STRUCTURE AND FUNCTION

- prime function is exchange of O_2 and CO_2
- other functions,
    a. blood reservoir
    b. heat exchange
    c. metabolism - synthesis & catabolism
    d. immunological and mechanical defence

- blood/gas barrier to diffusion ~ 50-80 m^2
- alveolar walls have two sides,
    a. active side → ~ 0.4 μm
    b. service side → ~ 1-2 μm

- (Nunn) ~ 200-600 million alveoli, depending upon height and size
- each alveolus ~ 0.2 mm in diameter at FRC, and is actually ***polyhedral*** not spherical
- blood/gas interface established by ventilation of airways and perfusion

- ***Cell Types in the Respiratory Tract***

a.	Capillary endothelium	- form ***calveoli*** ~ 0.1 um thick by 126 m^2
b.	Alveolar type I cells	- also 0.1 μm thick - have 1 nm gap junctions - impermeable to albumin - allow extravasation of mϕ's - unable to divide - highly sensitive to hyperoxia
c.	Alveolar type II cells	- rounded cells at septal junctions - produce surfactant - resistant to hyperoxia
d.	Alveolar type III cells	? function = "brush" cells
e.	Alveolar macrophages	- (mϕ) present in alveoli & airways - normal defence & scavenging
f.	PMN's	- not usually present - seen in smokers & 2° to NCF
g.	Mast Cells	
h.	Non-ciliated bronchial epithelial, "Clara", cells	
i.	APUD cells	

AIRWAYS AND FLOW

Main Airway Branches & Zones	
trachea R+L main bronchi lobar bronchi segmental bronchi bronchioles terminal bronchioles	• conducting zone • generations 1-16
respiratory bronchioles alveolar ducts atria alveolar sacs	• respiratory zone + primary lobule / or acinus • generations 17-23

• CZ doesn't contribute to gas exchange → ***anatomical dead space***
• RZ (including transitional zone) → most of lung volume ~ 3000 ml
• air flow → terminal bronchioles by ***bulk flow***
• then due to large increase in X-sectional area, flow v decreases and movement is by ***diffusion***
• within an acinus distances are short, ≤ 5 mm, and diffusion is rapid, ≤ 1 sec
• alveolar stability is maintained by ***surfactant***
• air velocity decreases at ***terminal bronchioles***, these are often a site of collection of foreign matter
• a normal tidal breath of ~ 500 ml requires $\delta P \sim 3$ cmH_2O due to high the compliance of lung tissue and low resistance to gas flow,

gas flow 1.0 l/s → $\delta P \sim 2$ cmH_2O

• this equates to a compliance, **C ~ 180 ml/cmH_2O**

BLOOD VESSELS AND FLOW

• initially arteries, veins and bronchi run together
• toward the periphery, veins → outside of primary lobules
bronchi & arteries → center

• capillaries ~ 7 μm diameter and are short → large surface area (SA)
• the pulmonary bed receives the entire CO, excluding true shunt flow
• the mean pulmonary arterial pressure ~ 15 mmHg
• RBC's traverse the capillary bed in ~ 0.75 sec and traverse ~ 3 alveoli
• the bronchial circulation supplies down to the terminal bronchioles but only a small fraction of this blood supply drains → pulmonary veins

LUNG VOLUMES

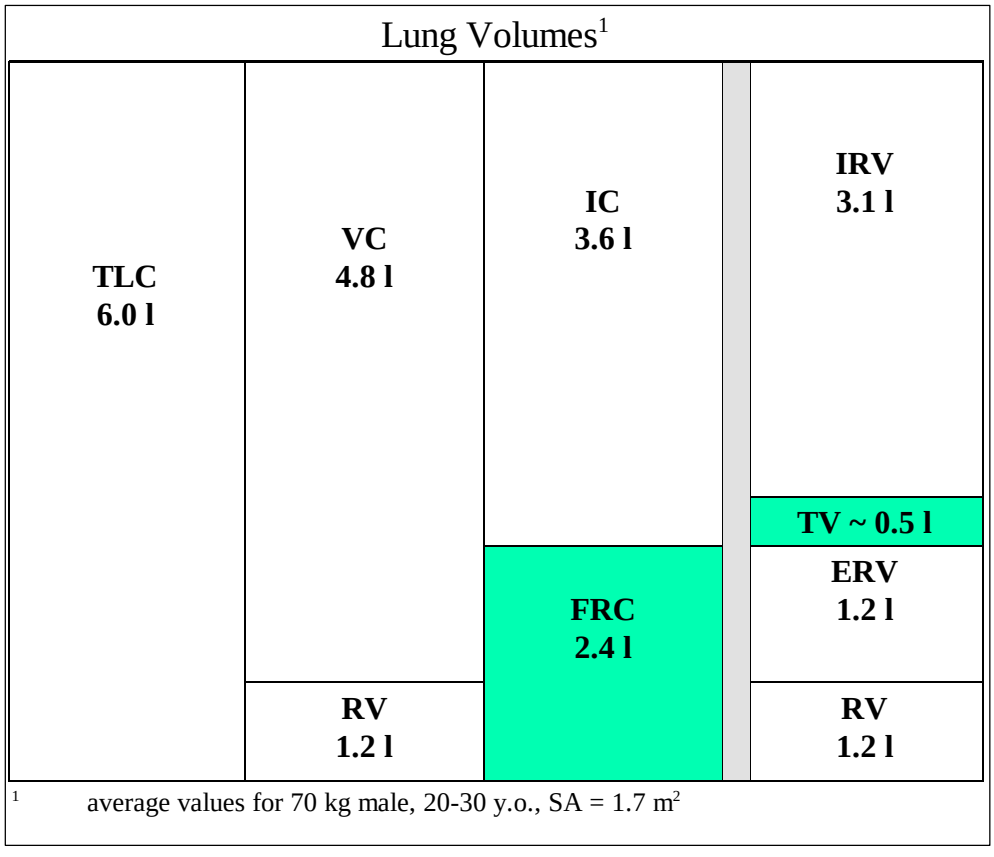
a. **primary lung volumes**

i.	RV	Residual Volume
ii.	ERV	Expiratory Reserve Volume
iii.	TV	Tidal Volume
iv.	IRV	Inspiratory Reserve Volume

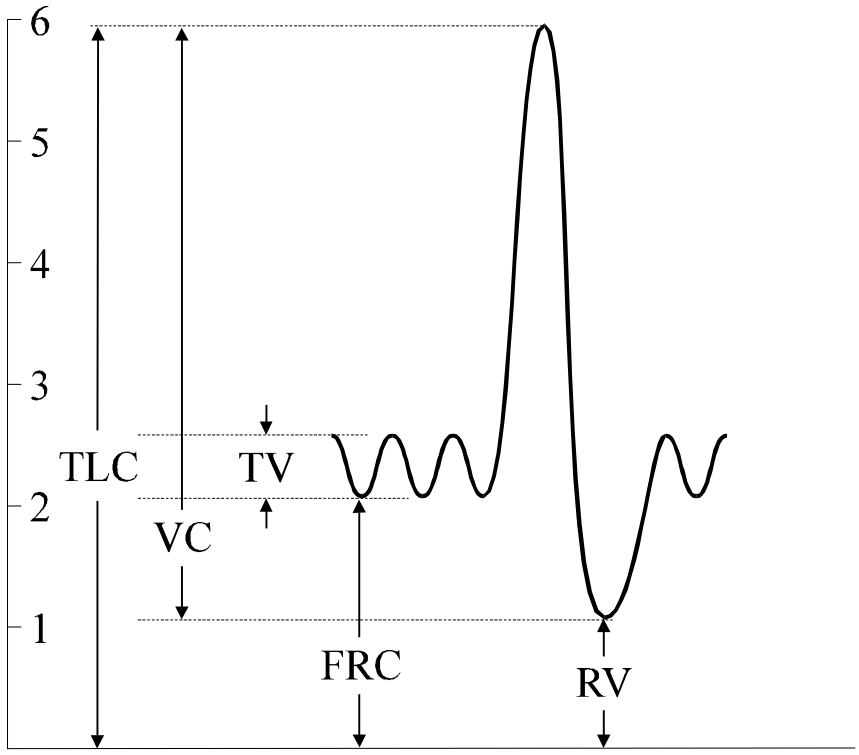
b. **secondary derived capacities**

i.	TLC	Total Lung Capacity
ii.	VC	Vital Capacity
iii.	IC	Inspiratory Capacity
iv.	FRC	Functional Residual Capacity

Def'n: ***volume*** refers to one of the 4 primary, ***non-overlapping*** subdivisions of TLC, each ***capacity*** includes two or more of the primary lung volumes



Measurement of FRC and RV



NB: these volumes ***cannot*** be measured by ***spirometry***,
as they contain gas which cannot be expelled from the lungs

- ***Functional Residual Capacity***

Def'n: the volume of gas left in the lungs at the end of normal tidal expiration

• FRC is the lung volume in which gas exchange is taking place
• small fluctuations of alveolar and arterial gas tensions occur with each tidal breath as fresh gas mixes with alveolar air

• FRC therefore acts as a ***buffer***,

1. maintaining relatively constant A & a ***gas tensions*** with each breath
2. preventing rapid changes in alveolar gas with changes in ventilation or inspired gas, eg. during induction or recovery from anaesthesia
3. increasing the average lung volume during quiet breathing,
reducing ***work*** of breathing due to shape of compliance curve

