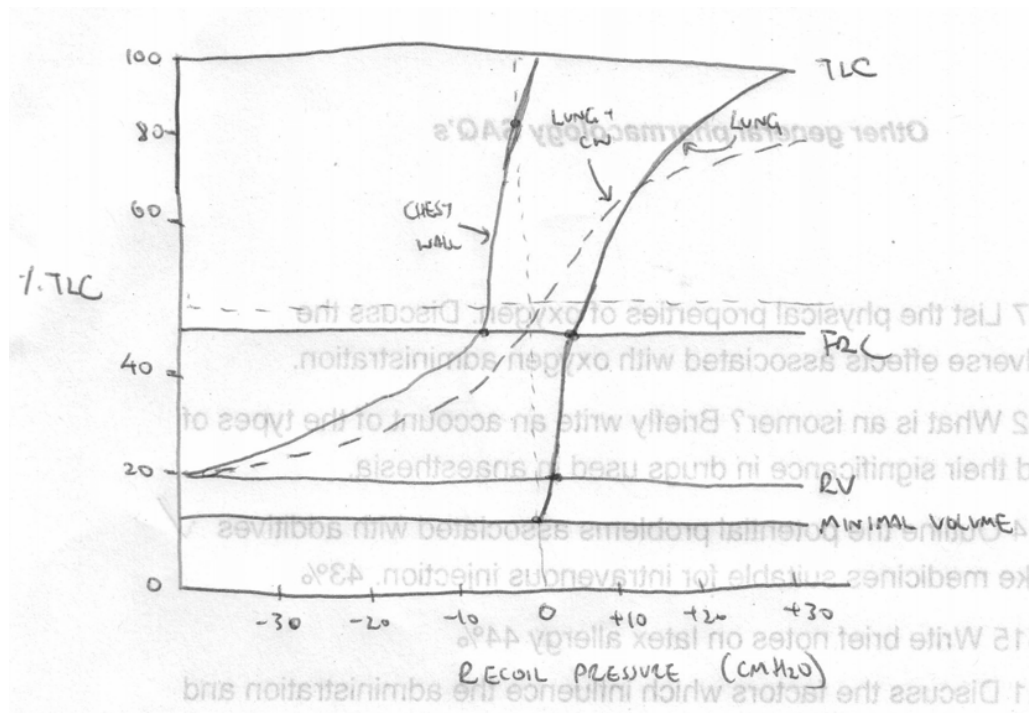


Normal lung with (homogenous lung time constants)

Lung with heterogeneity in lung time constant

- (d) *To describe the elastic properties of the chest wall and plot pressure-volume relationships of the lung, chest wall and the total respiratory system.*

Pressure-volume relationship of the lung, chest wall, and the total respiratory system:



(1) Compliance (and elastic properties) of the lung:

- (i) Lung has a tendency to collapse inwards
 - o Between RV and TLC, the recoil pressures of the lung is +ve (equivalent to a -ve $P_{\text{INTRAPLEURAL}}$) meaning that it has the tendency to collapse inwards
 - o The lung has a tendency to collapse inwards towards its “equilibrium point” (I.e. where the chest wall’s tendency to move out is balanced by the lungs tendency to collapse) – This occurs at the “Minimum volume” (which is less than RV and does not exist in reality) where the recoil pressure is zero (or equal to $P_{\text{ATMOSPHERIC}}$)
 - o This tendency of the lungs to collapse inwards is due to
 - (a) Elastic recoil of lungs, which is derived from the elastin and collagen fibres (and its geometrical arrangement) that form the lung parenchyma
 - (b) Surface tension of fluid lining the alveoli
- (ii) Lung compliance varies with opening alveolar pressure and volumes
 - At normal expanding pressures (Eg. $P_{\text{INTRAPLEURAL}}$ of -5 to -10 cmH₂O) and lung volumes (Eg. ~ FRC), the slope of the P-V curve is very steep – Thus, the lung is very compliant (~ 200 mL/cmH₂O)
 - At higher expanding pressures and lung volumes (Eg. ~ TLC), the P-V curve becomes flatter and compliance decreases

(2) Compliance (and elastic properties) of the chest wall:

- (i) Chest wall has a tendency to spring outwards
 - o From RV up until 80% of TLC (including FRC), the recoil pressure of the chest wall is -ve, meaning that the chest wall has a tendency to spring outwards
 - o The chest wall has a tendency to spring outwards towards its “equilibrium point” (I.e. where the chest wall’s tendency to move out is balanced by the lungs tendency to collapse) – This occurs at 80% of TLC where the recoil pressure is zero (or equal to $P_{\text{ATMOSPHERIC}}$)

- (ii) The chest wall is quite compliant ($\sim 200 \text{ mL/cmH}_2\text{O}$), especially at higher lung volumes (I.e. steeper curve)

(3) Total compliance of the respiratory system:

- (i) Determined by the compliances of the lungs and the chest wall
 - Since they occur in SERIES, the reciprocal of the “total compliance of the respiratory system” is determined by the sum of their reciprocals

$$\frac{1}{C_{\text{TOTAL}}} = \frac{1}{C_{\text{LUNG}}} + \frac{1}{C_{\text{CW}}}$$

- As C_{LUNG} and C_{CW} are $\sim 200 \text{ mL/cmH}_2\text{O}$ each, the total compliance of the respiratory system is $\sim 100 \text{ mL/cmH}_2\text{O}$
- (ii) At FRC, the whole respiratory system is at its “equilibrium point” as the recoil pressure of the whole respiratory system is zero (or equal to $P_{\text{ATMOSPHERIC}}$) – This is because the recoil pressures of the lung and chest wall balance out (I.e. $+5 \text{ cmH}_2\text{O}$ inwards by the lung and $-5 \text{ cmH}_2\text{O}$ by the chest wall)
- (iii) At lung volumes $>$ FRC, the recoil pressure of the system is +ve, which suggests that the whole respiratory system has a tendency to collapse inwards
- (iv) At lung volumes $<$ FRC, the recoil pressure of the system is -ve, which suggests that the whole respiratory system has a tendency to spring outwards

Factors influencing compliance of the respiratory system:

- Factors affecting lung compliance:
 - (1) Lung volume:
 - The lung is most compliant at FRC due to its position on the P-V curve; compliance decreases at low lung volumes (due to AW closure) and at high lung volumes (due to increased recoil pressure of the chest wall and lungs)
 - (2) Lung size:
 - Due to larger lung volumes, the static compliance of an adult lung is larger than that of a neonate despite the pressure changes being relatively the same for a given standardized unit of lung volume
 - The difference in lung size can be accounted for by determining the “specific compliance”
 - (3) Effect of posture/gravity:
 - Due to the effect of gravity, the weight of the lungs cause basal alveoli to be compressed and thus having smaller opening lung volumes and less –ve $P_{\text{INTRAPLEURAL}}$ (cf. apical alveoli)
 - Thus, it places them on a more favourable position on the P-V curve such that they are more compliant
 - (4) Pulmonary blood volume:
 - Pulmonary venous congestion (Eg. LVF) reduces the compliance of the lung
 - (5) Lung elastic recoil due to surface tension:
 - Surface tension is produced by the attraction between H_2O molecules, which cause them to adopt the smallest shape possible (Eg. sphere) – This produces filling pressures that comply with the Law of LaPlace:

$$P = 2T/r$$

- The implications of surface tension are:
 - (i) Intramural pressures generated cause small alveoli to collapse and empty their gas into larger alveoli
 - (ii) Alveoli become stiffer and their compliance decreases

- Surfactant (DPPC produced by type 2 pneumocytes) opposes the aforementioned effects of surface tension, thereby increasing lung compliance
- (6) Disease states:
 - Reduced lung compliance
 - Fibrous diseases of the lung
 - Alveolar oedema
 - Increased pulmonary venous pressures (Eg. LVF)
 - Atelectasis and consolidation
 - Acute asthma attack (lungs are less compliant due to hyperinflated lung volumes, which moves it to less compliant parts of the P-V curve)
 - Increased compliance
 - Normal aging lung and emphysema (due to loss of elastic recoil from alveolar loss)
- Factors affecting chest wall compliance generally reduce compliance:
 - Obesity (Ie. prevents expansion of thoracic volume)
 - Chest wall conditions (Eg. scleroderma, burn scars, kyphoscoliosis)
 - Anaesthesia (diaphragmatic paralysis by anaesthetic agents, supine positioning restricting diaphragmatic movement, thoracic pooling of blood, use of PEEP or low lung ventilation)
 - Raised IAP (Ie. resist downwards diaphragmatic movements)

(e) *To describe the properties of surfactant and relate these to its role in influencing respiratory mechanics.*

Overview of surface tension:

- "Surface tension" is defined as the force across an imaginary line 1 cm long in the surface of a liquid
- Mechanism:
 - o Surface tension occurs only at gas-liquid interface where forces of attraction between liquid molecules are much greater than those between gas and liquid molecules, thereby causing the surface area of the liquid to become small as possible
 - o In the event that the liquid molecules form a sphere (Eg. bubble or alveolus), the pressure generated produced inside the sphere is determined by La Place's Law:

$$P = \frac{4 \times [\text{Surface tension}]}{\text{Radius}} \quad \text{If both surfaces of the sphere are involved (Eg. bubble)}$$

$$P = \frac{2 \times [\text{Surface tension}]}{\text{Radius}} \quad \text{If only one surface of the sphere is involved (Eg. alveolus)}$$

Overview of pulmonary surfactant:

Contents of surfactant:

- (1) Lipids (90%)
 - o (a) Phospholipids (Dipalmitoyl phosphatidyl choline and Phosphatidyl glycerol)
 - o (b) Cholesterol
- (2) Surfactant proteins (8%)
- (3) Carbohydrates (2%)

Production of surfactant:

- Type II alveolar epithelial cells produce surfactant and store it in cytoplasmic lamellated bodies, where it is then secreted into alveoli

Aside: There are two types of alveolar epithelial cells:

- Type I cells – Very thin (as they lack organelles) and thereby allows gas exchange to occur. They are unable to divide, thus in the event of lung damage, they are replaced by conversion of type II cells into type I cells
- Type II cells – They produce surfactant and act as stem cell for production of type I cells

- The major components of surfactant (Eg. DPPC) is produced from fatty acids that is either extracted from blood or directly synthesised in lung
- Turnover of surfactant is very RAPID
- Surfactant is produced LATE in foetal life (Ie. premature babies get RDS 2° lack of DPPC)

Effect of surfactant:

- Surfactant causes an attenuation of surface tension at the air-liquid interface in alveoli that is dependent on the surface area of the alveolus:
 - o This is because the magnitude of surfactant's effect depends on its [] on the surface of alveolus – In alveoli with a small surface area, surfactant is more concentrated and therefore has a more drastic effect at reducing surface tension, than compared with alveoli with a larger surface area

- The variation in surface tension with varying alveolar surface area produces “hysteresis”
- Note – Saline and detergent differ from surfactant as they attenuate surface tension INDEPENDENT of surface area

Mechanism of surfactant:

- DPPC is an amphipathic molecule whose (i) Hydrophobic dipalmitoyl group lies with alveolar gas, and (ii) Hydrophilic choline group lies with alveolar wall fluid
- The alignment of DPPC in the liquid-air interface of the alveolus effectively produces a force that opposes the attractive force between liquid molecules that is responsible for surface tension
- This repulsive force is greatest when DPPC is most concentrated (I.e. in alveoli with the smallest SA)

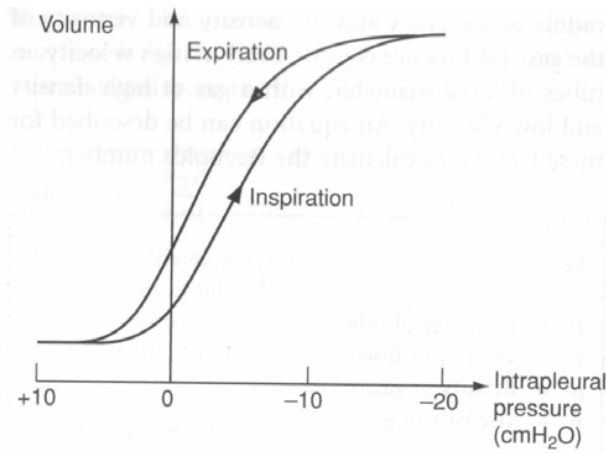
Physiological advantages of surfactant:

- (1) Reduces alveolar surface tension
 - This increases lung compliance and effectively reduces the work of breathing
- (2) Keeps alveoli dry (I.e. preventing pulmonary oedema)
 - Surface tension collapses alveoli, which reduces PHYDROSTATIC around the capillaries and effectively promotes capillary-to-alveolar fluid flow
 - Surfactant prevents this transudative process from occurring
- (3) Promotes alveolar stability
 - According to LaPlace’s law, alveoli with a smaller radius will generate a greater pressure than alveoli with a larger radius (assuming surface tension remains constant), thereby creating a pressure gradient that favours small alveoli emptying into larger ones
 - This effect is the basis of “atelectasis” whereby small (and collapsed) alveoli have a tendency to collapse and blow into bigger ones
 - However, surfactant prevents this from occurring as it significantly reduces the surface tension in very small alveoli, thereby alleviating this pressure gradient between alveoli of different sizes and preventing the small-to-large alveoli emptying phenomenon

Nb. Alveolar stability is further promoted by “Interdependence” – Alveoli are supported structurally by other alveoli, thus any change in volume of one group of alveoli is opposed by an adjacent group (Eg. one group collapses, the adjacent ones expand and stretches them open)

(f) *To explain the vertical gradient of pleural pressure and its significance.*

Pressure-volume relationship of the lungs:

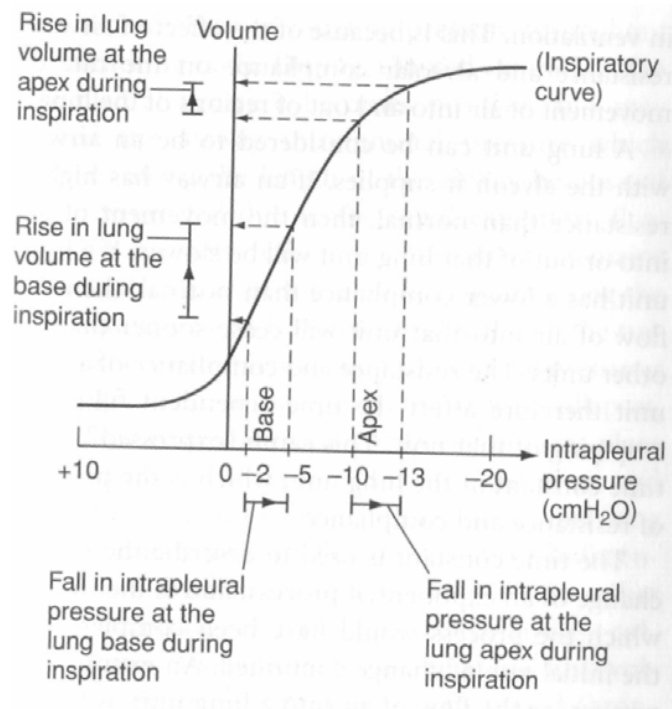


- The lung volumes expands in a sigmoidal manner (NOT linearly) with decreasing (or more -ve) $P_{\text{INTRAPLEURAL}}$. This produces two notable features:
 - At less -ve $P_{\text{INTRAPLEURAL}}$, the alveoli are relatively compressed but lie within the steep part of the curve – Thus, a greater increase in alveolar volume will occur with a fall in $P_{\text{INTRAPLEURAL}}$ (Ie. highly compliant alveoli)
 - At more +ve $P_{\text{INTRAPLEURAL}}$, the alveoli are relatively well-expanded but lie within the flat part of the curve – Thus, a smaller increase in alveolar volume will occur with a fall in $P_{\text{INTRAPLEURAL}}$ (Ie. poorly compliant alveoli)
- The lung volume at ANY given pressure is GREATER on expiration than inspiration (“Hysteresis”), which is due to the effect of surfactant on surface tension of fluid lining the alveoli
- In the absence of expanding lung pressure (Ie. when $P_{\text{INTRAPLEURAL}}$ is atmospheric), the lung still has air inside of it – This lung volume is equal to FRC
- When $P_{\text{INTRAPLEURAL}}$ is $> P_{\text{ATM}}$, AW closure occurs and traps air in the alveoli – The volume at which this happens is the “Closing Capacity”
- $P_{\text{INTRAPLEURAL}}$ is subatmospheric (or -ve), which causes the lung to have a tendency to collapse inwards. This is caused by the elastic recoil of the lung, which is the result of (i) Surface tension of fluid in the alveoli, and (ii) Elastic tissues of the lung (Eg. geometrical arrangement of elastin and collagen in lung parenchyma)