• methods of measurement,

1. closed circuit helium dilution
2. closed circuit nitrogen washout
3. body plethysmograph

■ ***Closed Circuit Helium Dilution***

• rebreathing takes place from a spirometer of known volume (V_1) and helium concentration (C_1)
• as He is relatively ***insoluble*** in blood, it therefore equilibrates between the lung and spirometer
• volumes are calculated by ***conservation of mass***, ie. $C_1 \times V_1 = C_2 \times (V_1+V_2)$, depending upon the starting point,

i. from end ***tidal*** expiration → FRC
ii. from end ***forced*** expiration → RV

NB: in some types of pulmonary disease areas of lung are poorly, or unventilated, therefore will result in ***underestimation***
ie. only ***communicating*** volume is measured

■ ***Closed Circuit Nitrogen Dilution***

• using N_2 washout, the patient breaths 100% O_2
• if the alveolar N_2 = 80% and the volume of N_2 collected is 4.0 l, then the initial lung volume must have been 5.0 l
• relies upon N_2 being relatively insoluble and moving slowly from blood to alveolar air

■ ***Body Plethysmograph***

• includes both ***communicating*** and ***non-communicating*** thoracic gas volume
• the later includes both non-ventilated lung and extrapulmonary gas
• the subject, in an air-tight box, breathes through a mouthpiece which closes at end expiration and the subject inhales against closed airway

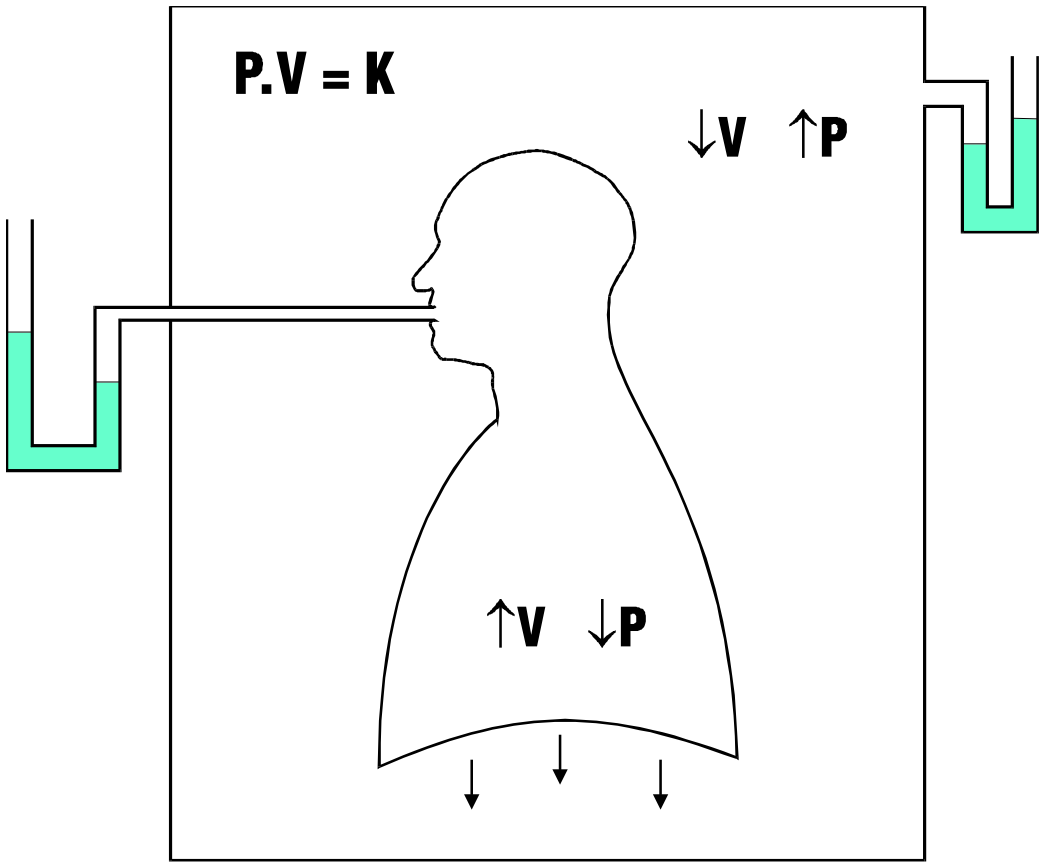
Using **Boyle's Law**: $PV = K$ at constant T

$P_{b1}.V_{b1} = P_{b2}.(V_{b1} - \delta V)$, where δV applies for the box & lung

$P_{L1}.V_{L1} = P_{L2}.(V_{L1} + \delta V)$, where V_{L1} = FRC

thus,

$$FRC = \frac{P_{L_2} \times \delta V}{\left(P_{L_1} - P_{L_2}\right)}$$



- an ***increase*** in FRC indicates lung hyperinflation and may be due to,
    1. loss of lung elastic recoil
    2. increased expiratory resistance to breathing
    3. PEEP

- FRC and RV usually increase together
- an increase in RV, without an increase in TLC leads to a reduced VC
- the normal ratio **RV/TLC ~ 15-30%** (1.2/6.0 l)
- hyperinflation, in itself, does not produce pulmonary disability
- alterations of V/Q are far more important clinically
- disadvantages of a high FRC,
    1. ↓ rate of alteration of alveolar gas composition - eg. anaesthetic induction
    2. mechanical disadvantage for respiratory muscles,
       limits ability to increase ventilation on demand
    3. ↑ dead space
    4. ↑ mean intrathoracic pressure & ↓ venous return

- ***Factors Affecting FRC***

1. **body size** - FRC ∝ height (~ 32-51 ml/inch)
2. **sex** - females ~ 90% of male FRC (= height)
3. **age** - work by Nunn → no correlation!
   - others have shown small increase
4. **diaphragmatic muscle tone**
   - originally, FRC believed to = equilibrium for lung/chest wall system
   - diaphragmatic tone maintains FRC ~ 400 ml above true relaxed state
     → ↓ FRC with ***anaesthesia***
5. **posture** - ↓ FRC in the supine position ~ 0.5-1.0 l
6. **lung disease**
   i. loss of lung ER with emphysema → ↑ FRC
   ii. increased expiratory resistance with asthma & external apparatus
   → ↑ FRC
7. **chest wall** - increased abdominal contents → ↓ FRC
8. **alveolar-ambient pressure gradient** * PEEP increases the FRC

- ***Residual Volume***

Def'n: the volume of gas in the lung at the end of maximal expiration

- determined by the balance of expiratory muscle activity and the resistance to volume decrease by the lungs and chest wall

Vital Capacity

Def'n: the maximum volume that can be exhaled following a maximal inspiration

VC = IRV + TV + ERV

- VC and its components are measured by ***spirometry***, either bell (Benedict-Roth), or wedge
- variations in VC occur with,

1. height, weight and surface area - VC roughly proportional to ***height***
2. age - ↓ VC with increasing age
3. sex - M > F
4. posture - less when supine, cf. sitting or standing

- ***Reductions of Vital Capacity***

1. **Pulmonary**
   - reductions in the distensibility of lung tissue
   - reductions in the absolute volume of lung, (obstruction, atelectasis, pneumonia)

2. **Non-pulmonary**
   - these may be due to limitation of,

   i. respiratory movements - neuromuscular
   ii. thoracic expansion - musculoskeletal, position
   iii. diaphragmatic descent - pregnancy, obesity, ascites, etc.
   iv. expansion of lung - occupying intrathoracic space

- a reduction in VC occurs in many diseases, however by itself doesn't signify pulmonary disease, eg. VC may be normal in emphysema
- normal values,

1. **IC ~ 75% of VC** (= TV + IRV)
2. **ERV ~ 25% of VC**

VENTILATION

Def'n: minute volume = V_T × respiratory frequency
~ 500 ml × 15 bpm
~ 7500 ml/min

the actual volume of gas entering the lung is greater due to effects of ***R***

Alveolar Ventilation

Def'n: volume of fresh gas entering the alveoli per breath,

alveolar ventilation, $V_A = V_T - V_D^{Anat}$

this is better defined as the volume of fresh gas entering the alveoli and effective in arterialising mixed venous blood, ie.,

$V_A = V_T - V_D^{Phys}$ so,

$\mathbf{V_T = V_A + V_D^{Phys}}$ where V_A ***does not*** = alveolar volume

- measurements should be made on the ***expired volume*** due to the effects of R, therefore,

$$V_A = V_E - V_D^{Phys}$$

- ***Alveolar Gas Tensions***

  i. P_{aO2} ~ 101 mmHg
  ii. P_{aCO2} ~ 40 mmHg

• assuming $P_{ICO2} = 0$, and since there is no gas exchange in V_D^{Phys}, then

$V_{CO2} = V_A \times F_{ACO2}$, where $F_{ACO2} = \%CO_2 / 100$ ml

• at end-tidal gas approximates alveolar gas, then,

$V_A = V_{CO2} / F_{E'CO2}$, gaining $F_{E'CO2}$ from an IR analyser

• as P_{CO2} is directly proportional to F_{CO2}, so

$$P_{aCO_2} \propto \frac{\dot{V}_{CO_2}}{V_A}$$

NB: in normal subjects alveolar and arterial P_{CO2} are virtually equal

Anatomical Dead Space V_D^{Anat}

Def'n: the volume of the ***conducting airways*** in which no gas exchange takes place, or

that part of the inspired volume which is expired ***unchanged*** at the beginning of expiration, or

"the volume of gas exhaled before CO_2 reaches the alveolar plateau - according to Fowler (1948)" (Nunn - now the commonly used definition)

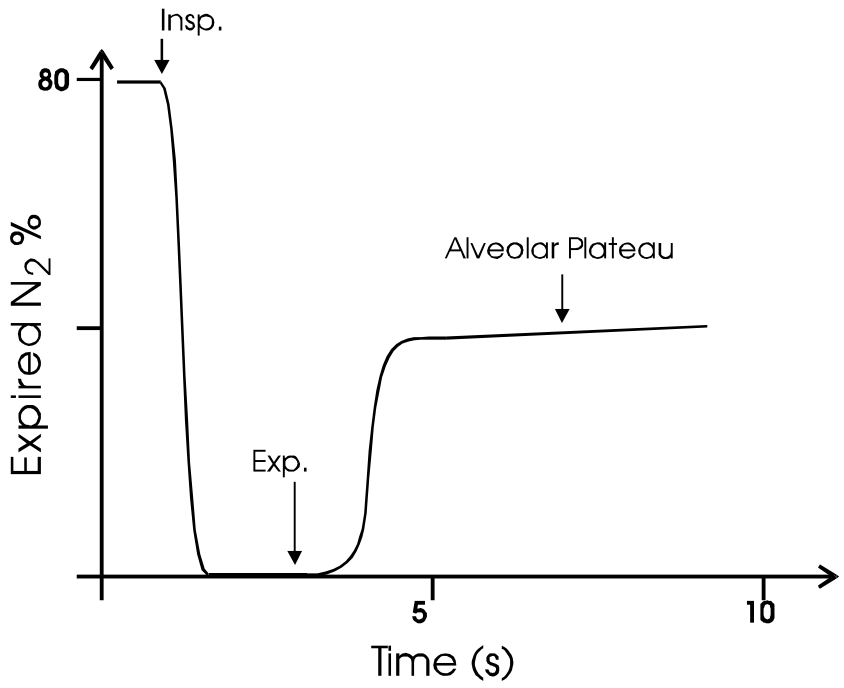
• also termed the ***series dead space*** and is equal to the boundary between convective gas transport and diffusion

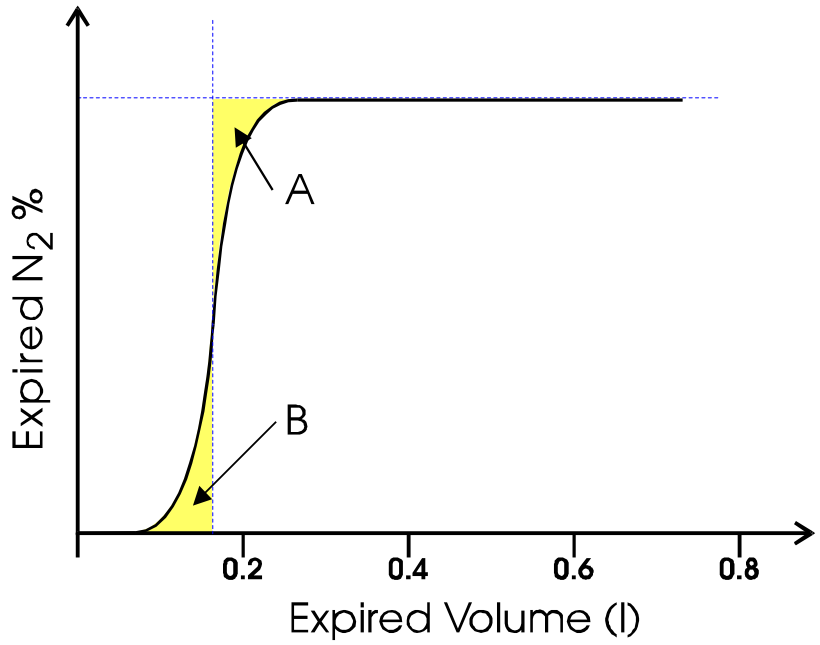
• the two commonly used methods of measurement are,

1. Fowler's method - tracer washout
2. Bohr's method - conservation of mass

- ***Fowler's Method***

• single breath analysis using an ***indicator gas*** (**N_2**,CO_2, O_2, He) to mark the transition between dead space and alveolar gas
• following inspiration of 100% O_2, a plot of V_{EXP} vs. %[N_2] → ***wash-in phase***
• the mid-point of the wash-in (where area A = area B below) measures the transition from conducting airways to the transition from dead space to alveolar gas
• in patients with non-uniform distribution of ventilation, ie. regions of the lung with different ***time constants***, a slow "wash-in" is seen and the method is inaccurate





- ***Bohr's Method***

NB: based on fact that V_D doesn't contribute to expired CO_2, therefore by the ***conservation of mass*** principle

$$V_T \cdot F_{ECO2} = V_A \cdot F_{ACO2}$$

and as $V_A = V_T - V_D$

by sub'n $V_T \cdot F_{ECO2} = (V_T - V_D) \cdot F_{ACO2}$

$$V_T \cdot F_{ECO2} = V_T \cdot F_{ACO2} - V_D \cdot F_{ACO2}$$

so, dividing by V_T $F_{ECO2} = F_{ACO2} - (V_D / V_T) \cdot F_{ACO2}$

giving,

$$\frac{V_D}{V_T} = \frac{F_{ACO_2} - F_{\bar{E}CO_2}}{F_{ACO_2}}$$

Bohr Equation (1891)

• originally used to measure F_{aCO2}, using estimates of V_D^{Anat} from autopsy cast specimens
• not used to estimate V_D^{Anat} until the ***constancy of alveolar air*** was established by Haldane and Priestly (1905)

1. F_{aCO2} is estimated from $ETCO_2$ with a rapid gas analyser
2. the mean expired concentration from a Douglas bag

• as for the above, patients with a non-uniform distribution of ventilation, ie. regions of the lung with different ***time constants***, a horizontal plateau is not seen and F_{aCO2} and mean alveolar CO_2 cannot be estimated

- ***Factors Affecting Anatomical Dead Space***

1. ***Body Size*** - ↑ V_D^{Anat} with increasing body size
   - in ml ~ lean body weight in lb, or ~ 2.2 ml/kg
2. ***Age*** - ↑ V_D^{Anat} with increasing age (?V_D/V_T)
3. ***Lung Volume*** - ↑ V_D^{Anat} with increasing volume
   ~ 20 ml/l increase in lung volume from FRC
4. ***Posture*** - ↓ V_D^{Anat} with supine posture → supine ~ 101 ml
   sitting ~ 147 ml (Fowler)
5. ***Respiratory Flow Pattern***
   - decreased, using Fowler technique, with low V_T due to the mixing affect of the heart beat below the carina, and the cone advance of laminar flow, seen at low flow velocities
6. ***Hypoxia***[§] - bronchoconstriction → ↓ V_D^{Anat}
7. ***Drugs and Anaesthetic Gases***[§] - bronchodilatation → ↑ V_D^{Anat}
8. ***Lung Disease*** - emphysema → ↑ V_D^{Anat}
   - loss or excision of lung → ↓ V_D^{Anat}
9. ***Endotracheal Intubation*** - ↓ V_D^{Anat} ~ 50%
   - but there is the additional volume of the circuit
10. ***Position of the Jaw & Neck*** - increases with jaw protrusion in non-intubated subjects

NB: [§]minimal effects

Alveolar Dead Space V_D^{Alv}

Def'n: that part of the inspired gas which passes through the anatomical dead space and enters alveoli, however is ***ineffective*** in arterialising mixed venous blood

also termed ***parallel dead space***

- does not represent the actual volume of these alveoli
- the cause is failure of adequate perfusion of the alveoli to which gas is distributed,

a. alveoli with ***no perfusion*** → V/Q infinite

b. alveoli with ***reduced perfusion*** → V/Q > 0.8

- the separation of alveoli into these two groups = ***Riley analysis***
- normally is minimal in healthy subjects but increases with disease

▪ *Factors Affecting Alveolar Dead Space*

1. ***Age*** - ↑ V_D^{Alv} with increasing age
2. ***Pulmonary Arterial Pressure***
   - a decrease in PA pressure (eg. hypotension) decreases perfusion to the upper parts of the lung → ↑ zone 1 & ↑ V_D^{Alv}
3. ***Posture***
   - V_D^{Alv} increases in the upright and lateral positions due to exaggeration of hydrostatic differences → ↑ zone 1
   - this is theoretical, no data is available (Nunn)
4. ***IPPV***
   - increases V_D^{Alv} due to exaggeration of hydrostatic failure of perfusion
   - also decreases total pulmonary blood flow
   - applied wave-form IPPV with short inspiration (t < 0.5 s), → increases V_D^{Alv} due to maldistribution of ventilation
5. ***Tidal Volume*** - as V_T increases, so V_D^{Alv} increases but the ratio remains constant
6. ***Oxygen*** - hyperoxic vasodilatation → ↑ V_D^{Alv}
   - hypoxic vasoconstriction → ↓ V_D^{Alv}
7. ***Anaesthetic Gases*** - ↑ V_D^{Alv} but not known why!
   - ↑ subcarinal V_D ~ 70 ml
8. ***Lung Disease*** - ↑ V_D^{Alv} increased in multitude of diseases
   i. ARDS → microemboli & ventilation of non-vascular air spaces
   ii. IPPV & lateral posture → gross V/Q mismatch