Vertical gradient of pleural pressure due to gravity causes regional variations in ventilation:

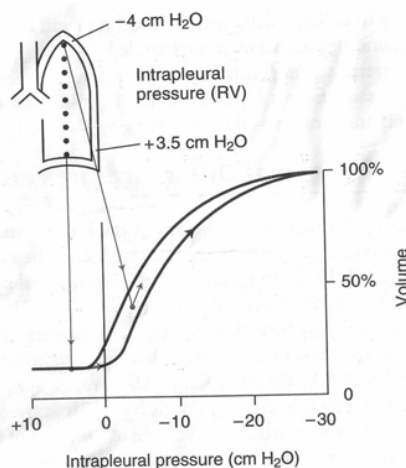
- The distribution of $P_{\text{INTRAPLEURAL}}$ is variable from apex to base of an erect lung because of the effects of gravity (or weight of the lungs):
 - $P_{\text{INTRAPLEURAL}}$ at the base is less -ve (-2.5 cmH₂O), whereas the $P_{\text{INTRAPLEURAL}}$ at the apex is more -ve (-10 cmH₂O)
 - This produces less radial traction on basal alveoli, thereby leading to smaller resting volumes (cf. apex)
- Furthermore, direct compressive effects of gravity also causes basal alveoli to have a smaller opening volume compared with apical alveoli (Ie. due to weight of lungs squashing alveoli at the bases)
- As a result of these effects:
 - Basal alveoli have a smaller resting volume and a less -ve $P_{\text{INTRAPLEURAL}}$, which places them at the steeper part of the P-V curve – This means despite their small resting size, these alveoli have a greater rise in alveolar volume for a given fall in $P_{\text{INTRAPLEURAL}}$, and are thus highly compliant
 - Apical alveoli have a larger resting volume and a more -ve $P_{\text{INTRAPLEURAL}}$, which places them at the flatter part of the P-V curve – This means in spite of their large

- resting size, these alveoli have a smaller rise in alveolar volume for a given fall in $P_{\text{INTRAPLEURAL}}$, and thus not very compliant
- Since the degree of alveolar ventilation is measured by the change in alveolar volume per unit resting volume, it is clear that basal alveoli are better ventilated than apical alveoli (I.e. basal alveoli have small resting volumes and are able to expand its volumes heaps with a fall in $P_{\text{INTRAPLEURAL}}$)



Distribution of ventilation changes at low lung volumes:

- At low lung volumes (I.e. towards RV), the vertical $P_{\text{INTRAPLEURAL}}$ gradient from apex to base that is produced by gravity still exists, BUT:
 - o $P_{\text{INTRAPLEURAL}}$ is LESS negative as a whole throughout the lung – Thus, overall the alveoli are not well expanded
 - o $P_{\text{INTRAPLEURAL}}$ can be greater than $P_{\text{ATMOSPHERIC}}$ at basal alveoli, thus causing alveolar and airway closure
- The effect on regional variations in ventilation is INVERTED, such that:
 - o (i) Basal alveoli have collapsed and are NOT ventilated
 - o (ii) Apical alveoli now fall onto the steep part of the P-V curve, and become well-ventilated lung units



(g) *To explain the physics of gas flow and the significance of the relationship between resistance and flow in the respiratory tract.*

Overview of air flow in the respiratory tract:

- In order for air flow to occur through a tube (such as the respiratory tract), a pressure gradient (P_{GRADIENT}) needs to exist between the ends of the tube
- This P_{GRADIENT} depends on the:
 - o (i) Rate of flow (V)
 - o (ii) Pattern of flow (turbulent, laminar, transitional)

Types of air flow in the respiratory tract:

The nature in which gas flows is determined by the “Reynolds number” (Re):

$$Re = \frac{2rvd}{\eta}$$

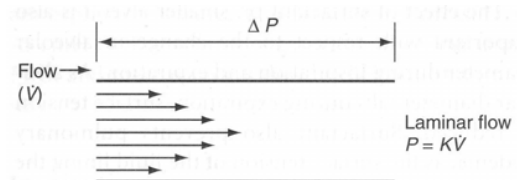
r = radius
v = velocity of gas flow
d = density of gas
 η = viscosity of gas

- There are three patterns in which gas moves through the airways:
 - o Turbulent flow is likely if Re > 4000
 - o Transitional flow occurs with Re 2000-4000
 - o Laminar flow is likely if Re < 2000

There are three types of flows:

(1) Laminar flow:

- Occurs when “viscous” forces are dominant:
 - o Tubes with small radius
 - o Low air flow velocity
 - o Highly viscous (and low density) gases
- As a result, in the respiratory tract this occurs at:
 - o (i) Small airways (esp straight and smooth-walled tubes), such as the terminal bronchioles
 - o (ii) Low flow rates (Eg. low RR)
- Features of laminar flow:
 - o Presence of a “Velocity profile” of air flow
 - There are concentric tubes parallel to the wall, each with varying degrees of air flow such that the velocity at the centre is the greatest
 - High axial velocity flow minimises resistance to air flow



- o Airway resistance can be calculated by Hagen-Poiseuille's equation:

$$R = \frac{8nl}{\pi r^4}$$

n = viscosity
l = length
r = radius

Therefore, airway resistance is:

- (i) Proportional to the viscosity of gas and length of the tube
- (ii) Inversely proportional to the fourth power of the radius

Thus, in airways conducting laminar flow:

- Length of the airways and the viscosity of gas remain constant (and do not contribute to AW resistance)
- Radius of the airways is the ONLY key variable influencing airway resistance

- Driving pressure is proportional to flow rate:

$$P = K \cdot V = R \cdot V$$

K = Constant

P = Driving pressure

V = Air flow rates

R = Airway resistance

- Thus, air flow rates can be determined as follows:

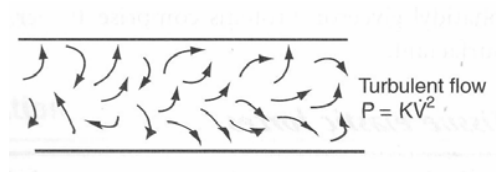
$$V = \frac{P}{R} = \frac{P \times (\pi r^4)}{8nl}$$

Thus, in airways conduction laminar flow, air flow rates are proportional to:

- (i) Pressure gradient generated
- (ii) Radius to the 4th power

(2) Turbulent flow:

- Occurs when “Inertial” forces are dominant:
 - Tubes with large radius (Eg. large calibre airways, such as the nose, pharynx, larynx and trachea)
 - High air flow velocity (Eg. high RR with exercise)
 - High density (low viscous) gases
- As a result, in the respiratory tract this is found in:
 - (i) Large airways (esp with branch points), such as the nose, pharynx, larynx and trachea
 - (ii) High flow rates (Eg. high RR with exercise)
- Features of turbulent flow:
 - Air movement occurs in disorganised stream lines (Ie. no “velocity profile” or high axial flow velocity) and eddy currents form, which produce increased resistance to air flow



- Driving pressure is proportional to the square of the flow rate

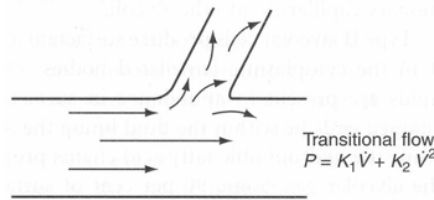
$$P = K \cdot V^2 = R \cdot V^2$$

Thus, in airways conducting turbulent flow, the need for a greater driving pressure to generate air flow is largely due to the high degree of resistance caused by eddy currents

(3) Transitional flow:

- Airflow is a mixture of both laminar and turbulent flow – This is due to a balance of inertial and viscous forces that occurs with:

- Tubes with mid-sized radius (Eg. most of bronchial tree)
- Medium air flow velocity
- Medium density and viscous gases
- As a result, in the respiratory system this is found in mid-sized airways (esp with irregular lining due to mucous, cilia, debris), which would be most of the bronchial tree



- Driving pressure is determined by both (i) the flow rate, and (ii) the square of the flow rate:

$$P = K \cdot V + K \cdot V^2 = R \cdot V + R \cdot V^2$$

Thus, in airways conducting transitional flow, the need for a slightly higher driving pressure to generate flow rates (cf. laminar flow) is due to a presence of some eddies currents (which generate resistance to air flow) in laminar flow

- (h) *To describe the factors affecting airway resistance, and how airway resistance may be measured.*

Overview of airway resistance:

- Airway resistance is defined as the frictional resistance caused by gas flow through the airways
- It is calculated as driving pressure (difference between mouth and alveolar pressure) divided by the flow rate

$$\text{Airway resistance} = \frac{(P_{\text{MOUTH}} - P_{\text{ALVEOLI}})}{\text{Flow rate}}$$

P_{ALVEOLI} – Measured using body plethysmography
 P_{MOUTH} – Measured using mouth piece

- Airway resistance is generally low ($\sim 2 \text{ cmH}_2\text{O/L/sec}$) – The significance of this is that only a driving pressure of $1 \text{ cm H}_2\text{O}$ is needed to generate air flow!

Main site of airway resistance:

- Mid-sized bronchi (up to 7th generation) are the main site of airway resistance – This is because it has a comparatively smaller cross-sectional area than the smaller airways in spite of its larger airway calibre
- Small airways produce a comparatively small amount of airway resistance – In spite of their small calibre, there are several small airways arranged in parallel to produce a comparatively larger cross-sectional area

Factors that affect airway resistance:

(1) Type of airflow in the airway:

- The type of air flow in the respiratory tract is determined by the “Reynolds number” (Re):

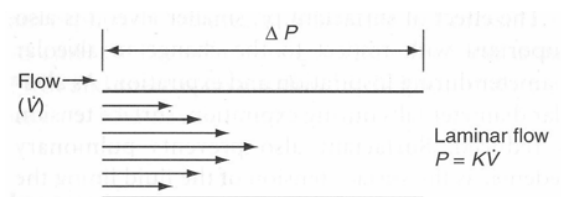
$$\text{Re} = \frac{2rvd}{\eta}$$

r = radius
 v = velocity of gas flow
 d = density of gas
 η = viscosity of gas

- There are three patterns in which gas moves through the airways:
 - o Turbulent flow is likely if Re > 4000
 - o Transitional flow occurs with Re 2000-4000
 - o Laminar flow is likely if Re < 2000

(a) Laminar flow:

- o In the respiratory tract, this type of flow occurs when “viscous” forces predominate:
 - (i) Small airways (esp straight and smooth-walled tubes), such as the terminal bronchioles
 - (ii) Low flow rates (Eg. low RR)
- o There is presence of a “Velocity profile” of air flow
 - There are concentric tubes parallel to the wall, each with varying degrees of air flow such that the velocity at the centre is the greatest
 - High axial velocity flow minimises resistance to air flow



- Airway resistance can be calculated by Hagen-Poiseuille's equation:

$$R = \frac{8nl}{\pi r^4}$$

n = viscosity
l = length
r = radius

Thus, in airways conducting laminar flow:

- Length of the airways and the viscosity of gas remain constant (and do not contribute to AW resistance)
- Radius of the airways is the ONLY key variable influencing airway resistance

- Driving pressure is proportional to flow rate:

$$P = K \cdot V = R \cdot V$$

K = Constant

P = Driving pressure

V = Air flow rates

R = Airway resistance

- Thus, air flow rates can be determined as follows:

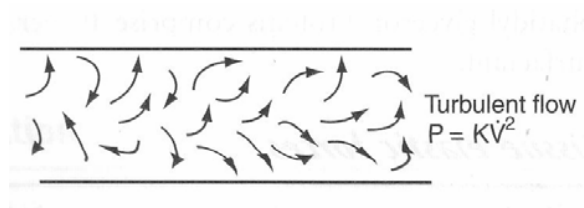
$$V = \frac{P}{R} = \frac{P \times (\pi r^4)}{8nl}$$

Thus, in airways conduction laminar flow, air flow rates are proportional to:

- (i) Pressure gradient generated
- (ii) Radius to the 4th power

(b) Turbulent flow:

- In the respiratory tract, this occurs when "Inertial" forces predominate:
 - (i) Large airways (esp with branch points), such as the nose, pharynx, larynx and trachea
 - (ii) High flow rates (Eg. high RR with exercise)
- Air movement occurs in disorganised stream lines (Ie. no "velocity profile" or high axial flow velocity) and eddie currents form, which produce increased resistance to air flow



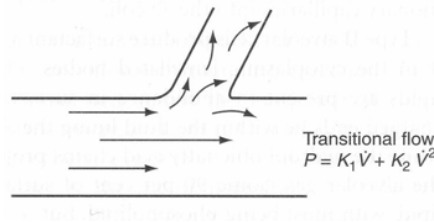
- Driving pressure is proportional to the square of the flow rate

$$P = K \cdot V^2 = R \cdot V^2$$

Thus, in airways conducting turbulent flow, the need for a greater driving pressure to generate air flow is largely due to the high degree of resistance caused by eddie currents

(c) Transitional flow:

- Airflow is a mixture of both laminar and turbulent flow – This is due to a balance of inertial and viscous forces
- In the respiratory tract, this occurs in mid-sized airways (esp with irregular lining due to mucous, cilia, debris), which would be most of the bronchial tree

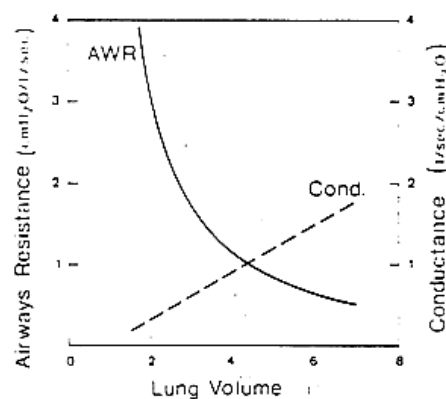


- Driving pressure is determined by both (i) the flow rate, and (ii) the square of the flow rate

Thus, in airways conducting transitional flow, the need for a slightly higher driving pressure to generate flow rates (cf. laminar flow) is due to a presence of some eddy currents (which generate resistance to air flow) in laminar flow

(2) Radius (or calibre) of the airways (esp for airways conducting laminar flow):

- (a) Lung volume
 - Lung volume is inversely related to airway resistance, such that at TLC airway resistance is at its lowest