- ***Measurement of Alveolar Dead Space***

NB: estimated from the arterial - end tidal P_{CO2} difference

• gas from ***non-perfused alveoli*** will contain some CO_2, since these receive mixed alveolar gas from anatomical dead space prior to fresh gas
• gas from ***poorly perfused alveoli*** will contain more CO_2 than from non-perfused alveoli but the P_{CO2} will be less than the mixed alveolar P_{CO2} as represented by the arterial P_{aCO2}

** hence the end-tidal alveolar gas will have a ***lower*** P_{CO2} than the P_{aCO2}

• this is used in a modification of the Bohr equation to calculate the ratio of V_D^{Alv}/V_T
• here the equation becomes $(P_{aCO2} - P_{E'CO2}) / P_{aCO2}$
• where $P_{E'CO2}$ is the ***end-tidal*** $\mathbf{CO_2}$

$$\frac{V_D^{Alv}}{V_T} = \frac{P_{aCO_2} - P_{E'CO_2}}{P_{aCO_2}}$$

• this is as compared with Bohr's original equation, viz.

$$\frac{V_D}{V_T} = \frac{F_{ACO_2} - F_{\bar{E}CO_2}}{F_{ACO_2}}$$

Bohr Equation (1891)

Physiological Dead Space

Def'n: V_D^{Phys} = Total Dead Space
= $V_D^{Alv} + V_D^{Anat}$

or, that part of the tidal volume which does not participate in gas exchange and is ineffective in arterialising mixed venous blood, because either,

1. it doesn't reach the alveoli - V_D^{Anat}
2. it reaches alveoli with no capillary flow, or
3. it reaches alveoli with inadequate flow - V_D^{Alv}

- in normal supine man, $V_D^{Alv} \sim 0$, therefore,

$$\mathbf{V_D^{Phys} \sim V_D^{Anat} \sim 150\ ml}$$

Measurement of Physiological Dead Space

- using the Bohr Equation to measure V_D, the value for ***alveolar*** $\mathbf{CO_2}$ is taken as the $ETCO_2$
- if "ideal" alveolar P_{CO2} is taken as arterial P_{aCO2}, then the equation yields physiological dead space,

$$V_D^{Anat}/V_T = (F_{ACO2} - F_{ECO2}) / F_{ACO2}$$ the ***Bohr Equation***

- but since P_X and F_X are proportional, then

$$V_D/V_T = (P_{ACO2} - P_{ECO2}) / P_{ACO2}$$ where P_A is end-expired

- substituting P_{aCO2} as the ***ideal alveolar*** value,

$$\frac{V_D^{Phys}}{V_T} = \frac{P_{aCO_2} - P_{\bar{E}CO_2}}{P_{aCO_2}}$$

Enghoff Modification (1938)

*** normally = 0.2 to 0.35**

- this ratio is more useful as it tends to remain constant, c.f. the actual value for V_D^{Phys} which may vary widely with changing tidal volumes
- expired gas is collected in a Douglas bag and the difficulty is getting only expired gas
- due to difficulties in the measurement of this, clinically the relationship between P_{aCO2} and ventilation is used, ie.

$$P_{aCO2} \propto V_{CO2} / V_A$$

DIFFUSION

Def'n: the constant random ***thermal motion*** of molecules, in gaseous or liquid phases, which leads to the ***net transfer*** molecules from a region of higher concentration to a region of lower concentration (thermodynamic activity)

Fick's Law

Def'n: the ***rate of transfer*** of a gas through a sheet of tissue is,

a. proportional to the ***area*** available for transfer

b. proportional to the gas ***tension difference***

c. inversely proportional to the tissue ***thickness***

$$\dot{\mathbf{V}}_{gas} = \frac{A.D}{T} \times (P_{gas_1} - P_{gas_2})$$

NB: where D = the diffusion constant

Determinants of Gas Diffusion

1. Characteristics of the Gas
2. Pressure Gradient
3. Membrane Characteristics

- ***Characteristics of the Gas***

a. **Molecular Weight** $V \propto 1/\sqrt{MW}$

Graham's Law: relative rates of diffusion are inversely proportional to the square root of the gas molecular weight

- thus, lighter gases diffuse faster in gaseous media than heavier gases
- lighter molecules for given energy have faster velocities
- therefore, O_2 diffuses more rapidly than CO_2 in the gas phase (1.17 : 1)
- in health, diffusion distances in the alveoli are small (< 100 μm), however where distances are increased, regional differences in P_{O2} can occur
- this is only of importance in the gaseous pathway from ambient air to blood

b. **Solubility Coefficient**

Henry's Law: the amount of a gas which dissolves in unit volume of a liquid, at a given temperature, is directly proportional to the ***partial pressure*** of the gas in the equilibrium phase

- relative solubilities of CO_2 & O_2 in water ~ **24:1**
- combining this with Graham's Law from above, the relative rates of diffusion
- from alveolus to rbc for **CO_2:O_2 ~ 20.7 : 1**
- therefore, diffusion of CO_2 is rarely, if ever, a clinical problem
- solubility determines the limitation to the rate of diffusion, gases being either

i. ***diffusion limited***, as for CO, which due to its high solubility in blood does not reach equilibrium during the passage of blood through the alveoli

ii. ***perfusion limited***, as for N_2O, which due to its very low solubility reaches pressure equilibrium very early with perfusing blood

■ ***Transmembrane Pressure Gradient***

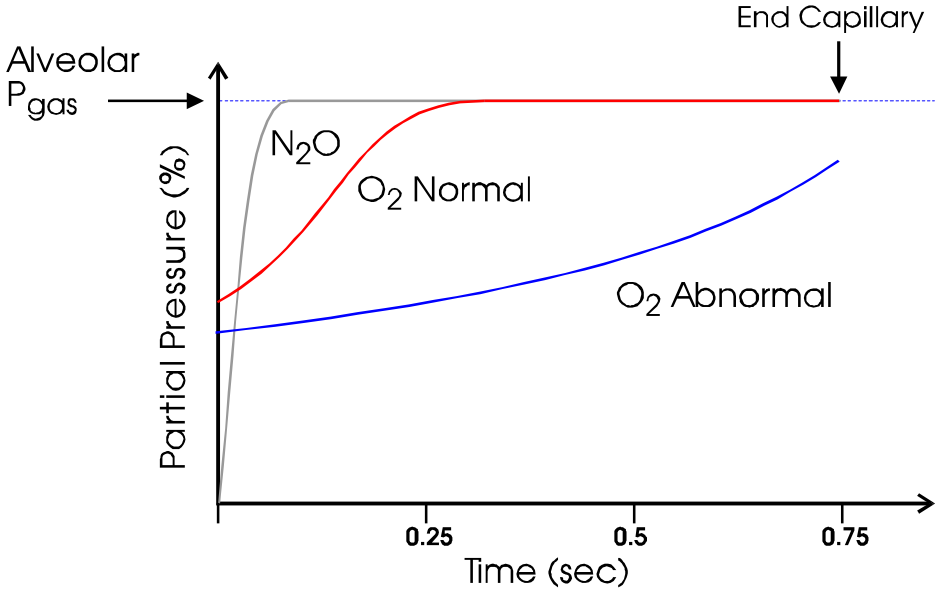
• the rate of O_2 diffusion is dependent on the integrated mean P_{O2} difference between alveoli and pulmonary capillary blood, therefore depends upon,

1. the F_IO_2
2. alveolar ventilation
3. pulmonary capillary blood flow
4. oxygenation of Hb

• Hb acts as a "sink" for O_2, limiting the rise in P_{aO2}
• oxygenation of Hb represents the likely rate limiting factor in O_2 transfer at a P_{aO2} of 101 mmHg,

a. equilibrium is reached in ~ 0.3 s

b. transit time for a rbc ~ 0.75 s



• with either a lower P_{aO2}, or an impairment of diffusion (alveolar-capillary block) equilibrium may not be reached
• this will be exacerbated by conditions of increased CO, where the transit time is reduced
• the diffusion path is composed of a number of segments,

a. at FRC, alveolar diameter ~ 200 μm → diffusion ~ 10 ms
b. alveolar + capillary membrane on "active side" ~ 0.5 μm
c. pulmonary capillaries ~ 7 μm (~ rbc)
d. oxygenation of Hb

• therefore, the diffusion path within the ***RBC*** is greater than across the lung
• the oxygenation of Hb is sufficiently slow to be the rate limiting step

Diffusing Capacity (DC)

Def'n: the rate of gas transfer / partial pressure difference for the gas

$$\rightarrow \quad \delta Q / \delta P_{GAS}$$

• the term is comparable with electrical ***conductance***
• for oxygen this becomes,

$$DC_{O2} = MRO_2 / (P_{cO2} - P_{aO2})$$

• as it is impossible to measure the mean P_{cO2}, an approximation is the ***Bohr integration*** procedure, by assuming,

a. the end $P_{cO2} - P_{aO2}$ difference
b. the rate of transfer of gas $\propto \delta PO_2$ along the capillary

→ mean value by integration

• however, this has been shown to be false, as assumption (b) doesn't hold true
• ie. the rate of uptake of O_2 by Hb is a ***non-linear*** function of the δPO_2, depending upon the state of oxygenation of Hb
• factors which will ***reduce*** the diffusing capacity are,

a. decreased capillary transit time $\propto$ ↑ CO
b. decreased capillary blood volume
c. pulmonary congestion
d. alveolar capillary block

NB: V/Q mismatch is indistinguishable from decreased diffusing capacity

Diffusing Capacity for Carbon Monoxide

• this is used as a substitute for oxygen, due to the intractable difficulties in measuring DC_{O2}
• it is convenient as the diffusion barrier is the same but the affinity of Hb for CO is so high that the mean P_{cCO} can be ignored, and the equation simplifies to,

$$DC_{CO} = \text{CO uptake / alveolar } P_{CO}$$

• the differences in the solubility and vapour densities of the two gases are such that the diffusion rate, to the point of entry into the RBC, for O_2 is ~ 1.23 times that of CO
• although the affinity of CO for Hb is ~ 250 times that of O_2, the reaction rate is in fact slower, and is affected by the F_IO_2
• thus, by altering the F_IO_2, the different components of diffusion resistance to CO can be studied (solving simultaneous equations for below)

• the second component, within the RBC, is not really a matter of diffusion but a product of the pulmonary capillary blood volume (Vc) and the reaction rate with Hb (rate = θ)
• thus, the total diffusing capacity, analogous to ***conductance***, is given by,

$$1/DC_L = 1/DC_M + 1/(Vc.\theta)$$

• and, under similar conditions $\rightarrow$ $\mathbf{DC_{MO2} \sim 1.2 \times DC_{MCO}}$

• methods for the measurement of DC_{CO} include,

1. ***steady state***
   - subject breaths 0.3% CO for 1 minute
   - alveolar P_{CO} is calculated from modified alveolar air equation
   - uptake is from inspired & expired F_{CO} by IR analysis
2. ***single breath***
   - VC breath of (0.3% CO + 10% He) held for 10 s
   - no He enters blood, thus ratio F_I/F_E gives concentration of CO and the alveolar P_{CO} from the F_{ECO}
3. ***rebreathing***
   - same mixture as (b) rebreathed from reservoir

BLOOD-FLOW AND METABOLISM

• mixed venous blood from RV →

i. main pulmonary artery (PA)
ii. branches of PA with bronchi/bronchioles
iii. central acinar arterioles
iv. pulmonary capillaries
v. small peripheral acinar pulmonary veins
vi. pulmonary vv. with bronchi/bronchioles
vii. 4 main pulmonary vv. to left atrium (LA)

▪ *Comparison with Systemic Circuit*

• mean PA pressure ~ 15 mmHg, (25/8 mmHg)
• flow is therefore more ***pulsatile*** than in the systemic circuit → S:D ratio of 3:1 vs. 3:2
• vessel walls are much thinner with less muscle, ~ 30% c.f. systemic vessels
• the circuit is required to accept the entire CO at any given moment and not concerned with diverting blood flow, except in ***hypoxia***
• therefore, PA pressure is consistent with lifting blood to the apex only
• the lower pressure thereby reducing RV workload
• the resistance drop around pulmonary circuit is relatively constant, c.f. the stepwise reduction in the systemic circuit
• approximately one half of the resistance is in the microcirculation
• the pulmonary capillary pressures are hydrostatically dependent → ***zones 1-4***
• pericapillary pressure closely approximates alveolar pressure but is slightly less (Nunn ~ Atm-10mmHg)

▪ *Factors Affecting Extra-Alveolar Vessels*

• the arterial and venous transmural pressures may be significantly reduced by the radial traction of lung parenchyma on vessel walls, thus reducing perivascular pressure
• pressures may fall below the intrapleural pressure → E-A vessel diameters ↑ with inspiration
• vascular resistance = δP / Flow
~ (15-5 mmHg)/5.0 l/min
~ 2.0 mmHg/l/min c.f. systemic = 21.5
~ 160 dyne.sec.cm^{-5}

• however, not all vessels are open at resting CO, increases in flow →

a. recruitment
b. distension

NB: both of which decrease R_V

• smooth muscle tone largely determines vessel calibre, therefore,

Factors Affecting Vessel Calibre	
Contraction and ***increase*** R_V	Dilatation and ***decrease*** R_V
• noradrenaline	• isoproterenol
• adrenaline (α)	• aminophylline
• dopamine (α)	• ganglion blockers
• $PGF_{2\alpha}$ • thromboxane A_2	• PGE_1 • PGI_2
• histamine (H_1)	• histamine (H_2)
• serotonin	• acetylcholine
• angiotensin II	• bradykinin

• there is a plentiful supply of SNS vasoconstrictor nerves via the ***cervical ganglia***
• these may decrease flow ~ 30%
• both α & β receptors supply smooth muscle of arteries and veins
• effects are seen predominantly in vessels > 30 µm diameter, but the effects are far less than those seen in the systemic side
• central increases in SNS tone do have significant effects on the pulmonary circulation
• the effects of alterations in PNS tone are less certain
• ***alveolar hypoxia*** causes ***vasoconstriction*** in a non-linear fashion,

a. resembles the shape of the HbO_2 dissociation curve
b. response curve has a "P_{50}" ~ 30 mmHg
c. mediator may be one of the cytochromes, ***metalloporphyrin***

• this phenomenon is important in ***cor pulmonale*** and ***sleep apnoea syndrome***

Measurement of Pulmonary Blood Flow (CO)

- ***Fick Principle***

Def'n: the rate of appearance, or disappearance, of any substance from any organ, is given by the A-V concentration difference multiplied by the blood flow,

O_2 consumed = A-V [O_2] difference × blood-flow

• therefore pulmonary blood-flow, or CO, is equal to the body MRO_2 divided by the arterial/mixed venous [O_2] difference:

$$\dot{Q} = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}$$

• where CvO_2 is taken from PA blood
• the patient rebreathes O_2 into a Benedict-Roth spirometer through a soda-lime absorber and the rate of O_2-uptake is determined from the slope of the tracing
• alternatively CO_2 excretion could be used

- ***Indicator Dilution***

• based on the ***conservation of mass*** principal
• using indocyanine green, or a radioactive isotope injected into an arm vein
• the indicator concentration in serial arterial samples is used to derive the average $[I]_{art.}$ after one circulation through heart, where

$$CO = \frac{Mass\ Injected}{\int^{t_1} [I]_a . \delta t}$$

- ***Thermodilution***

• same as (b) but cold saline is injected into RA and the δT measured in the PA using a thermistor on flow-directed catheter
• has the advantages of ***no recirculation*** and ability for ***repeated measurements***
• however, requires multiple correction factors for heat gain in catheter and speed of injection

- ***Body Plethysmograph***

• used to measure instantaneous pulmonary blood flow by measuring **N_2O *uptake***
• a gas mixture of 21%-O_2 + 79%-N_2O breathed from a rubber bag inside a plethysmograph
• N_2O is highly soluble (~ 34x N_2) & is taken-up in series of steps coinciding with the heart rate
• as N_2O uptake is ***flow limited***, instantaneous flow can be calculated

NB: all except the later measure total pulmonary ***blood flow*** (including shunt), whereas plethysmography → pulmonary ***capillary flow***

- ***Radioactive Perfusion Scan***

• using ^{133}Xe and a scintillation gamma camera to determine ***regional differences***

Regional Differences

• perfusion in the normal upright lung varies from apex to base,

→ basal ~ 12-15x apical perfusion (West - vital capacity breaths)

• later work done by Nunn suggests that ***at FRC*** this difference in flow is only **~ 3x** (fig 7.4, p152)
• during ***exercise*** regional differences become ***less*** due to a greater part of the increase in flow being directed to the mid & upper zones
• ***lung volume*** is an important determinant of vessel resistance,

1. alveolar vessels - $\uparrow V_L$ stretches capillaries → $\uparrow R_V$
2. extra-alveolar vessels - $\uparrow V_L$ increases radial traction → $\downarrow R_V$

• the increased vessel resistance seen at low volumes for the E-A vessels affects the critical opening pressure
• for any flow to occur, P_a must be several $cmH_2O > P_v$
• regional perfusion variations with hydrostatic pressure give 3 hypothetical zones from apex to base,

1. Zone 1 $P_A > P_a > P_v$ No Flow
2. Zone 2 $P_a > P_A > P_v$ Flow $\propto P_a$-P_A gradient
3. Zone 3 $P_a > P_v > P_A$ Flow $\propto P_a$-P_v gradient

• zone 2 is unusual in that flow is determined by a-A pressure gradient c.f. the normal a-v gradient

→ Starling resistor or "waterfall effect"