- Mechanism:
 - (i) When LV exceeds FRC, radial traction provided by lung parenchyma causes intrathoracic airways to open up, thus decreasing airway resistance
 - (ii) -ve transpleural pressure at large lung volumes maintains patency of smaller airways, thus decreasing airway resistance
- (b) Tone of bronchial smooth muscle, which is affected by:
 - Irritants (Eg. cigarette smoke) – Cause bronchial constriction
 - Low PACO₂ – Cause bronchial constriction
 - Histamine (from mast cells) – Cause bronchial constriction
 - Leukotrienes (and some prostaglandins) – Cause bronchial constriction
 - ANS control:
 - PNS (major influence) – Vagal ACh on mAChR cause bronchial constriction
 - SNS (minor influence) – Circulating Adr on Beta-2 receptors causes bronchial dilation
 - Non-cholinergic, non-adrenergic nerve stimulation cause bronchial dilation
- (c) Airway oedema and secretions (Eg. asthma, airway irritation from smoking) – Reduces airway calibre, leading to increased resistance

- (d) Extrinsic compression (Eg. lung tumours, pneumothorax, pulmonary haemorrhage, or dynamic airway compression with forced expiration) – Reduces airway calibre, leading to increased resistance

(3) Density and viscosity of inspired gas:

- Increases in density gas causes increased AW resistance due to promotion of turbulent air flow
- Increases in gas viscosity lead to increased AW resistance in airways conducting laminar air flow (as per Hagen-Poiseuille's equation)
- However, density has a GREATER effect than viscosity on overall airway resistance – This is because most airway resistance occurs in the bronchi where non-laminar flow occurs, and where density (or inertial forces) is a vital factor

- (i) *To define closing capacity and its relationship to airway closure and explain its clinical significance and measurement.*

Definition of closing capacity:

- It is the lung volume at which small airways and alveoli in the dependent parts of the lung first begin to close
- Alternatively, it can be defined as:

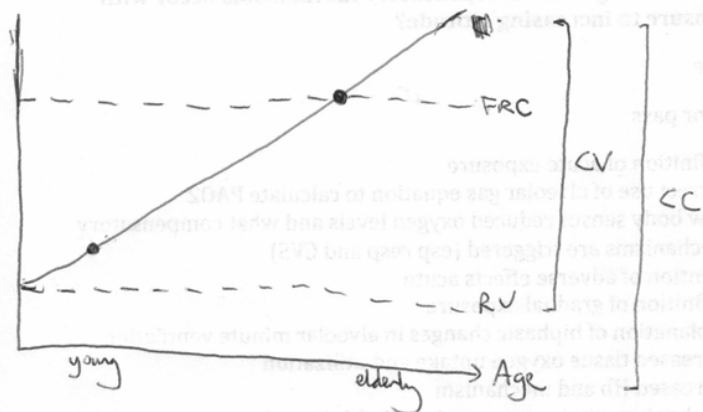
$$\text{"Closing capacity"} = \text{"Closing volume"} + \text{"Residual volume"}$$

Pathophysiology and clinical significance of closing capacity:

- Airways and alveoli in the dependent parts of the lung are much smaller (cf. non-dependent regions), thus with expiration to low lung volumes below FRC these dependent airways and alveoli begin to collapse at "closing capacity" and trap gas distally, thereby causing "atelectasis"
- During atelectasis, a shunt forms ($V/Q = 0$) as the alveoli affected are not ventilated but remain perfused. This leads to impaired gas exchange that results in arterial hypoxaemia

Effect of age on closing capacity:

- Ageing is associated with a loss of lung elastic recoil, which produces a less -ve intrapleural pressure and causes airways and alveoli to be even smaller (esp at the bases), and hence more susceptible to collapse
- Thus, closing volume (and thus closing capacity) increases with age such that:
 - o In young persons, closing capacity (and atelectasis) occurs at very low lung volumes (Eg. near to RV only)
 - o In older persons, closing capacity (and atelectasis) occurs at higher lung volumes – Closing capacity EQUALS FRC at age 44 (when supine) and at age 66 (when erect)
- Rising closing capacity with age is the MAIN reason for increasing arterial hypoxaemia with age
- Note: FRC does NOT decrease with age!



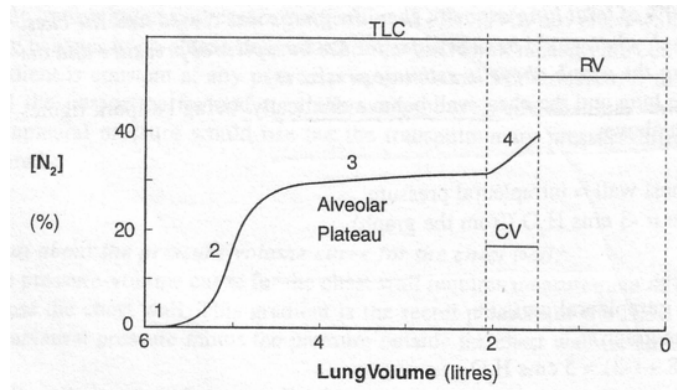
Effect of lung disease on closing capacity:

- Lung disease that causes a loss of lung elastic recoil (Eg. emphysema) produces the same effect on airways and alveolar size as aging
- As a result, closing volume (and closing capacity) will occur at higher lung volumes (I.e. towards FRC rather than RV), thereby causing arterial hypoxaemia

Measuring closing capacity:

- Closing volume is determined using the "Single breath N₂ test" (similar to Fowler's method):
 - o Following a VC breath of 100% O₂, the patient slowly exhales and a expired [N₂] is measured with a rapid N₂ analyser

- A plot of $[N_2]$ vs volume of gas expired is made:



- Phase 1: N_2 in anatomical dead space
- Phase 2: N_2 from anatomical dead space and alveolar gas
- Phase 3: Alveolar plateau is formed by N_2 in pure alveolar gas
- Phase 4: Late in expiration when AW closure starts to occur, expired $[N_2]$ begins to rise above the alveolar plateau. The volume expired from the start of this to the end of maximal expiration is the “Closing volume”
- Basis for phase 4:
 - Basal AW closure is indicated by a rise of $[N_2]$ from N_2 -rich apical alveolar gases. Apical alveoli are rich in N_2 because:
 - (i) During initial inspiration from RV, the first part of inspired gas (which is the anatomical dead space gas rich in N_2) goes mainly into the apical alveoli
 - (ii) Apical alveoli are larger and more poorly ventilated (cf. basal alveoli). Thus, the $[N_2]$ of apical alveolar gases are less diluted when breathing in 100% O_2
- Residual volume can be determined using the “Single breath N_2 test” – Volume of gas remaining in the lungs at the end of maximal expiration
- Closing capacity is determined by summing “closing volume” and “residual volume”

(j) *To describe the work of breathing and its components.*

Determining work of breathing:

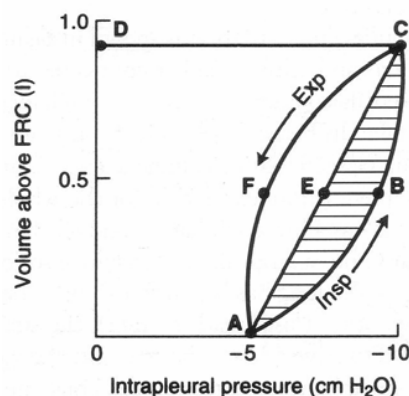
- “Work” is defined as the pressure change for a given change in volume, or vice versa (or alternatively, a force acting over a distance)
- Work is measured in “Joules”, such that 1 J is required to move 1L of gas in response to a pressure gradient of 1 kPa

$$\text{Work} = \text{Pressure} \times \text{Volume}$$

Factors influencing the work of breathing:

- (1) Elastic forces of the lung, which is derived from:
 - (a) Force to deform elastic lung tissues (Eg. elastin fibres in the AW and alveoli) (50%)
 - (b) Force to overcome alveolar surface tension (50%)
- (2) Non-elastic forces of the lung (aka. “Tissue resistance”), which is derived from:
 - (a) AW resistance (80%)
 - (b) Viscous tissue resistance (friction from lungs sliding over chest wall, and diaphragm over abdominal organs) (20%)

Work of breathing occurs during a TV breath:



- Work of breathing during inspiration of a TV breath:
 - Inspiration is an active process requiring contraction of respiratory muscles (diaphragm, accessory muscles) to increase thoracic volume and generate a –ve intrapleural pressure, which thus leads to net air flow into the lungs
 - Work done by inspiratory muscle is used to overcome:
 - (i) Elastic forces (area 0AECD0; unhatched), where the work done against these forces is then stored as potential energy
 - (ii) Tissue resistance forces (area ABCEA; hatched), where the work done against these forces is then completely lost as heat
 - Thus, the “total work of inspiration” is equal to the area of 0ABCD0, which is the sum of the areas of work required to overcome both (i) Elastic forces and (ii) Tissue resistance forces
- Work of breathing during expiration of a TV breath:
 - Expiration is a passive process because it relies on stored potential energy derived from expanding the elastic lung structures during inspiration (represented by area 0AECD0) to generate the elastic recoil required to decrease thoracic volume, generate a +ve intrapleural pressure, and thus force air out of the lung
 - This stored energy during expiration is released as:

- (i) Work to overcome the tissue resistance forces (represented by area AECFA) – This is covered by 50% of the stored elastic potential energy of area 0AECD0
- (ii) Work dissipated as heat (represented by the difference in areas of AECFA and 0AECD0) – This is covered by 50% of the stored elastic potential energy of area 0AECD0

Total work and efficiency of breathing:

- O₂ cost of breathing:
 - During a normal TV breath at rest, the total work of breathing is low – The inspiratory muscles consumes 3 mL O₂/min, which is ~1% of the body's total O₂ consumption at rest (VO₂ = 250 mL O₂/min)
 - O₂ consumption of breathing increases by up to 30% with hyperventilation (due to an increase in either minute volume or RR)
- Total work and efficiency of breathing:
 - Difficult to measure – It is calculated by measuring O₂ cost of breathing, then assuming efficiency as:

$$\% \text{ efficiency} = \frac{\text{Useful work}}{\text{Total energy expended (O}_2 \text{ cost)}} \times 100\%$$

- Normal efficiency is estimated at 5-10%

Increased work of breathing:

- (1) Increased elastic work of the lungs:
 - Breathing large lung volumes – This increases the total work of inspiration by extending the line AEC to a higher volume above FRC, and thus increasing the area 0AECD0
 - Poorly compliant lungs (Eg. restrictive lung disease, absence of surfactant) – This increases the total work of inspiration by reducing the slope of AEC, and thus increasing the area 0AECD0
- (2) Increased resistance forces (Eg. turbulent flow with rapid RR, lung disease associated with increased AWR)
 - This increases the total work of inspiration by producing a larger area ABCEA (I.e. it bulges out)
 - This also causes AECFA to bulge out and increase its area, such that when stored elastic potential is insufficient to overcome this tissue resistance force, expiration becomes an active process requiring work as expiratory muscles are recruited

Minimising the work of breathing:

- (1) By reducing elastic work of the lungs:
 - (i) Increasing lung compliance (Eg. pulmonary surfactant reduces alveolar surface tension) – This decreases the total work of inspiration by reducing the slope of AEC, and thus reducing the area 0AECD0
 - (ii) Breathing smaller large volumes – This decreases the total work of inspiration by retracting the line AEC to a lower volume above FRC, and thus reducing the area 0AECD0

Nb. Patients with pulmonary fibrosis reduce work of breathing by taking faster and smaller breaths (higher RR, smaller TV) – Although AW resistance is increased with faster RR, the elastic work (and overall work by the lungs) in a non-compliant lung is minimised by taking smaller TV breaths

- (2) By reducing tissue resistance work of the lungs:
 - (i) Viscous forces are minimised in the presence of pleural and peritoneal fluid
 - (ii) Reduce AW resistance by promoting laminar flow (when $Re < 2000$)
 - Reducing gas density (Eg. heliox)
 - Reducing air flow rates or RR
 - Increasing AW calibre
 - According to Poiseuille-Hagen equation, resistance is decreased by 16X when the radius is doubled
 - Achieved by bronchodilators, volatile agents and increased lung volume (Eg. PEEP)

Nb. Patients with obstructive lung disease reduce work of breathing by taking slower and larger breaths (slower RR, larger TV) – This minimises tissue resistance forces caused by AW resistance (by increasing airway calibre at high lung volumes, and promoting laminar flow with slower RR or airflows)

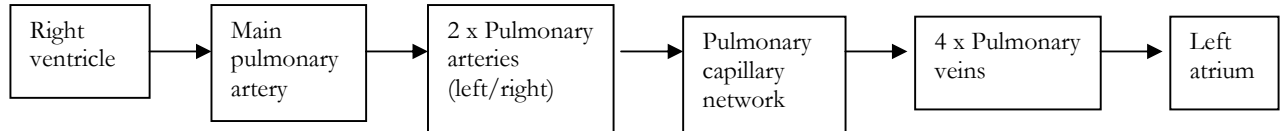
(k) *To describe altered lung mechanics in common disease states.*

VIII. PULMONARY CIRCULATION

(a) ***To outline the vascular anatomy and structure of the pulmonary and bronchial circulations.***

Overview of the pulmonary circulation:

Vascular anatomy:



Structural features:

- (i) Thin-walled vessels
- (ii) Little smooth muscle present
- (iii) Very distensible
- (iv) Short pulmonary artery

Overview of the bronchial circulation:

- Bronchial circulation comprises a MERE fraction of that of the pulmonary circulation → only 1% of C.O. (whereas pulmonary circulation receives 100% of C.O.)
- “Bronchial arteries” (branch of thoracic aorta) → provides blood supply to the conducting AWs down to the terminal bronchioles
- A proportion of blood from the “Bronchial veins” drains as a shunt into the pulmonary vein then finally into LA or LV (along with some coronary venous blood) → contributes to the physiologically-observed “Alveolar-arterial PO₂ gradient difference”!