• throughout ***zone 2***, P_a increases causing recruitment of additional vessels
• in ***zone 3*** the normal a-v gradient (relatively constant), determines flow and increases in flow down this zone are predominantly due to distension, as vessel pressure rises but P_A is constant
• at low V_L, resistance of basal E-A vessels increases due to loss of radial traction and flow again decreases → ***zone 4***
• although passive forces dominate vessel resistance, ***alveolar hypoxia*** causes marked vasoconstriction and regional blood-flow changes
• O_2 responses are absent at P_{aO2} > 100 mmHg and only become significant when P_{aO2} < 70 mmHg
• this effect minimises V/Q mismatch, reducing alveolar dead space
• high altitude → generalised constriction and ↑ RV workload

• this mechanism also functions in utero, where hypoxic pulmonary vasoconstriction (HPV) maintains the high PA pressure
• this diverts blood through the ductus arteriosus, with < 15% perfusing lung
• at birth, gasping markedly decreases PA resistance by radial traction and increased P_{aO2}
• decreased pH also → vasoconstriction and increased sensitivity to O_2

Water Balance

Starling's Law

$$\dot{Q} = k.[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

Def'n: **Q** = net fluid flow
s = the reflection coefficient of the capillary wall for plasma proteins, and
k = the filtration coefficient

NB: approximate values

P_c	~ 10 mmHg	
P_i	~ 10 mmHg	subatmospheric
π_c	~ 28 mmHg	
π_i	~ ??	but 20 mmHg in lung lymph

• the net effect is an ***outward*** pressure producing a lung lymph flow of **~ 20 ml/hr** in a resting adult male

→ perivascular + peribronchial lymphatics
then the hilar lymph nodes

• cf. total body lymph flow ~ 146 ml/hr, or 3.5 l/d
• early pulmonary oedema causes engorgement of perivascular lymphatics
• seen as Kerley B lines on CXR

VENTILATION - PERFUSION RELATIONSHIPS

• the V/Q ratio is the crucial factor in determining alveolar and, therefore, pulmonary capillary P_{O2} and P_{CO2},

NB: Alveolar P_{O2} is determined by the rate at which O_2 is supplied to the alveolus by ventilation, relative to its rate of removal by pulmonary capillary blood flow

Alveolar P_{CO2} is determined by the rate at which CO_2 is supplied to the alveolus by pulmonary capillary blood flow, relative to its rate of removal by ventilation

• PiO_2 of inspired air = 20.93% of $(P_{Atm} - P_{H2O})$
= 0.2093 . (760-47mmHg)
~ **149 mmHg**

• as gas exchange occurs the mean P_{aO2} falls to ~ 101 mmHg
• this varies only by 2-3 mmHg with each breath, FRC helping to maintain the constancy of alveolar air
• the P_{aCO2} of mean alveolar air is determined by CO_2 production and alveolar ventilation,

$$P_{aCO2} = K.(V_{CO2}/V_A) \qquad K = 0.863 \text{ BTPS}$$

• ratio of **CO_2** ***excretion*** to **O_2** ***uptake*** by the lung = the ***respiratory exchange ratio (R***),

$$R = \frac{F_{ECO_2}}{F_{IO_2}.\left(F_{EN_2}/F_{IN_2}\right) - F_{EO_2}}$$

NB: in health ***R ~ 0.8***

N_2 is unaffected by gas exchange and corrects for unequal volumes on inspiration and expiration

this equation assumes equilibrium of the ***inert gas*** species

Distribution of V/Q Ratios

- ***Physiological***

• in the "normal" upright lung, from apex to base (West),

1. ↑ ***ventilation*** ~ 3x
2. ↑ ***perfusion*** ~ 12x

• consequently, the V/Q ratio varies from a high value at apex to low value at the base
• as most of the blood flow, and a greater amount of ventilation goes to the bases, basal values are closer to overall ***mean ~ 0.8***

Regional Differences in Upright Lung (West)

	V_L %	V_A l/min	Q_L l/min	V/Q	P_{aO2} mmHg	P_{aCO2} mmHg	P_{N2} mmHg	R	pH
Apex	7 8 10	0.24 0.33 0.42	0.07 0.19 0.33	**3.3** 1.8 1.3	**132** 121 114	**28** 34 37	553 558 562	2.0 1.3 1.1	7.51
Mid.	11 12 13	0.52 0.59 0.67	0.50 0.66 0.83	1.0 0.9 0.8	108 102 98	39 40 41	566 571 574	0.92 0.95 0.78	
Base	13 13 13	0.72 0.78 0.82	0.98 1.15 1.29	0.73 0.68 **0.63**	95 92 **89**	41 42 **42**	577 579 582	0.73 0.68 0.65	7.39
Total	100	5.09	6	**0.85 mean**					
Mixed Alveolar					**101**	**39**	572		
Mixed Arterial					**97**	**40**	575		
PA-aO_2 Difference					**4**	**1**	3		

• therefore, in the normal lung, the effects of uneven V/Q ratios are insignificant as shown by the ***A-a differences***
• the efficiency of exchange is about 97-98% of the theoretical maximum
• these figures were measured with ***VC breaths*** from RV
• measurements taken by Nunn, with tidal breaths at FRC, showed far less variation from base to apex

- ***Pathological***

• diffuse pulmonary disease may result in a gross scatter of V/Q ratios
• this most commonly results in ***hypoxaemia***, CO_2 usually being compensated

1. regions with ***high V/Q*** ratios **R > 0.8**
   - ventilation in excess of perfusion contributes to ***alveolar dead space***
   - alveolar gas tensions approach those of inspired air,

     → alveolar O_2 increases and CO_2 decreases,
     as do the end pulmonary capillary pressures

2. regions with ***low V/Q*** ratios **R < 0.8**
   - ventilation below perfusion requirements, contributes to ***physiological shunt***
   - alveolar gas tensions approach those of mixed venous blood,

     → alveolar O_2 falls and CO_2 increases,
     as do the end pulmonary capillary pressures

- ***Effects on Arterial Blood***

1. **CO_2**
   - regions of high V/Q compensate for regions of low V/Q due to the almost ***linear*** slope of the CO_2-dissociation curve within the physiological range
   - therefore, the end capillary C_{CO2} differences parallel end capillary P_{CO2} differences
   - the decreased C_{CO2} from high V/Q regions compensating for the increased C_{CO2} from underventilated areas
   - further, if overall alveolar ventilation is normal, an elevation of P_{aCO2} leads to an increase in alveolar ventilation and a return to normal

2. **O_2**
   - this does not apply to O_2 transfer, due to the ***sigmoid*** shape of the HbO_2 dissociation curve
   - blood from regions of high V/Q will have increased P_{O2} but only a minimally increased C_{O2} due to the "flat" portion of the curve
   - however, blood from regions with low V/Q will have both a decreased P_{O2} and C_{O2} due to the "steep" fall of the curve in this region
   - therefore, mixed alveolar gas will be compensated by high and low P_{O2}'s but mixed end capillary blood will be disproportionately desaturated by the low C_{O2} from low V/Q regions

NB: this leads to an overall ***Alveolar-arterial P_{O2} gradient***

- ***Physiological Adjustments to Non-Uniform V/Q Ratios***

1. low V/Q regions
   - lead to a fall in P_{aO2}, which causes regional ***pulmonary vasoconstriction*** and diversion of blood to better ventilated regions of the lung
   - reduced regional perfusion therefore approaches reduced ventilation with a return of *R* toward normal
2. high V/Q regions
   - lead to a decrease in P_{aCO2}, which causes regional ***bronchoconstriction*** and diversion of ventilation to better perfused regions of the lung
   - reduced regional ventilation therefore approaches reduced perfusion with a return of *R* toward normal

- ***Measurement of Non-Uniformity of V/Q Ratios***

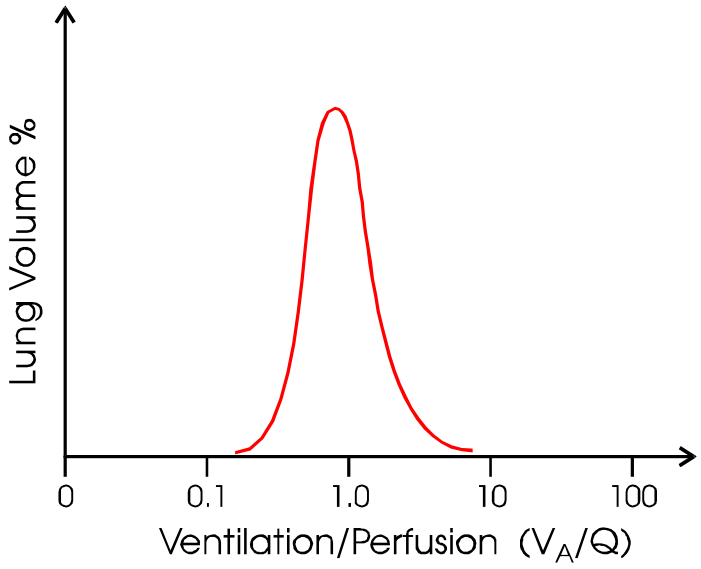
1. inhalation of ^{133}Xe
   - scintillation counters determine distribution of ventilation
   - subsequent breath-holding and uptake of ^{133}Xe indicates regional perfusion
   - comparison of these $\rightarrow$ V/Q
2. estimation of alveolar and physiological ***dead space***
   - using the Enghoff modification of the Bohr equation
3. estimation of ***venous admixture***
   - using the shunt equation (below) will indicate areas of low V/Q

Regional Variation in V/Q

- expressed in terms of the ***ventilation-perfusion ratio equation***:

$$\dot{V}/\dot{Q} = 0.863 \times R \times \frac{\left(C_{aO_2} - C_{\bar{v}O_2}\right)}{P_{aCO_2}}$$

- normally, when plotted against ***% lung volume*** the ratio varies from 0.5 to 5 and follows a log-normal distribution with a ***mean ~ 0.8*** (see below)
- gas exchange (air-flow / blood flow), occurs most efficiently at a value of V/Q slightly >1.0
- outside of range 0.4 to 4, exchange is severely impaired
- lung disease may widen the distribution, or scatter of V/Q ratios, without altering the mean
- alternatively, disease may skew the distribution left or right
- both of which impair gas exchange, increasing the $P_{A\text{-}aO2}$ gradient
- also conveniently shown on O_2-CO_2 plot(West 10.4)



VENOUS ADMIXTURE

Def'n: refers to the degree of admixture of ***mixed venous*** blood with arterialised ***pulmonary end capillary*** blood, which would be required to produce the observed pulmonary end-capillary to arterial P_{O2} difference

NB: where $P_{c'O2}$ is taken as the "ideal" alveolar P_{aO2}

venous admixture is therefore a ***calculated***, not an actual amount

Components of Venous Admixture

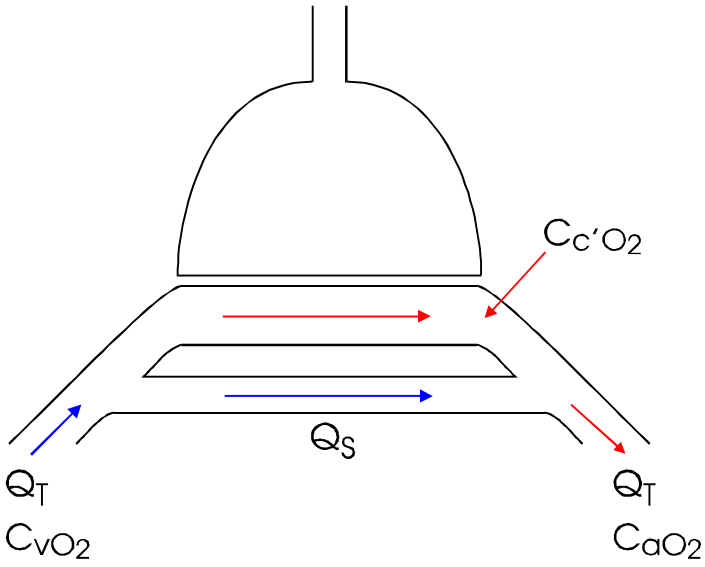
- ***Anatomical, or Absolute Shunt***

1. physiological
   - coronary blood enters LV via the thesbian veins
   - some bronchial artery blood enters the pulmonary veins
2. pathological
   - congenital heart disease with R→L shunt
   - perfusion of non-ventilated alveoli
   - pulmonary arterio-venous shunts (haemangioma)

- ***Regions of Low V/Q***

1. physiological
   - normal scatter of V/Q ratios
   - changes with posture - ie. erect vs. supine, lateral decubitus
2. pathological
   - abnormal scatter of V/Q ratios
   - alveolar-capillary block

- ***Measurement of Venous Admixture***



NB: by the ***conservation of mass***,

$$Q_T \cdot C_{aO2} = (Q_T - Q_S) \cdot C_{cO2} + (Q_S \cdot C_{vO2})$$

$$Q_T \cdot C_{aO2} = Q_T \cdot C_{cO2} - Q_S \cdot C_{cO2} + Q_S \cdot C_{vO2}$$

- dividing by Q_T

$$C_{aO2} = C_{cO2} - (Q_S/Q_T) \cdot C_{cO2} + (Q_S/Q_T) \cdot C_{vO2}$$

so, $$C_{aO2} - C_{cO2} = (Q_S/Q_T) \cdot (C_{vO2} - C_{cO2})$$

and, $$Q_S/Q_T = (C_{aO2} - C_{cO2}) / (C_{vO2} - C_{cO2})$$

- then by multiplying N & D by -1

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_{c'O_2} - C_{aO_2}}{C_{c'O_2} - C_{\bar{v}O_2}}$$

The Shunt Equation

NB: normally expressed as a fraction of CO **~ 2-3%**

C_{aO2} is measured directly by arterial puncture
C_{cO2} is taken as the "ideal" alveolar P_{O2} from the alveolar air equation (see over)

Alveolar Air Equation

a. **Rossier, Mean** (simplest form)

$P_{AO2} = P_{iO2} - (P_{aCO2} / R)$ R = ***respiratory exchange ratio***

b. **Riley**

$P_{AO2} = P_{iO2} - (P_{aCO2} /R) \times (1-F_IO_2(1-R))$

c. **West**

$P_{AO2} = P_{iO2} - (P_{aCO2}/R) + K$ $K = [F_IO_2 \times P_{aCO2} \times ((1-R)/R)]$

d. **Selkurt**

$P_{AO2} = P_{iO2} - P_{aCO2} \times [F_IO_2 + (1-F_IO_2)/R]$

e. **Filley, MacIntosh & Wright** (1954)*

$$P_{AO_2} = P_{iO_2} - P_{aCO_2} \times \left(\frac{P_{iO_2} - P_{\bar{E}O_2}}{P_{\bar{E}CO_2}} \right)$$

NB: this equation allows for disequilibria of inert gasses,
therefore may be used during induction / recovery from anaesthesia

- the differences between the P_{AO2} calculated by (b) & (c) are due only to inert gas exchange
- therefore, these may be used to calculate the ***concentration effect***

- ***Shunt vs. V/P Inequality***

• when breathing 100% O_2, the equation simplifies as the effects of R become negligible
• ie., as O_2 is taken up across the alveoli, only O_2 enters and the alveolar [O_2] remains approximately constant, thus,

$$\mathbf{P_{AO2} \sim \quad (P_{Atm} - 47) - P_{aCO2}}$$

1. if oxygenation is impaired by ***shunt*** the P_{aO2} will rise, not to maximum values, but by an amount always less than the rise in P_{iO2}
   (see ***iso-shunt diagram***, Nunn 7.11)
2. if oxygenation is impaired by abnormal ***V/Q scatter***,
   then P_{aO2} will rise by approximately the same amount as P_{iO2}

NB: *therefore,*

1. the shunt ratio for 100% O_2 → ***anatomical shunt***
2. the shunt ratio for air → ***physiological shunt***
3. the alveolar-arterial P_{N2} difference is a specific method for determining V/Q scatter, uninfluenced by shunt

Alveolar-Arterial P_{O2} Gradient

• normal gradient **~ 15 mmHg** (2 kPa)
• this may be up to 38 mmHg (5 kPa) in the elderly
• an ***increased*** gradient may be caused by,

1. pulmonary collapse / consolidation
2. neoplasm
3. infection
4. alveolar destruction
5. drugs - vasodilators
   - volatile anaesthetics
6. hormones - pregnancy & progesterone
   - hepatic failure
7. extrapulmonary shunting

NB: this is the commonest clinical cause of ***arterial hypoxaemia***

Factors Affecting P_{A-aO2} Gradient:

1. **venous admixture**
   - proportional relationship for small shunts
   - this relationship is lost for large shunts
   - all shunted blood is not mixed venous
   - $C_{c'O2}$ is derived from $P_{c'O2}$, which is *assumed* to equal ideal P_{aO2}

2. **alveolar P_{AO2}**
   - profound ***non-linear*** effect
   - gradient is greatest when P_{AO2} is high
   - thus for any given fall in P_{AO2}, P_{aO2} will fall to a ***lesser*** degree
   - the $C_{c'O2}$ - C_{aO2} difference is not significantly influenced by P_{AO2} due to the shape of Hb-O_2 curve at the P_{O2} of alveolar gas
   - the effect on ***tension*** is solely due to the conversion of content to tension
   - under normal circumstances, $\mathbf{P_{aO2} \sim 5 \times F_IO_2}$

3. **cardiac output**
   - ***inverse*** relationship at a constant MRO_2 (refers to content, not tension)
   - mixed venous blood is more desaturated at a low CO, therefore at a given shunt ratio increases A-a difference
   - however, a decrease in CO nearly always decreases Q_S/Q_T, so the A-a gradient is little altered

4. **oxygen consumption**
   - determines C_{vO2} for a given ventilation

5. **Hb concentration**
   - principally affects ***tension*** difference, not content
   - due to position on the flat portion of the curve at alveolar P_{O2}

6. **P_{50} of dissociation curve**

7. **alveolar ventilation**
   - $\uparrow V_A \rightarrow \uparrow P_{aO2}$ at a constant MRO_2
   - $\downarrow P_{aCO2} \rightarrow \downarrow$ CO and $\uparrow$'s the A-a difference at a constant MRO_2
   - the small $\downarrow$ pH has a minimal effect increasing the A-a difference

Compensation for $P_{A\text{-}aO2}$ Gradient

- for patients hypoxaemic breathing room air, the primary aim is to remove the ***cause*** of the hypoxaemia
- when this is not immediately possible, relief of hypoxaemia can be achieved by increasing F_IO_2
- broadly, hypoxaemia may be due to one of two causes, or a mixture thereof,