- (b) *To describe the physiological features of the pulmonary circulation and compare them with those of the systemic circulation.*

Important to note – Pulmonary and systemic circulations are in SERIES and thus have very similar blood flows ($\approx$ C.O. $\sim$ 5 L/min)

Factor	Systemic circulation	Pulmonary circulation
Vascular anatomy		
<i>Anatomical differences</i>	- Thick-walled vessels - Contains smooth muscles - Minimally distensible - Long aorta	- Thin-walled vessels - Little smooth muscle present - Very distensible - Short pulmonary artery
Pressure		
<i>Circuit pressures</i>	High pressure circuit - 5-6x $\uparrow$ arterial pressure (MAP, SBP, DBP) cf. pulmonary circulation - 10x $\uparrow$ inlet vs outlet pressures cf. pulmonary circulation	Low pressure circuit
<i>Inlet vs outlet pressures</i>	100 mmHg (LV) – 2 mmHg (RA) = 98 mmHg	15 mmHg (RV) – 5 mmHg (LA) = 10 mmHg
<i>Arterial pressures</i>	MAP $\sim$ 100 mmHg $\rightarrow$ SBP $\sim$ 120 mmHg and DBP $\sim$ 80 mmHg	MAP $\sim$ 15 mmHg $\rightarrow$ SBP $\sim$ 25 mmHg and DBP $\sim$ 8 mmHg
<i>Capillary pressures</i>	Symmetrically distributed $\rightarrow$ most pressure drop upstream of capillary bed	Highly variable due to hydrostatic effects of pulmonary circulation $\rightarrow$ usually midway b/t pulmonary arterial and venous pressures (8-12 mmHg)
Resistance		
<i>Circuit resistance</i>	High resistance circulation ($\sim$ 20 mmHg/L/min or 1000 dyne.s.cm ⁻⁵)	Low resistance circulation ($\sim$ 1-2 mmHg/L/min or 100 dyne.s.cm ⁻⁵)
<i>Distribution of resistance</i>	Mainly at arterioles (where thick SM wall is influenced by various intrinsic and extrinsic factors)	Evenly spread throughout pulmonary circulation
<i>Determinants of vascular resistance</i>	- (1) ANS control $\rightarrow$ SNS influence of arteriolar tone is the main determinant of SVR - (2) Autoregulation $\rightarrow$ by tissue metabolism - (3) $\uparrow$ PaCO₂ and $\downarrow$ pH $\rightarrow$ $\downarrow$ SVR - (4) Circulating factors (Eg. NAd, Adr, Etc.)	- (1) $\uparrow$ PAP/PVP $\rightarrow$ $\downarrow$ PVR due to capillary recruitment/distension - (2) PVR is minimal at FRC $\rightarrow$ with high lung volumes, alveolar vessels stretch and collapse causing $\uparrow$ PVR. With low lung volumes, extra-alveolar vessels are compressed causing $\uparrow$ PVR - (3) $\downarrow$ PAO₂ causes pulmonary vasoconstriction $\rightarrow$ $\uparrow$ PVR - (4) $\uparrow$ PaCO₂ and $\downarrow$ pH $\rightarrow$ $\uparrow$ PVR - (5) ANS control $\rightarrow$ SNS (α causes vasoconstriction; β causes vasodilation); PNS (mAChR causes vasodilation) - (6) Circulatory factors (5-HT, histamine)
Blood flow		
<i>Nature of blood flow</i>	Receives entire C.O. ($\sim$ 5 L/min), but flow is continuous due to damping of high pressures by high resistance vessels	Receives entire C.O. ($\sim$ 5 L/min), but flow is pulsatile due to low damping by low resistance capacitance vessels
<i>Importance of blood flow</i>	- (1) High pressures allow C.O. to be distributed to various organs (in	Low pressures allow the pulmonary circulation to accept the entire C.O. of the

<i>characteristics</i>	spite of variable hydrostatic pressures; i.e. raised arm) - (2) Resistance vessels allow blood flow to be regulated at certain organs in view of changing demand (E.g. shock)	RV with very little rise in pressure. This: - (1) Minimises the workload on the right-side of the heart - (2) Prevents transudation of fluid into interstitial spaces/alveoli - (3) Still provides adequate $P_{\text{PULM ARTERIAL}}$ to perfuse the entire lung (esp the apices) → allows for maximal alveolar gas exchange
<i>Distribution of blood flow</i>	- (1) Tissue metabolic demand (autoregulation) - (2) Gravity/posture (venous pooling)	- (1) Gravity/posture (influences hydrostatic pressure and West zone distribution) - (2) Intrathoracic pressure (influences hydrostatic pressure and West zone distribution) - (3) Cardiac cycle - (4) Autoregulation (esp hypoxic pulmonary vasoconstriction)
<i>Functions</i>		
<i>Functions of the circulatory system</i>	- (1) Delivers O_2 and nutrients to all body tissues - (2) Removal of CO_2 and waste products	- (1) Facilitate O_2/CO_2 gas exchange - (2) Filtration (of blood and gas) - (3) Immunological (IgA, macrophages) - (4) Metabolic (surfactant production, AII activation, bradykinin inactivation, protein synthesis, protease activity) - (5) Acid-base balance - (6) Drugs (route of absorption for volatile agents and bronchodilators; uptake of fentanyl, propofol, lignocaine) - (7) Reservoir (of blood and gas) - (8) Thermoregulation

- (c) *To explain the factors that affect pulmonary vascular resistance.*
- (d) *To describe the control of pulmonary vascular tone.*
- (e) *To outline the mechanisms which raise pulmonary vascular resistance, and to describe the circulatory effects of such a rise.*

Overview of the pulmonary vascular resistance:

- Pulmonary circulation is a very low resistance circuit:
 - o “Pulmonary vascular resistance” (PVR) → resistance of the vasculature within the pulmonary circulation → normally 1-2 mmHg/L/min (or Wood units) or 100 dyne/sec/cm⁵

$$PVR = \frac{(P_{PULM\ ARTERIAL} - P_{PULM\ VENOUS})}{\text{Cardiac output}}$$

$$\approx \frac{RVP - LAP}{C.O.} = \frac{15\ \text{mmHg} - 5\ \text{mmHg}}{5\ \text{L/min}} = 2\ \text{mmHg/L/min}$$

- o It's resistance is 1/10th that of the systemic circulation (which is 20 mmHg/L/min or 1000 dyne/sec/cm⁵)
- o This is b/c pulmonary vessels – (i) lack the high-resistance muscular arterioles characteristic of systemic vessels, and (ii) are very distensible
- Significance of a low resistance circuit:
 - o As the pulmonary circulation receives the entire C.O. (5 L/min) → its low PVR means that it is a low-pressure circuit (1/10th pressure of systemic circulation – I.e. pressure drop is 10 mmHg in pulmonary circulation cf. 98 mmHg in systemic)
 - o This allows C.O. to be distributed in a thin film over a vast area of alveolar walls for gas exchange to occur, while providing sufficient pulmonary arterial pressure to distribute blood to the non-dependent parts of the lung (I.e. apices)

Important to note – “Pulmonary vascular impedance” is a better measure for the pulmonary circuit than “Pulmonary vascular resistance” → this is b/c:

- “Impedance” is a better measure for a circulatory system with continuous pulsatile flow, such as seen with the pulmonary circuit (due to its thin-walled vessels, which does not provide much damping and produces more pulsatile blood flows)
- “Resistance” is a better measure for a circulatory system with constant flow, such as seen with the systemic circulation (due to its muscular arterioles that damp well and provide more constant blood flows)

Factors that influence pulmonary vascular resistance:

PVR is HIGHLY variable (as influenced by several PASSIVE and ACTIVE factors) → as blood flow within pulmonary circulation is laminar, its resistance is determined by “Hagen-Poiseuille’s equation”:

$$\text{Vascular resistance} = \frac{8\eta l}{\pi r^4}$$

Where vascular resistance is:

- Directly proportional to (i) Length of the tube (l), and (ii) Viscosity of the medium (η)
- Inversely proportional to the 4th power of the radius of the tube

(1) Viscosity:

- Blood viscosity (or haematocrit) is a passive factor → viscosity is directly proportional to PVR

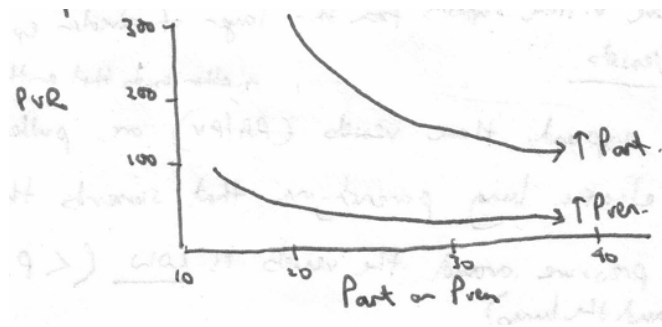
(2) Length:

- Length of the pulmonary circuit cannot be altered → thus it is a non-determinant of PVR

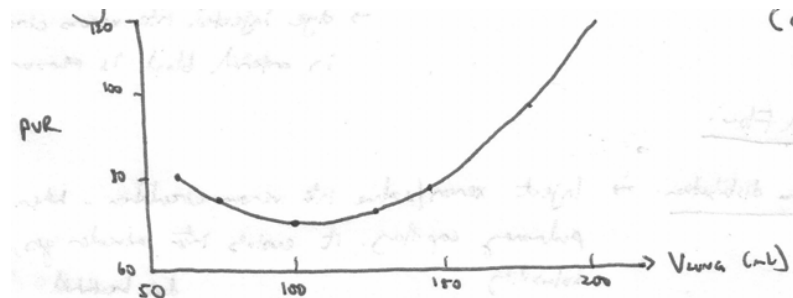
(3) Radius:

Important to note – Pulmonary vessel radius is a MAJOR determinant of PVR as it is –
(i) influenced by several factors (active and passive), and (ii) inversely related to PVR by its fourth power

- (a) Passive factors → more important (cf. active factors)
 - (i) Pulmonary vascular pressure:
 - ↑ in pulmonary arterial or venous pressures → further ↓ in PVR
 - This occurs via:
 - (i) Recruitment – Closed pulmonary vessels begin to open up and conduct blood as pressure rises → this is the MAIN mechanism for ↓ PVR at low pulmonary vascular pressures
 - (ii) Distension – Opened pulmonary vessels distend even further as pressure continues to rise (I.e. ↑ patency by changing shape from a near-flattened to a more circular one) → this is the MAIN mechanism for ↓ PVR at higher pulmonary vascular pressures



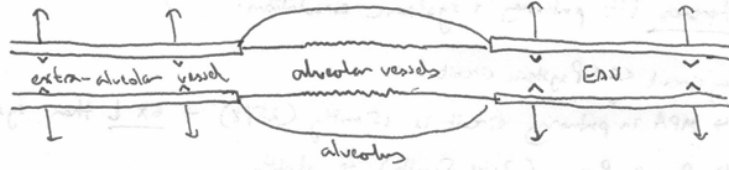
- (ii) Lung volume:
 - At low V_{LUNG} , PVR is high due to narrowing of extra-alveolar vessels
 - At high V_{LUNG} , PVR is even higher (cf. low V_{LUNG}) due to – (a) ↓ in alveolar vessel caliber 2° to stretching and thinning of the alveolar wall (main factor), but also (b) $P_{ALVEOLAR} > P_{CAPILLARY}$, which causes alveolar vessels to collapse
 - At FRC, PVR is at its LOWEST



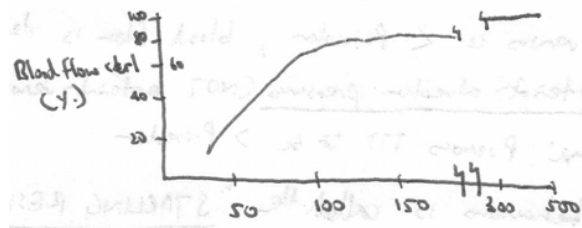
Aside – Alveolar vs. Extra-alveolar vessels:

- Alveolar vessels (Eg. capillaries/larger vessels in the corners of alveolar walls):
 - Calibre is determined by the “**Transmural pressure**” (pressure difference b/t inside and outside of capillaries) → if $P_{ALVEOLAR} > P_{CAPILLARY}$, then vessels collapse as the capillaries receive little support from the thin-layered alveolar epithelium

- Extra-alveolar vessels (Eg. PA, PV, other vessels that run through the parenchyma):
 - o Calibre is determined by **lung volume** → EAVs are pulled open with lung inflation due to radial traction of expanding lung parenchyma surrounding them



- (b) Active factors
 - o (i) Alveolar PO₂ (Major factor)
 - ↓ ALVEOLAR (NOT arterial) PO₂ causes contraction of SM in the walls of small pulmonary arterioles ("Hypoxic pulmonary vasoconstriction")
 - Mechanism – Pulmonary arteriolar walls adjacent to alveoli become hypoxic, → causing:
 - Vascular endothelial cells to ↑ release of endothelins and ↓ release of NO due to inhibition of NOS
 - Perivascular cells to ↑ release of vasoconstrictor substances
 - Altered VSMC channel function → affects mainly K⁺ channels, leading to ↑ IC [Ca²⁺] and vasoconstriction
 - Response is non-linear – P_AO₂ < 70 mmHg invokes vasoconstriction such that at extremely low P_AO₂, blood flow almost ceases; at P_AO₂ > 100 mmHg there is little change in PVR



- Role of response → shunt blood away from hypoxic areas of lungs to better ventilated parts of the lung to minimize V/Q mismatching
- o (ii) Blood pH and PaCO₂:
 - Acidic conditions (such as due to ↑ PaCO₂) induce vasoconstriction (esp in the context of alveolar hypoxia) → ↑ PVR
- o (iii) ANS:
 - SNS outflow – α-receptors → vasoconstriction and ↑ PVR; β-receptors → vasodilation and ↓ PVR
 - Vagal ACh on mAChR → vasodilation and ↓ PVR
- o (iv) Other vasoactive factors and drugs:
 - 5-HT, histamine, PGs, inotropes → pulmonary vasoconstriction and ↑ PVR
 - NO, milrinone, sildenafil → pulmonary vasodilation and ↓ PVR

Measuring pulmonary vascular resistance:

PVR is commonly measured using a "Swan-Ganz catheter" by measuring (i) mean pulmonary arterial pressure (PAP), (ii) Mean pulmonary capillary wedge pressure (PCWP) and (iii) Cardiac output (C.O.):

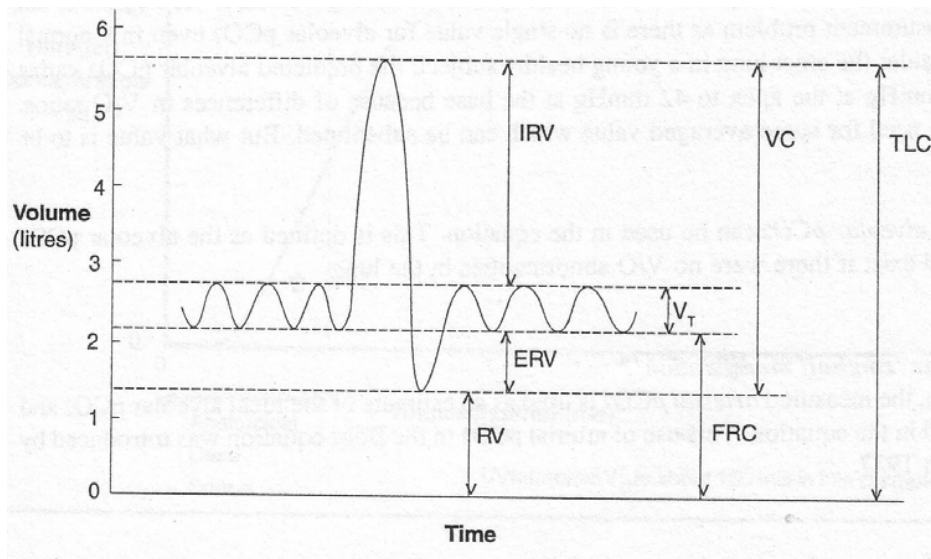
$$PVR = \frac{(\text{Mean PAP} - \text{PCWP}) \times 80}{\text{C.O.}}$$

(f) *Describe the pulmonary circulation in the foetus and the newborn.*

See notes on “Foetal and Neonatal Physiology”

IV. PULMONARY GAS VOLUMES AND VENTILATION

- (a) *To explain the measurement of lung volumes and capacities, and to indicate the normal values.*



Lung volumes are base units (measured in mL or mL/kg). There are four volumes:

- (1) Residual volume (RV):
 - o Volume of air remaining in the lungs after maximal expiration
 - o 15-20 mL/kg (or 1000 – 1200 mL)
- (2) Expiratory reserve volume (ERV):
 - o Additional volume that can be expired from FRC or resting expiratory state
 - o 15 mL/kg (or 1500 mL)
- (3) Tidal volume (TV):
 - o Volume of normal “resting” breath (or the volume difference between FRC and “resting” inspiratory volume)
 - o 7 mL/kg (or 500 mL)
- (4) Inspiratory reserve volume (IRV):
 - o Additional volume of air that can be inspired above “resting” inspiratory volume
 - o 45 mL/kg (or 3000 mL)

Lung capacity describes any combination of two or more lung volumes (measured in mL or mL/kg). There are four capacities:

- (1) Total lung capacity (TLC):
 - o Total lung volume of air in the lung following maximal inspiration (equal to the sum of RV, ERV, TV and IRV)
 - o 75-80 mL/kg (or 6000 mL)
- (2) Functional residual capacity (FRC):
 - o Lung volume remaining at the end of a normal tidal breath (equal to the sum of RV and ERV)
 - o 30 mL/kg (or 2200 mL)
- (3) Inspiratory capacity (IC):
 - o Total volume that can be inspired from FRC or resting expiratory state (equal to sum of TV and IRV)
 - o 50 mL/kg (or 3500 mL)
- (4) Vital capacity (VC):
 - o Maximal volume expired after a maximal inspiration (equal to sum of IRV, TV, and ERV)
 - o 60-70 mL/kg (or 4500-5000 mL)

Measurement of lung volumes:

(1) Spirometer:

- Can measure most lung volumes, EXCEPT for RV as spirometry measures gas expired from the lungs only
- Since RV cannot be measured, TLC and FRC cannot be obtained

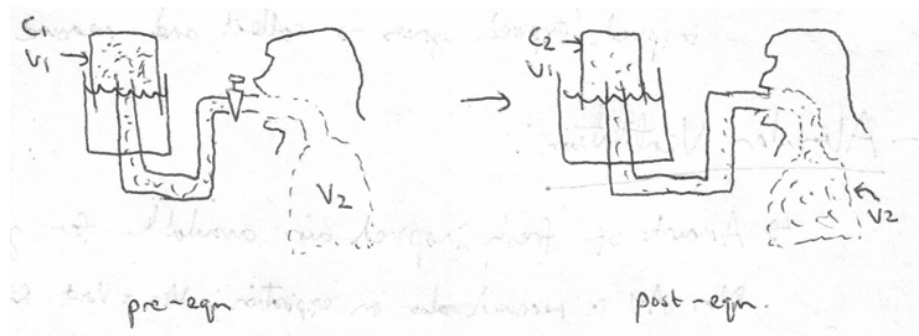
(2) Gas dilution method:

- Used to measure RV (and TLC and FRC)
- Two types:
 - o (a) Helium wash-in method:
 - Subject is connected to spirometer with a known [He] and volume of helium. After a few breaths, [He] in the spirometer and lung equilibrates
 - Since no helium is lost in the system:

Amount of helium *prior* to equilibrium = Amount of helium *after* equilibrium

$$C_1 V_1 = C_2 (V_1 + V_2)$$

$$V_2 = \text{FRC} = \frac{V_1 (C_1 - C_2)}{C_2}$$



- o (b) N₂ wash-out method:
 - Subject breathes in 100% O₂ for a few minutes and washes out all N₂ from the lungs
 - [N₂] is obtained after the first exhaled breath. Then [N₂] and volume of gas are collected after 7 minutes
 - Then assuming the lungs contains 80% N₂ at FRC, the volume of FRC can be calculated:

$$V_1 \times 80\% = [V_1 \times C_3] + [V_2 \times C_2]$$

V1: Lung volume (Nb. [N₂] in lung before washout is ~ 80%) = FRC V2: Volume exhaled over 7 minutes C2: [N₂] in exhaled volume (V2) C3: [N₂] in lung after exhalation (sample end-expiratory gas with N₂ meter)

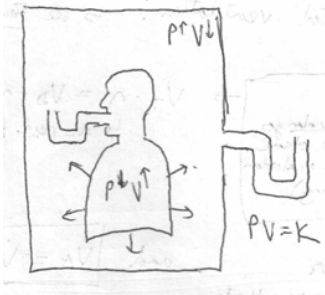
- Main disadvantage of these methods is that ONLY ventilated lung volumes are measured:
 - o In healthy lungs, where all lung units are well-ventilated, the lung volumes estimated using these methods are accurate
 - o BUT in the presence of lung disease where gas trapping occurs, the volume of unventilated lung units are not measured by these methods, and thus the lung volumes can be underestimated

(3) Body plethysmograph:

- Used to measure RV (and TLC and FRC)
- Method – Patient sits in an airtight box, and after end of normal expiration, a shutter closes the mouth piece and the patient is asked to make respiratory efforts. With

inspiration against a closed AW, the V_{LUNG} increases slightly and the P_{AIRWAY} decreases. Conversely, V_{BOX} decreases slightly and P_{BOX} increases

- As Boyle's Law states that "Pressure x Volume" is constant (assuming a constant temperature), thus:



$$\begin{array}{ccc}
 P_1 V_1 = P_2 (V_1 - \Delta V) & ; \Delta V = \text{Change in } V_{LUNG} \text{ or } V_{BOX} \\
 \swarrow \quad \searrow & \\
 \text{(Pre-inspiratory box P + V)} & \text{(Post-inspiratory box P + V)} \\
 \\
 P_3 V_2 = P_4 (V_2 + \Delta V) & ; P_3/P_4 = \text{Mouth pressures} \\
 \swarrow \quad \searrow & \\
 \text{(Pre-inspiratory lung P + V)} & \text{(Post-inspiratory lung P + V)} \\
 \\
 \text{Using } \Delta V, V_2 \text{ can be obtained as } V_2 = \text{FRC}
 \end{array}$$

- The advantage of this method is that it is able to measure total gas volume of the lung, including trapped gas in closed lung units (as seen in diseased lungs), unlike the "gas dilution methods" which will give spuriously low lung volumes in the setting of lung disease

(b) *To describe the factors influencing lung volumes and capacities.*

Factors influencing FRC:

- FRC is determined by:
 - (i) A balance of outward elastic recoil of the chest wall with inward elastic recoil of the lung
 - (ii) Diaphragmatic muscle tone (which pulls the diaphragm away from the lungs)
- As a result, FRC is affected by the following factors:
 - (1) Height (FRC proportional to height)
 - (2) Gender (FRC is 10% more in males)
 - (3) Position (FRC reduces by 30-50% when supine due to force of abdominal contents on the diaphragm)
 - (4) Abdominal swelling, such as obesity, pregnancy, ascites, Etc.(FRC decreases)
 - (5) Diaphragmatic tone (reduced tone with anaesthesia causes a fall in FRC)
 - (6) Lung and chest wall disease
 - Reduced FRC due to reduced compliance – Pulmonary fibrosis, kyphoscoliosis, neuromuscular disorders, APO, age
 - Increased FRC due to increased compliance – COPD/asthma
 - (7) IPPV/PEEP (FRC increases)
- FRC is NOT affected by age (Note – Closing volume increases with age such that closing capacity is the same as FRC at age 44 when supine and age 66 when erect, thereby causing atelectasis)

Factors influencing TLC:

- At TLC, the forces due to inspiratory muscles are counterbalanced by elastic recoil of lung and CW
- As a result, TLC is determined by:
 - (1) Strength of respiratory muscles (TLC increases with strength)
 - (2) Body size (TLC increases with body size)
 - (3) Gender (TLC is higher in males)
 - (4) Compliance of chest wall and lungs
 - Low compliance (Eg. restrictive lung disease, APO, kyphoscoliosis, obesity, age, Etc.) will reduce TLC
 - High compliance (Eg. obstructive lung disease) will increase it

Factors influencing VC:

- VC is an important measure in patients with lung disease (esp restrictive disease) as it estimates maximal inspiratory and expiratory effort (Ie. strength of respiratory muscles)
- Since VC is difference of TLC and FRC, VC is determined by:
 - (1) TLC – Factors that reduce TLC will reduce VC
 - (2) FRC – Factors that reduce FRC will reduce VC

(c) *To define dead space and apply the Bohr Equation and Alveolar Gas Equation.*

Minute ventilation:

- Defined as the total volume of air leaving the lung each minute

$$\text{Minute ventilation} = \text{TV} \times \text{RR} = 500 \text{ mL} \times 15 \text{ breaths/min} = 7500 \text{ mL/min}$$

- It is the sum of (i) Alveolar ventilation and (ii) Dead space ventilation

$$\text{Minute ventilation} = \text{Alveolar ventilation} + \text{Dead space ventilation}$$

- Measuring MV – A subject breathing through a valve box that separates inspired/expired gases. The bag with expired gas is collected and measured (tidal volume) and multiplied by the respiratory rate

Alveolar ventilation:

- Defined as the amount of fresh inspired air available for gas exchange each minute
- The volume of fresh inspired air that exchanges gas (I.e. contains CO₂) is equal to the amount of “Ideal” alveolar gas

$$\begin{aligned} \text{Alveolar ventilation} &= \text{Minute ventilation} - \text{DS ventilation} (\approx \text{Anat. DS ventilation}) \\ &= [(500 \text{ mL}) \times (15/\text{min})] - [(150 \text{ mL}) \times (15/\text{min})] = 5250 \text{ mL/min} \end{aligned}$$

- Given the derivation of AV, it can be increased with:
 - (1) Higher TV (Most effective) – Reduces the proportion of dead space in each breath!
 - (2) Higher respiratory rate (least effective)
- Measuring AV:
 - (1) Subtracting dead space ventilation from minute ventilation – BUT anatomical DS is NOT easily measured by Fowler’s method
 - (2) Determined from PaCO₂ and rate of CO₂ elimination during expiration:

$$V_{\text{CO}_2} (\text{volume of CO}_2 \text{ exhaled per unit time}) = V_A \times (F_A \text{CO}_2)$$

$$\text{So, } V_A = V_{\text{CO}_2} / (F_A \text{CO}_2)$$

And PaCO₂ is proportional to F_ACO₂ [P_ACO₂ = F_ACO₂ × P_{BAROMETRIC}], such that:

$$\text{THUS, } V_A = \frac{(V_{\text{CO}_2}) \times P_{\text{BAROMETRIC}}}{\text{PACO}_2}$$

Note: In healthy subjects, PACO₂ and PaCO₂ are almost equal and either can be used

Alveolar ventilation and alveolar/arterial PCO₂ are inversely proportional – If alveolar ventilation is HALVED (and CO₂ production is steady), arterial (or alveolar) P_{CO₂} will DOUBLE (and vice versa)

Dead space ventilation:

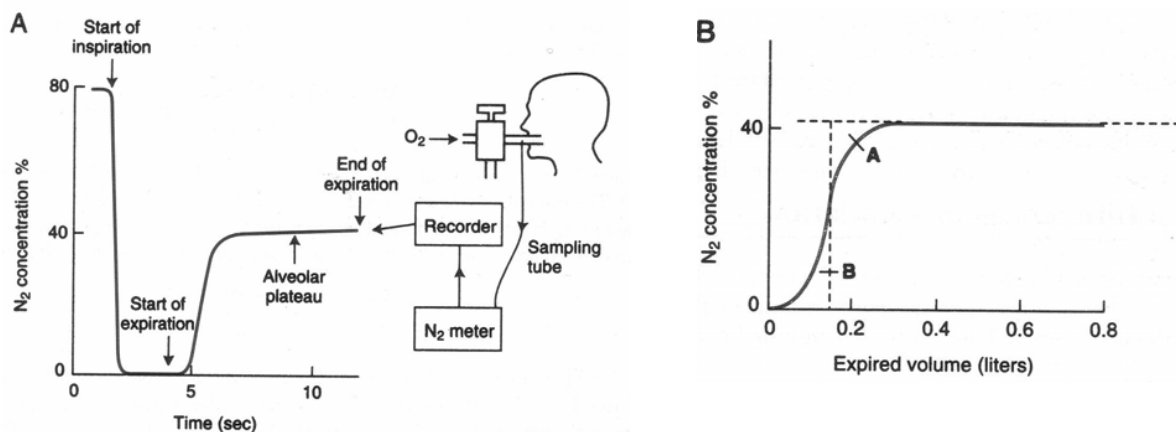
Definition of dead space:

- Ventilated alveoli that are unperfused (V/Q = infinity)
- Produces part of the inspired volume NOT participating in gas exchange (I.e. contains no CO₂)

There are 4 types of dead space:

(1) Anatomic dead space:

- Defined as the volume of air in conducting airways (usually 150 mL or 2.2 mL/kg)
- Size influenced by following factors:
 - (i) Depth of inspiration (larger breath causes traction on bronchi by lung parenchyma, thus increasing ADS)
 - (ii) Size of subject (bigger build, male gender increase ADS size)
 - (iii) Posture of subject (ADS increases with neck extension/jaw thrust, and decreased when supine)
 - (iv) Dilation of airways (use of bronchodilators or volatile agents dilate airways, leading to increased ADS)
- Measuring ADS (Fowler's method):
 - Subject breathes through a mouthpiece connected to sensitive pneumotachograph and gas sampling line that feeds into a rapid N₂ analyser
 - The subject inspires 100% O₂ then exhales and the [N₂] is measured over (i) Time and (ii) Expired volume such that two graphs are made



After inspiring 100% O₂ and then expiring, the of [N₂] increases as ADS is washed out by alveolar gas until an “Alveolar plateau” is reached (which represents pure alveolar gas)

ADS volume is determined by plotting [N₂] against expired volume:

- Where “area A” = “area B”, the expired volume equals ADS volume
- This represents the mid-point of transition from conducting zone to gas exchanging zones of lung

(2) Alveolar dead space:

- Defined as the part of inspired gas volume that passes through the anatomical DS to mix with alveolar gas, BUT is not perfused by capillary blood and thus does not exchange gas
- Causes include low C.O. states, PE, use of IPPV/PEEP
- Measuring alveolar DS:
 - (i) Using the Bohr equation to determine size of physiological dead space, and then subtracting anatomical dead space (as determined by Fowler's method)
 - (ii) Using a modified Bohr equation:

$$\frac{V_{ALV DS}}{V_T} = \frac{(P_a CO_2 - P_{END-TIDAL CO_2})}{P_a CO_2}$$

- (ii) Index of alveolar dead space is measured by ETCO₂-PaCO₂ gradient:
 - Usually gradient is 2-5 mmHg

- With increased amount of alveolar dead space, ETCO_2 is lowered and the gradient size increases

(3) Physiologic dead space:

- Defined as part of the inspired volume that does NOT participate in gas exchange – That being, the sum of anatomical and alveolar dead spaces
- As a result:
 - In normal lungs, alveolar dead space is minimal, thus physiological dead spaces EQUALS anatomical dead space
 - With lung disease, alveolar dead space increases, thus physiological dead space becomes LARGER than anatomical dead space
- Measuring physiological DS (Bohr's method):

CO_2 content of “mixed” expired gas = CO_2 content of “ideal” alveolar gas + CO_2 content of “dead space” gas

$$V_{\text{TIDAL}} \cdot F_{\text{E}}\text{CO}_2 = V_{\text{ALV}} \cdot F_{\text{A}}\text{CO}_2 + V_{\text{DS}} \cdot F_{\text{DS}}\text{CO}_2$$

Since “ideal” alveolar gas is involved in gas exchange (and dead space is not), ALL CO_2 expired and found in “mixed” expired gas must be derived from “ideal” alveolar gas. Therefore, the CO_2 content of “dead space” gas is zero (or $V_{\text{DS}} \cdot F_{\text{DS}}\text{CO}_2 = 0$)

And we know, $V_{\text{ALV}} = V_{\text{TIDAL}} - V_{\text{DS}}$. Therefore:

$$V_{\text{TIDAL}} \cdot F_{\text{E}}\text{CO}_2 = (V_{\text{TIDAL}} - V_{\text{DS}}) F_{\text{A}}\text{CO}_2$$

And rearrange:

$$V_{\text{DS}}/V_{\text{TIDAL}} = (F_{\text{ALV}} - F_{\text{E}})/F_{\text{ALV}}$$

Since partial pressure is proportional to fractional concentration:

$$V_{\text{D}}/V_{\text{T}} = (P_{\text{ACO}_2} - P_{\text{ECO}_2})/P_{\text{ACO}_2}$$

And alveolar and arterial P_{CO_2} are almost equal, hence:

Using this equation, the ratio of physiological DS to TV can thus be estimated by measurement of P_{CO_2} in arterial blood and mixed expired gas – Nb. In healthy individuals, $V_{\text{D}}/V_{\text{T}} \approx 0.2$ to 0.3 during resting breathing. This may be < 0.3 with exercise

(4) Apparatus dead space:

- Additional volume from breathing through mask and anaesthetic circuit tubing
- Acts in similar manner as “anatomical” dead space

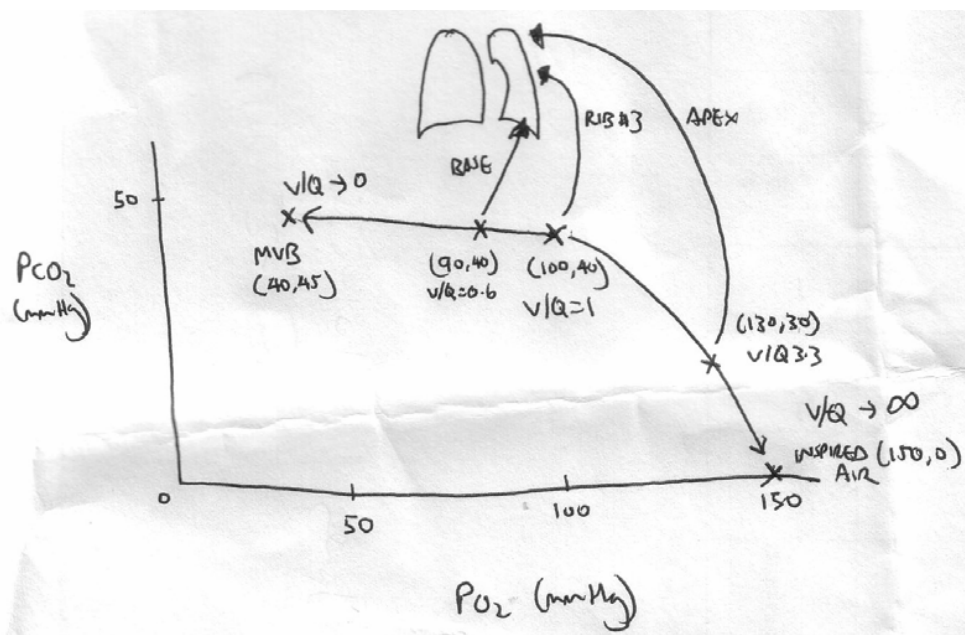
- (d) **Explain normal ventilation-perfusion matching, including the mechanisms for these as well as the normal values.**

Introduction to V/Q ratio:

- The partial pressures of a gas in the alveolar compartment and in end-capillary blood are determined by the:
 - (i) Rate at which gas enters the alveoli (Ventilation)
 - (ii) Rate of blood flow through the alveoli (Perfusion)

Effect of V/Q inequalities on gas exchange:

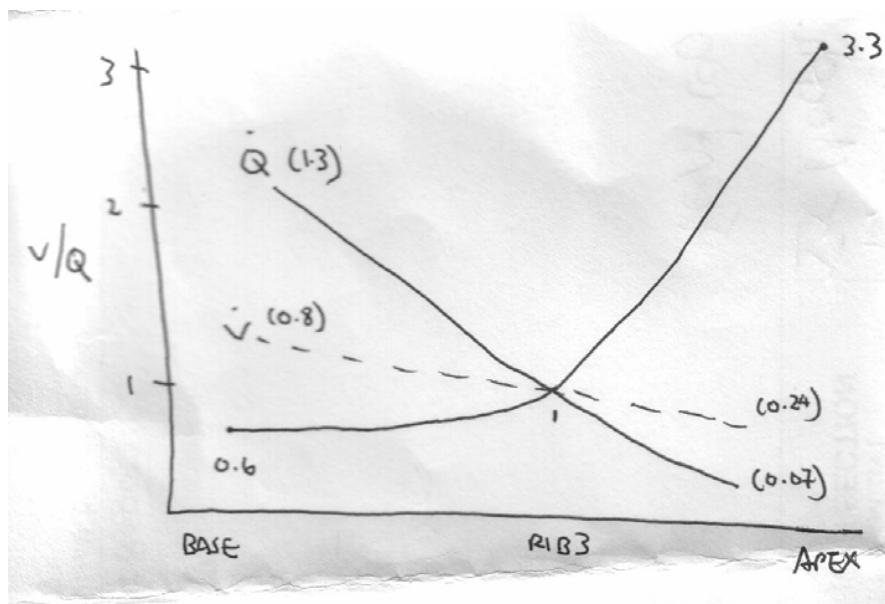
- “V/Q inequalities” are states in the lung where ventilation and perfusion of lung units are not ideally matched for gas exchange to occur
- There is a range of V/Q inequalities:
 - (1) $V/Q = 1$
 - Ventilation and perfusion are ideally matched for gas exchange to occur
 - Alveolar and end-capillary partial pressures of gas approaches that of “Ideal alveolar gas”, which is determined by – (i) Rate O_2 enters the lung (or rate CO_2 exits the lung), and (ii) Rate O_2 is taken up by blood (or rate CO_2 is removed from blood)
 - PAO_2 100 mmHg and $PACO_2$ 40 mmHg (assuming MVB content of PO_2 40, PCO_2 46; inspired gas content of PO_2 150, PCO_2 0)
 - (2) $V/Q < 1$
 - Alveoli are underventilated for the level of perfusion
 - “Shunt” occurs when $V/Q = 0$ – Alveoli are perfused but NOT ventilated
 - Alveolar and end-capillary partial pressures of gas approaches MVB content (usually PO_2 40, PCO_2 46)
 - (3) $V/Q > 1$
 - Alveoli are underperfused for level of ventilation
 - “Dead space” occurs when V/Q approaches infinity – Alveoli are ventilated but NOT perfused
 - Alveolar and end-capillary partial pressures of gas approaches that of inspired air (usually PO_2 150, PCO_2 0)
- O_2 - CO_2 diagram denotes ALL possible alveolar or end-capillary PO_2 / PCO_2 compositions for a V/Q of zero to infinity



- Note: Changes in PO_2/PCO_2 content of (i) Inspired gas (I.e. changing $P_{\text{BAROMETRIC}}$ or $FIO_2/FICO_2$) or (ii) MVB (I.e. changing VO_2/VCO_2) will SHIFT the line of the plot, and thus alter the possible alveolar or end-capillary PO_2/PCO_2 compositions

Regional V/Q mismatch within the lung:

- In an upright lung, regional differences in V' and Q' exist due to effects of gravity:
 - (1) V' and Q' FALL from base to the apex
 - Gravity causes hydrostatic pressures to be greater at the bases than at the apices (by 30 cmH₂O or 23 mmHg) resulting in pulmonary blood flow (Q') to decrease linearly from the base to the apex in an upright lung
 - Gravity causes basal alveoli to have a smaller opening volume than at the apices (and thus falls on a more compliant part of the P-V curve) causing alveolar ventilation (V') to decrease linearly from the base to the apex in an upright lung. The smaller alveoli volumes at the bases are due to:
 - Compressive effects of gravity on alveoli due to the weight of the lungs
 - Less -ve intrapleural pressure at the bases (-2.5 cmH₂O vs -10 cmH₂O at the apex) which attenuates radial traction on alveoli
 - (2) Q' falls FASTER than V' from base to the apex
 - (3) V/Q INCREASES from the base to the apex
 - Apex has $V/Q > 1$, thus alveolar and end-capillary partial pressures of gas approaches that of inspired air
 - At level of heart, $V/Q \sim 1$ and thus alveolar and end-capillary partial pressures of gas approaches that of "ideal" alveolar gas
 - Base has $V/Q < 1$, thus alveolar and end-capillary partial pressures of gas approaches MVB content



- Despite regional differences in V/Q due to gravity, the global V/Q ratio of the lungs is only 0.8 (as $V \sim 4$ L/min and $Q \sim 5$ L/min) – This contributes to a slightly reduced efficiency in gas exchange (which is significantly enhanced with lung disease)

Regional differences in gas exchange in apex versus base:

Factor	Apex	Base
Volume (%)	7	13
V/Q (V, Q in L/min)	3.3 (0.24, 0.07)	0.6 (0.8/1.3)
PO_2 (mmHg)	130	90

PCO ₂ (mmHg)	28	42
PN ₂ (mmHg)	553	582
pH	7.51	7.39
O ₂ conc (mL/100 mL)	20	19.2
CO ₂ conc (mL/100 mL)	42	49
R (CO ₂ out, O ₂ in [mL/min])	2 (8, 4)	0.66 (40, 60)

(e) *To describe the composition of ideal alveolar and mixed expired gases.*

Factors influencing alveolar gas content:

- (1) Adequacy of alveolar ventilation (or V/Q ratio)
 - o Alveolar ventilation delivers O₂ to and removes CO₂ from alveolar gas
 - o Thus, increased alveolar ventilation (relative to perfusion; I.e. high V/Q ratio) causes a rise in P_AO₂ and fall in P_ACO₂, whereas decreased alveolar ventilation (relative to perfusion; I.e. low V/Q ratio) causes a fall in P_AO₂ and rise in P_ACO₂
- (2) Inspired partial pressure of gas
 - o Alveolar partial pressure of a gas is proportional to the inspired partial pressure of a gas
 - o The inspired partial pressure is proportional to the (i) Barometric pressure and (ii) Fractional content of gas
 - o Thus, P_AO₂ increases with increased P_{BAROMETRIC} and/or FIO₂
- (3) Tissue metabolism (VO₂/VCO₂)
 - o This determines the CO₂ and O₂ composition of MVB that is delivered to the alveoli from pulmonary blood flow
 - o Thus, increased tissue metabolism causes a fall in P_AO₂ and rise in P_ACO₂ (and vice versa)

Content and partial pressure of CO₂ in alveolar gas:

- Fractional content of CO₂ in alveolar gas (FACO₂):

$$\text{Since } V_{\text{CO}_2} = V_{\text{ALV}} \times (F_{\text{ACO}_2}) + \cancel{V_{\text{DS}} \times (F_{\text{DS}}\text{CO}_2)} \rightarrow 0$$

$$F_{\text{ACO}_2} = \frac{V_{\text{CO}_2}}{V_{\text{ALV}}} = \frac{200 \text{ mL/min}}{4 \text{ L/min}} = 5\%$$

- Alveolar partial pressure of CO₂ (PACO₂):

$$P_{\text{ACO}_2} = P_{\text{BAROMETRIC}} \times [F_{\text{ICO}_2} + F_{\text{ACO}_2}]$$

$$\text{But } F_{\text{ICO}_2} \sim 0, \text{ so } P_{\text{ACO}_2} = P_{\text{BAROMETRIC}} \times [F_{\text{ACO}_2}]$$

$$\text{And since } F_{\text{ACO}_2} = V_{\text{CO}_2}/V_{\text{ALV}}:$$

$$P_{\text{ACO}_2} = P_{\text{BAROMETRIC}} \times \frac{(V_{\text{CO}_2})}{V_{\text{ALV}}}$$

Content and partial pressure of O₂ in alveolar gas:

- Alveolar partial pressure of O₂ (PAO₂) is calculated using the “Alveolar gas equation”:

$$P_{\text{A}}\text{O}_2 \approx P_{\text{IO}_2} - (P_{\text{ACO}_2}/R) \quad ; \quad \text{Nb. } \underline{\text{Arterial and alveolar PCO}_2 \text{ are interchangeable}}$$

- Fractional content of O₂ in alveolar gas (FAO₂):

$$F_{\text{AO}_2} = (P_{\text{AO}_2}/P_{\text{BAROMETRIC}}) \times 100\% = (100 \text{ mmHg}/760 \text{ mmHg}) \times 100\% = 13\%$$

Composition of “Ideal” alveolar gas:

- There are large variations in alveolar partial pressures of a gas due to regional variations in V/Q ratios (See O₂/CO₂ diagram)
- “Ideal” alveolar gas partial pressure is defined the partial pressure of a gas in the alveolus if no V/Q mismatching existed (I.e. V/Q = 1)
- The “Ideal” alveolar gas partial pressure will vary depending on:
 - o (1) Partial pressure of the inspired gas

- (2) Gas contents of MVB (which is determined by level of tissue metabolism)
- Thus, assuming a PIO₂ 150/PICO₂ 0 and PvO₂ 40/PvCO₂ 45 (at P_{BARO} = 760 mmHg and at resting conditions where VO₂ 250 mL/min and VCO₂ 200 mL/min):
 - PCO₂ of “ideal” alveolar gas is ~ 40 mmHg

$$P_{ACO_2} = P_{BAROMETRIC} \times \frac{(V_{CO_2})}{V_{ALV}} = 760 \times (250/4) = \sim 40 \text{ mmHg}$$

- PO₂ of “ideal” alveolar gas is ~ 100 mmHg

$$P_{AO_2} \approx P_{IO_2} - (P_{ACO_2}/R) = 150 - (40/0.8) = \sim 100 \text{ mmHg}$$

- Because alveolar gas equilibrates with pulmonary end-capillary blood, the content of pulmonary end-capillary blood (PcO₂/PcCO₂) should approximate that of “ideal” alveolar gas (assuming the lung unit as a whole has a V/Q ~ 1, which it normally does)

Composition of “Mixed expired” gas:

- Mixed expired gas contains a mixture of:
 - (1) “Ideal” alveolar gas that participates in gas exchange – Composition is PO₂ 100 mmHg/PCO₂ 40 mmHg
 - (2) Physiological dead space gas that does not participate in gas exchange – Composition is PO₂ 150 mmHg/PCO₂ 0 mmHg (Ie. same as inspired air content)
- In healthy persons, mixed expired gas composition should be similar to that of ideal alveolar gas as there will be minimal physiological dead space present
- In diseased lungs with more physiological dead space (Ie. due to increased alveolar dead space), then mixed expired gas will have reduced PCO₂ and increased PO₂ due to increased content contribution from dead space

VI. VENTILATION-PERFUSION INEQUALITIES

- (a) *To describe West's zones of the lung and explain the mechanisms responsible for them.*

West's zones of the lung:

There are 4 West's zones of the lung, each with varying levels of pulmonary blood flow → the uneven distribution of blood flow b/t these zones is due to:

- (1) Gravity-related differences in pulmonary vascular pressure gradients b/t the apex and base of an upright lung

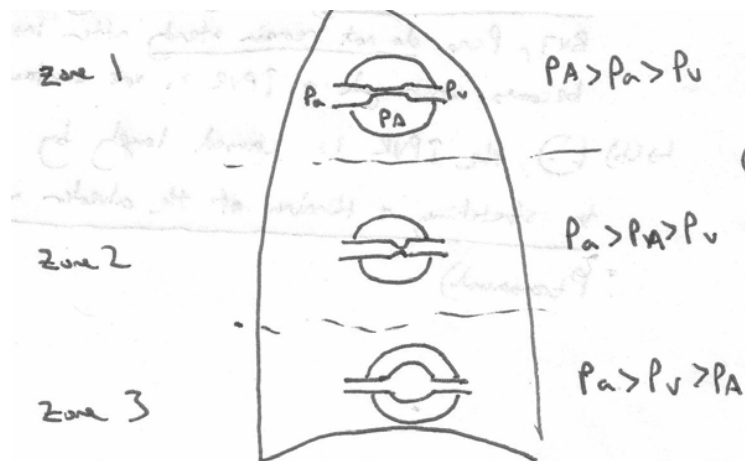
Important to note:

- Gravity produces a hydrostatic pressure gradient in the upright lung (I.e. $P_{\text{HYDROSTATIC}}$ at base is $\sim 30 \text{ cmH}_2\text{O}$ greater than at apex) → size of this gradient is dependent on the vertical dimensions of the lung (I.e. $\uparrow$ gradient with $\uparrow$ lung size)
- This effectively causes pulmonary vascular pressures (and pulmonary blood flow) to $\uparrow$ linearly from the apex to base also

Aside – MPA = 15 mmHg and PV = 5 mmHg → at the apex it is 10 mmHg less (so MPA = 5 mmHg and PV = -5 mmHg); at base 10 mmHg more (so MPA = 25 mmHg and PV = 15 mmHg)

- Importantly, the pulmonary arterial pressure is able to exceed the hydrostatic pressure gradient caused by gravity at the lung apex → ensures that blood reaches lung apices to maximise surface area for gas exchange

- (2) Transmural pressure across the alveolar vessel wall → balance b/t (i) pulmonary vascular pressures (arterial and venous) and (ii) alveolar pressure



West Zone 1 (At the apex):

- P_{ARTERIAL} and P_{VENOUS} are VERY LOW (due to minimal hydrostatic effects of gravity) and falls below P_{ALVEOLAR} → thus, alveolar vessels collapse and there is no pulmonary blood flow
- This zone does NOT exist under normal conditions as P_{ARTERIAL} (or pulmonary arterial pressure) is usually high enough to overcome P_{ALVEOLAR} , EXCEPT when:
 - o (i) P_{ARTERIAL} is significantly depressed (Eg. Hypotension, PE)
 - o (ii) P_{ALVEOLAR} is significantly raised (Eg. PPV, PEEP)

Aside – This produces poor-perfused alveoli at the apices with a high V/Q ratio ($\approx$ “Alveolar dead space”)

West Zone 2 (From apex down to 10 cm above heart level):

- P_{ARTERIAL} is higher (due to hydrostatic effects of gravity) and it exceeds P_{ALVEOLAR} , BUT P_{VENOUS} is still less than P_{ALVEOLAR}
- Pulmonary blood flow is intermittent as it is determined by differences in arterial-alveolar pressures → “Starling Resistor” effect, whereby blood flow is dependent on the pressure from outside the lumen (I.e. P_{ALVEOLAR}):
 - A lack of blood flow leads to a $\uparrow$ hydrostatic pressure, which $\uparrow P_{\text{ARTERIAL}}$ such that it eventually exceeds P_{ALVEOLAR} → opens up capillary beds to permit blood flow
 - Eventually, as blood flows the hydrostatic pressure $\downarrow$ leading to a $\downarrow$ in P_{ARTERIAL} such that it falls below P_{ALVEOLAR} → causes capillary beds to close and blood flow to return to a halt

West Zone 3 (From 10 cm above heart level down to the base):

- $P_{\text{ARTERIAL}} > P_{\text{VENOUS}} > P_{\text{ALVEOLAR}}$ → thus, pulmonary blood flow is determined by differences in arterial-venous pressures
- Towards the bases, arterial-venous pressure difference $\uparrow$ while P_{ALVEOLAR} remains constant → thus, the hydrostatic pressure within the capillary beds allows them to remain open independent of the respiratory cycle, thereby allowing pulmonary blood flow to occur continuously

Aside – This produces well-perfused alveoli at the bases with low V/Q ratio (adds to venous admixture/shunt)
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West Zone 4 (At lung base):

- Bases of the lungs are prone to atelectasis (and low lung volumes) due to the effect of gravity on lung parenchyma there
- The low lung volumes predispose EAVs to collapse → thus, leading to $\downarrow$ blood flow in those regions

(b) *To explain the shunt equation.*

(c) *To explain venous admixture and its relationship to shunt.*

Definition of venous admixture and shunting:

- “**Venous admixture**” (or “Virtual shunt”) → amount of mixed venous blood (MVB) that would need to be added to pulmonary end-capillary blood (PECB) to produce the observed fall in PaO_2 from the PcO_2
- “**Shunt**” (or “True shunt”) → blood that enters the arterial system without passing through ventilated areas of the lung

Important to note – Blood from “venous admixture” and “shunt” both attenuate PaO_2 and produce an A-a PO_2 gradient, but the key difference is that:

- Blood from a “shunt” has a PO_2 generally different from that of MVB → in most cases, it will have a $\text{PO}_2 < \text{PcO}_2$
- Blood from a “venous admixture” has a PO_2 equal to that of MVB (I.e. PvO_2)

Sources of blood that contribute to venous admixture:

- (1) Blood from “True shunts” → poorly oxygenated venous blood directly drain into the left side of the heart and mix with well-oxygenated PECB
 - o Physiological → Bronchial venous blood (drains bronchial circulation) and blood from Thebesian vessels (drains coronary venous blood)
 - o Pathological → Congenital heart disease with R-to-L shunting (Eg. VSD, ASD, PDA) and pulmonary AV fistulas
- (2) Blood from alveoli with V/Q ratio < 1 (or V/Q mismatch) → cause MVB to be poorly oxygenated as it passes through poorly ventilated lung areas before it enters the left side of the heart to mix with well-oxygenated PECB
 - o Physiological → Dependent lung units (as a result of gravity) have a $\text{V/Q} < 1$
 - o Pathological → Lung units have $\text{V/Q} < 1$ in COPD, pulmonary fibrosis, pneumonia, APO/LVF, atelectasis, PTX, pleural effusions, Etc.

Note – “ V/Q mismatch” is NOT a “true shunt” as blood has passed through areas of lung that have received some ventilation

Important to note → blood from both these sources contribute to venous admixture and ↓ PaO_2 , BUT in neither case is shunted blood actually consists of MVB (I.e. PO_2 of shunted blood sources not = PvO_2)

“Shunt Equation” and venous admixture:

$$\frac{Q_{\text{SHUNT}}}{Q_T} = \frac{C_c\text{O}_2 - C_a\text{O}_2}{C_c\text{O}_2 - C_v\text{O}_2}$$

Q_{SHUNT}	= Shunt blood flow
Q_T	= Cardiac output
$C_c\text{O}_2$	= O_2 content of PECB (theoretically obtained from <u>PAO_2 and O_2 ODC</u>)
$C_v\text{O}_2$	= O_2 content of MVB (obtained from <u>PA catheter sample of MVB</u>)
$C_a\text{O}_2$	= O_2 content of AB (obtained from <u>ABG sample</u>)

This equation calculates the amount of “venous admixture” or “virtual shunt” only (as a fraction of Q_s/Q_T) → this is b/c it measures the amount of shunt that would account for the observed ↓ in PaO_2 from PcO_2 should the shunt be entirely comprised of MVB

Important to note – The amount of “venous admixture” calculated by the shunt equation is a theoretical value that may NOT be equal to the amount of “shunt” → this is b/c actual blood shunted generally has a different PO_2 composition as MVB → hence, the amount of “shunt” or “true shunt” CANNOT be measured by this equation!

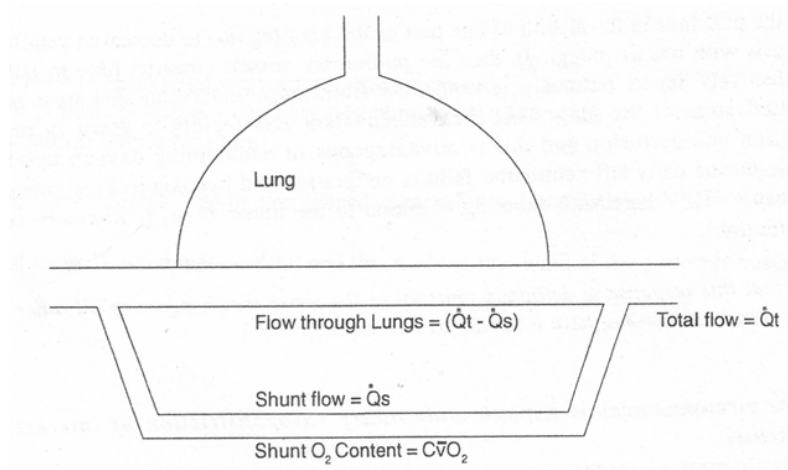
Important to note – Relative amount of “venous admixture” (or Q_s/Q_T) is normally $\sim 2-3\%$

Aside – Derivation of the “shunt equation”:

(O_2 leaving in arterial blood flow) = (O_2 carried in shunted blood flow) + (O_2 carried in pulmonary end-capillary blood flow)

$$\text{So, } Q^*_T \times CaO_2 = Q^*_{SHUNT} \times C_vO_2 + (Q^*_T - Q^*_{SHUNT}) \times C_cO_2$$

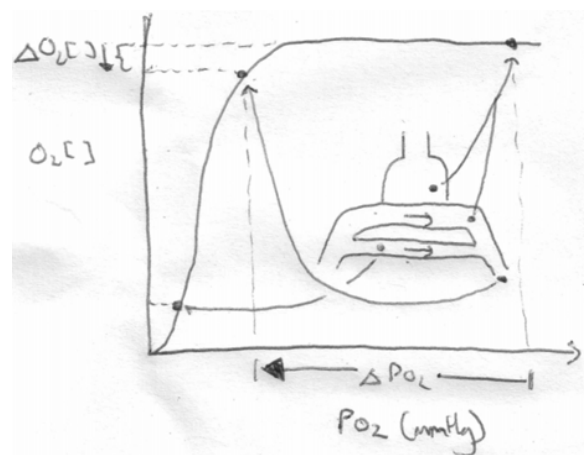
$$\text{Thus, } \frac{Q^*_{SHUNT}}{Q^*_T} = \frac{C_cO_2 - CaO_2}{C_cO_2 - C_vO_2}$$



Effect of venous admixture (and shunting) on oxygen and carbon dioxide:

(1) $\downarrow PaO_2$ and $\uparrow A-a PO_2$ gradient

- PO_2 of PECB places it in the upper flat part of the Hb ODC $\rightarrow$ thus, addition of a small quantity of poorly oxygenated shunted blood flow ($PO_2 < PcO_2$) added to a large volume well-oxygenated PECB produces a small fall in CaO_2 BUT a LARGER fall in PaO_2



- Since $PcCO_2$ is practically equivalent to $PAO_2 \rightarrow \downarrow$ in PaO_2 will cause $\uparrow A-a PO_2$ gradient

(2) $PaCO_2$ unchanged (or reduced)

- $PaCO_2$ can be relatively unchanged due to the steeper CO_2 dissociation curve (I.e. slight increase in arterial CO_2 content produces little change in $PaCO_2$)

- PaCO_2 can $\downarrow$ due to $\uparrow$ minute ventilation from – (a) Hypoxaemic stimulation of hypercapnoeic-ventilatory drive, and/or (b) Stimulation of chemoreceptors from the addition CO_2 from shunted blood

Effect of increasing FiO_2 on a venous admixture (and shunting):

Amount of venous admixture will $\downarrow$ but CANNOT be completely removed by $\uparrow \text{FiO}_2 \rightarrow$ this is b/c:

- $\uparrow \text{FiO}_2$ to 100% will cause $\uparrow \text{PiO}_2$ (and PAO_2) $\rightarrow$ will lead to $\uparrow \text{PaO}_2$ and CaO_2 as per “ O_2 flux equation” ($\text{CaO}_2 = [\text{Hb}] \times 1.34 \times \% \text{SaO}_2 + 0.003 \times \text{PaO}_2$)
- BUT this can never completely compensate for hypoxaemia caused by the shunt b/c:
 - o (1) $\uparrow$ in CaO_2 caused by $\uparrow \text{FiO}_2$ is only modest
 - At normal PAO_2 (~ 100 mmHg), Hb will already be very saturated with O_2 (i.e. lies at high flat part of ODC) $\rightarrow$ so $\uparrow \text{FiO}_2$ to 100% will add only small amounts of O_2 to blood in its dissolved form only
 - o (2) Addition of shunted blood (which is NOT exposed to $\uparrow \text{FiO}_2$) causes a significant fall in PaO_2 when added to well-oxygenated PECS
 - PO_2 of PECS places it in the upper flat part of the Hb ODC $\rightarrow$ thus, addition of a small quantity of poorly oxygenated shunted blood to a large volume well-oxygenated PECS produces a small fall in CaO_2 BUT a LARGER fall in PaO_2

- (c) *To describe and explain regional ventilation-perfusion inequalities, their clinical importance, and changes with posture.*
- (d) *To outline the methods used to measure ventilation-perfusion inequalities.*
- (f) *To explain the clinical significance of changes in anatomical and physiological dead space.*
- (g) *To explain the effect of ventilation-perfusion inequality on oxygen transfer and carbon dioxide elimination.*

Ventilation-Perfusion ratio and mismatch:

The [] of a gas in the alveolar compartment (and in end-capillary blood) is determined by:

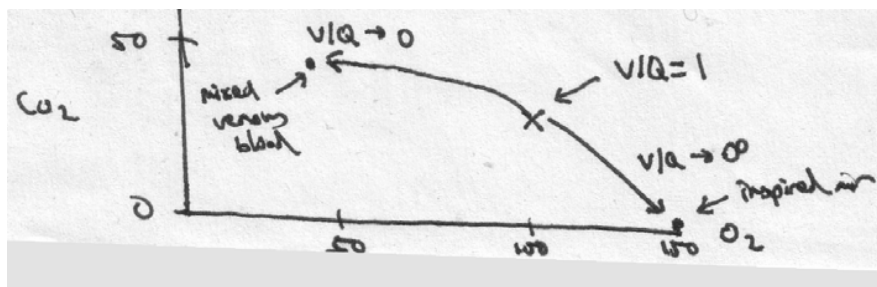
- (1) Rate at which gas enters the alveoli → Ventilation or “V”
- (2) Rate of blood flow through the alveoli → Perfusion or “Q”

$$\text{So, V/Q ratio} = \frac{\text{MV}}{\text{C.O.}} = \frac{(4 \text{ L/min})}{(5 \text{ L/min})} \approx 0.8$$

Alveolar gas content (and end-capillary blood content) thus changes with variations in V/Q ratio → assuming “Inspired air” has $P_{O_2} = 150$ and $P_{CO_2} = 0$, and “Mixed venous blood” (MVB) has $P_{O_2} = 40$ and $P_{CO_2} = 45$, then:

- (i) “Normal” V/Q of 1 → Alveolar $PO_2 = 100$ mmHg and $PCO_2 = 40$ mmHg
- (ii) V/Q → 0 (Ie. due to ↓ ventilation):
 - Alveolar PO_2 ↓ to 40 mmHg and PCO_2 ↑ to 45 mmHg → approaches that of MVB
 - So ↓ V/Q alveoli mimics that effect of a “Shunt”
- (iii) V/Q → infinity (Ie. due to ↓ perfusion):
 - Alveolar PO_2 ↑ to 150 mmHg and PCO_2 ↓ to 0 mmHg → approaches that of inspired air
 - So ↑ V/Q alveoli produce “Physiological Dead Space”

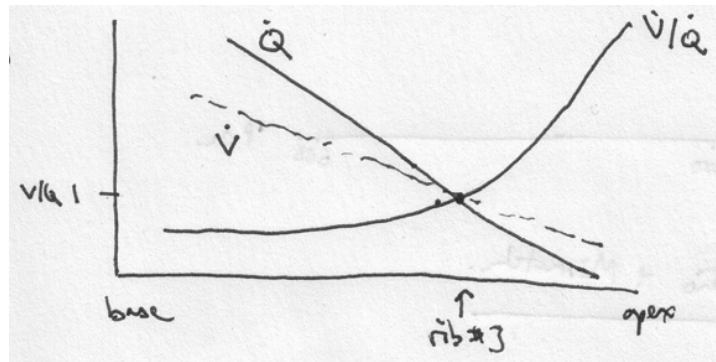
Important to note – This concept is demonstrated using the “ O_2 - CO_2 diagram”:



- * The line of the plot denotes ALL possible alveolar (or end-capillary) PO_2/PCO_2 compositions/combinations for a V/Q of zero to infinity
- * Any changes in PO_2/PCO_2 content of (i) inspired gas or (ii) mixed venous blood will SHIFT the line of the plot, and thus alter the possible alveolar PO_2/PCO_2 compositions/combinations

In a healthy lung, there are regional variations in gas exchange (and V/Q ratios) due to the effects of gravity on an upright lung:

- In an upright lung, $\dot{V}$ and $\dot{Q}$ RISE from apex to the base; $\dot{Q}$ rises FASTER than $\dot{V}$ → thus, $\dot{V}/\dot{Q}$ INCREASES from the base to the apex!



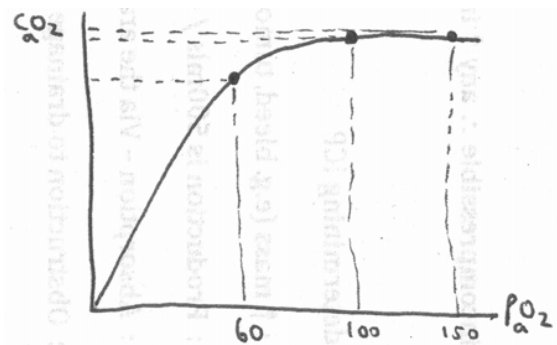
- These physiological regional differences in $\dot{V}/\dot{Q}$ ratio produce “ $\dot{V}/\dot{Q}$ mismatch” → ↓ efficiency in gas exchange

These gravity-related regional variations in $\dot{V}/\dot{Q}$ ratio causes:

- (1) ↓ PaO_2 :

Mechanism:

- (i) PO_2 of pulmonary end-capillary blood places it on the upper flat part of the “non-linear” nature of the O_2 dissociation curve → so:
 - o Alveoli at apex have high $\dot{V}/\dot{Q}$ alveoli that add very little O_2 to well-oxygenated pulmonary end-capillary blood → this is b/c Hb is already fully saturated and any ↑ PO_2 is dissolved in plasma, resulting in a minimal ↑ O_2 content
 - o Alveoli at base have low $\dot{V}/\dot{Q}$ ratio alveoli that markedly ↓ O_2 content of pulmonary end-capillary blood → this is b/c PO_2 at base is 40 mmHg lower cf. apex (I.e. 90 vs 130 mmHg), resulting in significant ↓ O_2 content
- (ii) Perfusion at base is greater cf. apex → so total pulmonary venous blood consists of a ↑ contribution of poorly-oxygenated blood from low $\dot{V}/\dot{Q}$ alveoli than well-oxygenated blood from high $\dot{V}/\dot{Q}$ alveoli → due to the “non-linear” nature of the O_2 dissociation curve, the ↓ CaO_2 results in a more significant ↓ in PaO_2



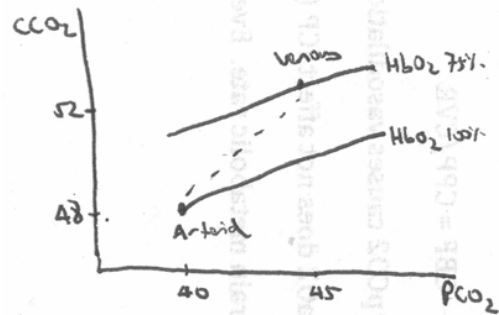
Important to note – Hypoxaemia due to $\dot{V}/\dot{Q}$ mismatch:

- (i) Can be corrected by ↑ FiO_2 (unlike a shunt)
- (ii) Cannot be corrected by ↑ ventilation (unlike hypercapnoea) → this is due to non-linear shape of O_2 dissociation curve (I.e. alveoli with ↓ $\dot{V}/\dot{Q}$ continue to produce poorly oxygenated blood despite ↑ MV while alveoli with ↑ $\dot{V}/\dot{Q}$ add only minimal O_2)

- (2) $\uparrow$ A-a PO_2 gradient $\rightarrow$ normally this is minimal (~ 5 -10 mmHg)
- (3) $\uparrow$ or no change in $PaCO_2$

Mechanism:

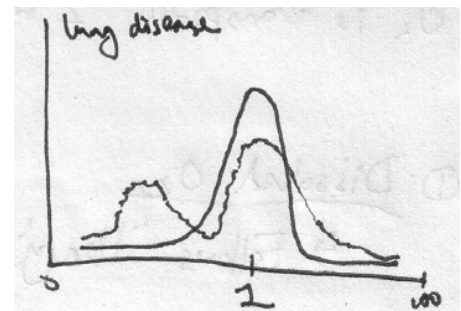
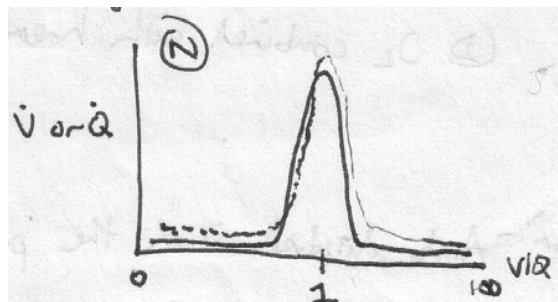
- (i) Well-perfused alveoli at the base have $\uparrow PCO_2$ (cf. apex) $\rightarrow$ causes $\uparrow PaCO_2$
- (ii) BUT hypercapnoea stimulates peripheral and central chemoreceptors to $\uparrow$ alveolar ventilation $\rightarrow$ normalises $PaCO_2$
- (iii) AND CO_2 dissociation curve is "linear" in its physiological range (unlike O_2) $\rightarrow$ so $\uparrow$ ventilation can effectively $\downarrow CO_2$ content of blood from some areas of lung to compensate for $\uparrow$ in CO_2 content of blood from poorly ventilated alveoli



Important to note – These effects are generally minimal (and trivial) in a “healthy” lung $\rightarrow$ BUT become significant in the context of lung disease (I.e. $\downarrow\downarrow\downarrow PaO_2$, $\uparrow\uparrow\uparrow$ A-a PO_2 gradient, $\uparrow\uparrow\uparrow PaCO_2$)

Distribution of V/Q ratios:

- In *normal people* $\rightarrow$ most V and Q goes to alveoli with $V/Q \sim 1$ (I.e. very few go to $\uparrow$ or $\downarrow V/Q$ alveoli)
- BUT in *patients with lung disease* $\rightarrow$ some V and Q goes to alveoli with $\downarrow V/Q$ s and $\uparrow V/Q$ $\rightarrow$ causes $\downarrow PaO_2$, $\uparrow$ A-a PO_2 gradient and $\uparrow PaCO_2$



Magnitude of V/Q mismatch can be determined by calculating the “Alveolar-arterial PO_2 (A-a PO_2) gradient” (See below) $\rightarrow$ if A-a PO_2 gradient is $\uparrow$ (> 15 mmHg), then V/Q mismatching exists

Important to note – Magnitude of alveoli with abnormal V/Q ratio contributing to $\uparrow$ A-a PO_2 gradient can be calculated:

- Alveoli with low V/Q ratio $\rightarrow$ produce alveoli that mimic a “shunt” $\rightarrow$ so contribution to $\uparrow$ A-a PO_2 gradient assessed by “Shunt equation”
- Alveoli with high V/Q ratio $\rightarrow$ produce alveoli that is “physiological dead space” $\rightarrow$ so contribution to $\uparrow$ A-a PO_2 gradient assessed by “Bohr equation”

Aside: Alveolar-arterial PO_2 gradient

Calculating “alveolar-arterial PO_2 (A-a PO_2) gradient”:

$$\text{A-a } PO_2 \text{ gradient} = (\text{“Ideal” alveolar } PO_2) - (\text{Arterial } PO_2)$$

Remember – “Ideal” alveolar PO_2 :

- PO_2 present in alveoli if – (i) no V/Q mismatch in lung existed, and (ii) lung was exchanging gas at same respiratory exchange ratio (R) as the real lung
- This is derived from the “Alveolar gas equation”:

$$PAO_2 = PIO_2 - (PACO_2/R) + F$$

Where: $PACO_2 \approx PaCO_2$

$$PIO_2 = FIO_2 \times (P_{\text{BAROMETRIC}} - P_{H_2O})$$

Important to note – To calculate A-a PO_2 gradient:

- $PAO_2 \rightarrow$ determined using “alveolar gas equation”, which requires (i) FiO_2 and (ii) $PaCO_2$ (measured by ABG)
- $PaO_2 \rightarrow$ measured by ABG

Magnitude of A-a PO_2 gradient $\rightarrow$ affected by 3 processes:

- (1) V/Q mismatch
- (2) Shunting
- (3) Diffusion abnormality (rarely)

Variations in A-a PO_2 gradient:

- A-a PO_2 gradient is normally low (5-15 mmHg) $\rightarrow$ this is due to:
 - o (1) Gravity-related regional variations in V/Q ratios (see above)
 - o (2) Small amounts of “physiological” shunting that occurs (Ie. drainage of bronchial and thebesian vessels into left heart)
- A-a PO_2 gradient becomes raised (> 15 mmHg) if (i) V/Q mismatch (Ie. lung disease), (ii) shunting or (iii) diffusion abnormality occurs

Important to note – A-a PO_2 gradient can be used as an index to quantify amount of V/Q mismatch, shunting, and/or diffusion abnormality is present!

Aside: Hypoxaemia

“Hypoxaemia” → presence of abnormally low PO_2 levels in arterial blood

There are five general mechanisms for hypoxaemia:

(1) Hypoventilation:

- There are several causes:
 - (a) CNS depression (Eg. Medication-induced)
 - (b) Chest wall factors (Eg. Trauma, deformity, obesity)
 - (c) Respiratory muscle paralysis
 - (d) ↑ resistance to breathing
- This results in ↓ PAO_2 (and PaO_2) and ↑ $PACO_2$ (and $PaCO_2$)
- Hypoxaemia can be corrected with ↑ FiO_2

Note:

- $PACO_2$ (and $PaCO_2$) is inversely proportional to alveolar ventilation (Ie. halving MV will double $PACO_2$ and $PaCO_2$)
- The “alveolar gas equation” shows that the ↓ in PAO_2 (and PaO_2) is slightly greater than the ↑ in $PACO_2$ (and $PaCO_2$)

(2) Diffusion:

- An immeasurably small difference in PO_2 exists between alveolar gas and end-capillary blood due to – (i) Incomplete diffusion of O_2 and also (ii) Shunting → this normal difference is exaggerated during:
 - (a) Exercise
 - (b) Abnormal thickening of the B-G barrier (Eg. interstitial lung disease)
 - (c) ↓ FiO_2
- This results in – (i) ↓ PaO_2 and (ii) ↑ A-a PO_2 gradient
- Hypoxaemia can be corrected with ↑ FiO_2

(3) Shunt (see above):

- Causes:
 - Physiological → Bronchial venous blood (drains bronchial circulation) and blood from Thebesian vessels (drains coronary venous blood)
 - Pathological → Congenital heart disease with R-to-L shunting (Eg. VSD, ASD, PDA) and pulmonary AV fistulas
- This results in – (i) ↓ PaO_2 , (ii) ↑ A-a PO_2 gradient, and (iii) $PaCO_2$ normal or ↓
- Hypoxaemia CANNOT be corrected with ↑ FiO_2 (cf. hypoventilation and diffusion impairment)

(4) V/Q mismatch (see above):

- Gravity-related regional variations in V/Q ratio produces a trivial ↓ PaO_2 , ↑ A-a PO_2 gradient and ↑ (or normal) $PaCO_2$ → this is exaggerated with pathology (Eg. atelectasis, PE, pneumonia, aspiration, bronchospasms, Etc.)
- Hypoxaemia can be corrected with ↑ FiO_2

(5) Low F_{iO_2} for the needs for the patient:

- F_{iO_2} may be insufficient to meet the metabolic demands of patient (Ie. ↑ demands due to recent surgery)
- Hypoxaemia is easily reversed by ↑ F_{iO_2}

Aside: Hypoxia

Tissue oxygenation → tissue O_2 balance is determined by:

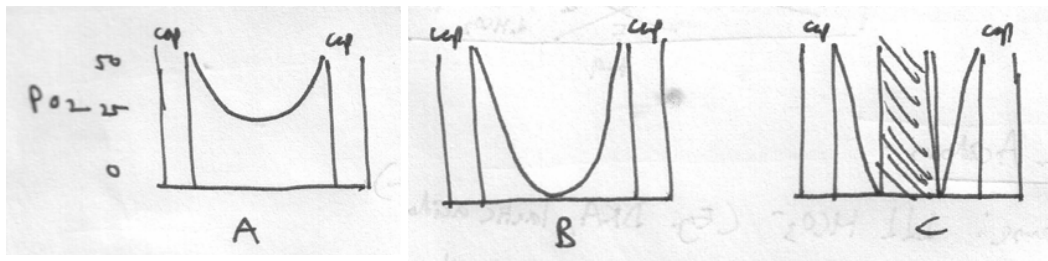
- (1) Tissue O_2 consumption → most drop in PO_2 in peripheral tissues occur immediately around the capillary walls such that PO_2 in tissues is uniformly LOW at ~ 3 mmHg (“Pasteur point”)

Important to note

- O_2 is a substrate for cytochrome oxidase (enzyme at end of ETC) → produces ATP (energy) from [O] phosphorylation of metabolic substrates in mitochondria
- Critically low level of cellular $PO_2 \sim 3$ mmHg (Pasteur point) can exist due to the very $\uparrow$ O_2 affinity by cytochrome oxidase
- [O] phosphorylation ceases (and anaerobic glycolysis proceeds) only when cellular $PO_2 < 3$ mmHg

- (2) O_2 delivery → high capillary blood PO_2 facilitates O_2 diffusion to mitochondria where PO_2 is very low

Schematic of PO_2 fall between capillaries:



* Fig A – O_2 delivery $>$ O_2 consumption → so tissue PO_2 is always adequate

* Fig B – PO_2 at one point of the tissue reaches ZERO (“critical situation”) due to either $\downarrow$ O_2 delivery or $\uparrow$ O_2 consumption

* Fig C – Further to “B”, anoxic regions exist and lactic acid is produced as a consequence of a shift from aerobic to anaerobic glycolysis

Tissue hypoxia → presence of abnormally low tissue PO_2 which compromises tissue function

There are 4 causes of tissue hypoxia:

- (1) Hypoxic hypoxia – $\downarrow$ PaO_2 (Eg. lung disease) causes $\downarrow$ CaO_2 → $\downarrow$ tissue O_2 delivery
- (2) Anaemic hypoxia – $\downarrow$ O_2 carrying capacity of blood (Eg. anaemia, CO poisoning) causes $\downarrow$ CaO_2 → $\downarrow$ tissue O_2 delivery
- (3) Circulatory hypoxia – $\downarrow$ tissue blood flow (Eg. shock) causes $\downarrow$ tissue O_2 delivery
- (4) Histotoxic hypoxia – Impaired tissue O_2 utilisation (Eg. cyanide poisoning of cytochrome oxidase in ETC)

Important to note – All causes of hypoxia is associated with $\downarrow$ tissue PO_2 EXCEPT “histotoxic hypoxia” where tissue PO_2 is normal or $\uparrow$

All causes of hypoxia can be managed with supplemental O_2 EXCEPT “histotoxic hypoxia”