1. hypoventilation
2. venous admixture

- if due to ***hypoventilation***, then P_{aO2} may be restored with a F_IO_2 between 21-30%
- this is seen with P_{aO2}-alveolar ventilation curves
- where increasing the F_IO_2 to 30% increases the P_{aO2} ~ 64 mmHg at all rates of ventilation

  - if due to ***V/Q scatter***, then increased F_IO_2 should readily correct hypoxia
  - if due to ***shunt***, much higher F_IO_2's are required

Shunt %	F_IO_2 to restore normal P_{aO2}
10%	• 30%*
20%	• 57%* *all ~ 3x but doesn't continue
30%	• 97%*
40%	• normal P_{aO2} cannot be restored
50%	• increasing F_IO_2 has almost no effect on P_{aO2}

NB: therefore, with large shunts,
treatment is better directed toward reducing Q_S/Q_T,
rather than increasing F_IO_2

GAS TRANSPORT - OXYGEN

• oxygen is transported in the blood in 2 forms,

i. dissolved in plasma

ii. reversibly bound to Hb

Dissolved Oxygen

Def'n: ***Henry's Law***: the amount of a gas which dissolves in unit volume of a liquid, at a given temperature, is directly proportional to the ***partial pressure*** of the gas in the equilibrium phase

Ostwald solubility coefficient for O_2 at 37°C = 0.0034 ml/100ml blood/mmHg

• therefore a P_{O2} of 100 mmHg → dissolved O_2 ~ 0.3 ml/100ml blood

• normal male breathing 100% O_2, dissolved O_2 = 2.0 vol%
• at 3 Atm. pressure, 100% O_2 = 6 vol% and can sustain life

Oxygen Carriage by Haemoglobin

- ***Haemoglobin-Oxygen Dissociation***

Def'n: functional Hb saturation = $\frac{O_2 \text{ combined with Hb} \times 100}{O_2 \text{ capacity of Hb}}$

• where the ***O_2 capacity*** is the maximal amount of O_2 that will combine with Hb at a high P_{O2}, usually ≥ 250 mmHg
• this is distinct from the fractional Hb saturation, which includes met-Hb and COHb
• O_2 capacity varies with [Hb] → 1 gm pure Hb combines with **1.39 ml O_2**

Important Values to Remember			
P_{O2} mmHg	% Saturation Hb [O_2] at 15 g Hg/100ml		
100	**97.5**	**20 ml.O_2**	**Arterial**
80	94.5		
60	89		
40	**75**	**15 ml.O_2**	**Mixed Venous**
26.3	50		
T = 37°C	P_{CO2} = 40 mmHg	pH = 7.4	Base Excess = 0

[1] Ca-vO_2 difference (at CO ~ 5.0 l/min) ~ 5ml.O_2/100ml

[2] the "normal" P_{aO2} ~ 102-(0.33 × age) mmHg

Factors Affecting Oxy-Hb Dissociation Curve

Def'n: affinity is measured by the $\mathbf{P_{50}}$, which is the P_{O2} when Hb is 50% saturated, at pH = 7.4, T = 37°C, and BE = 0,

$$\mathbf{P_{50} = 26.3\ mmHg}$$

NB: $\downarrow$ affinity of Hb for O_2 $\rightarrow$ a shift of the curve to the ***right*** and an **- P_{50}**
$\uparrow$ affinity of Hb for O_2 $\rightarrow$ a shift of the curve to the ***left*** and a **$^{-}P_{50}$**

Physiological Factors

- ***Hydrogen Ion***

• $\uparrow [H^+] / \downarrow$ pH $\rightarrow$ curve shifts to the ***right***,

ϕH = 0.1 ® δP_{50} = 2.5 mmHg

• this effectively impairs oxygenation in the lungs but increases the delivery to the tissues

- ***Carbon Dioxide***

• $\uparrow [CO_2]$ produces a ***pH-independent*** shift of the curve to the ***right*** with $\downarrow$ affinity for O_2

$\rightarrow$ the ***Bohr Effect***

• most of the desaturation occurring at tissue level is due to the lowered P_{O2} but an extra 1-2% is due to the $\uparrow [CO_2]$ and right shift of the curve
• at a constant O_2 extraction, the P_{vO2} will increase for any decrease in pH or right shift of the curve
• therefore, respiratory acidosis frequently raises the tissue P_{O2}, especially in brain
• further, the CO and CBF frequently increase, further aiding cerebral O_2 delivery

- ***Temperature***

• $\uparrow$ T shifts the curve to the ***right***

- ***2,3-Diphosphoglycerate 2,3-DPG***

• formed in the RBC as an intermediary in the Embden-Meyerhof glycolytic pathway, the ***Rapoport-Luebering shunt***
• synthesised from 1,3-DPG by ***2,3-DPG mutase***
• re-enters the glycolytic pathway by conversion to 3-phosphoglycerate, catalysed by ***2,3-DPG phosphatase***
• the plasma elimination half-life, $t_{½}$ ~ 6 hrs
• binds to one of the b-***chains*** of Hb favouring deoxygenation, thereby shifting curve to the ***right***
• exerts a permissive role for the effects of CO_2 and pH
• thus, in stored blood deficient in 2,3-DPG, the Bohr effect is less
• increasing the pH increases the activity of the mutase and decreases the activity of the phosphatase → ***alkalosis*** may be associated with a shift of the curve to the right

• ***acidosis*** inhibits RBC glycolysis and decreases 2,3-DPG formation

• thyroid hormones, GH, and androgens increase 2,3-DPG
• ***exercise*** increases 2,3-DPG within 60 mins, but this effect may not be seen in athletes
• ***high altitude*** triggers a substantial rise in 2,3-DPG secondary to the respiratory alkalosis

• 2,3-DPG has a low binding affinity for the gamma-chains of Hb_F ($143^{His\text{-}Val}$)
• this results in the higher affinity of Hb_F for O_2, thereby enabling placental transfer of greater amounts of O_2
• the effects of DPG are only seen in the P_{50} range 15-34 mmHg

Alterations in Health and Disease

1. **Exercise**
   - increased T, P_{CO2}, and $[H^+]$ shift curve to the ***right*** increasing O_2 availability
   - effectively increases the δPO_2 driving diffusion for a given O_2 extraction
2. **Acid-Base Disturbances**
   i. ***acidosis***
      - improves O_2 release for several hours
      - eventually offset by the decline in RBC production of 2,3-DPG, due to inhibition of glycolysis
      - subsequent increases in 2,3-DPG are seen due to enhanced activity of 2,3-DPG mutase and inhibition of the phosphatase

   ii. ***alkalosis***
      - immediate shift of the curve to the left
      - offset by ↑ 2,3-DPG formation & right shift of curve

3. **Altitude**
   - after 24-48 hrs there is a marked shift of the curve to the ***right*** due to increased levels of 2,3-DPG secondary to the ***respiratory alkalosis***
   - the P_{50} increases by ~ 3.8 mmHg
   - this was ***not*** confirmed by Severinghaus *et al*.
   - further, an altitude of ~ 4000m $\rightarrow$ P_{aO2} ~ 52 mmHg
   - a shift of the curve under these conditions has only minimal advantage, as the decrease in P_{aO2} means lung oxygenation is impaired to a degree only marginally outweighed by the increase availability to the tissues

4. **Hyperoxia**
   - produces a small shift of curve to the ***left***, due to decreased 2,3-DPG

5. **Congestive Cardiac Failure**
   - produces a shift of curve to the ***right***, with increased levels of 2,3-DPG, proportional to the severity of the CCF

6. **Anaemia**
   - produces a ***right*** shift, due to proportionately increased levels of 2,3-DPG

7. **Right Left Shunt with Hypoxaemia**
   - produces a ***right*** shift, with increased levels of 2,3-DPG

8. **Hyperthyroidism** - shift to the right
   Hypothyroidism - shift to the left *due to changes in 2,3-DPG levels

9. **Carbon Monoxide** & **Methaemoglobin**
   - shift of the curve to the ***left***, also decreases 2,3-DPG and available Hb

10. **Foetal Hb** - greater affinity c.f. Hb_A as decreased binding 2,3-DPG
    $\rightarrow$ P_{50} ~ 19 mmHg

11. **Stored Blood Bank**
    - RBC's show a progressive fall in 2,3-DPG levels with increasing affinity for O_2 and ***left*** shift of curve
    - following transfusion, there is ~ 50% recovery of 2,3-DPG within 4 hrs, but several days are required for normal values
    - this only becomes clinically important in massive T_X in a hypothermic patient
    - storage in citrate-phosphate-dextrose (CPD) produces less of a decrease than ACD
    - ACD $\rightarrow$ almost complete depletion in 3 weeks with a P_{50} ~ 15 mmHg

NB: 1. in general, research has ***failed*** to demonstrate that 2,3-DPG is of major importance in clinical problems of oxygen delivery
2. changes in the P_{50} mediated by changes in 2,3-DPG are of ***marginal significance*** in comparison to changes in P_{aO2} and tissue perfusion
3. anaesthetic gases bind significantly to Hb, however, this does not result in any significant shift of the curve

HAEMOGLOBIN

• Hb is carried within RBC's for 2 reasons,

a. provide an optimal chemical environment

b. prevents a large rise in the plasma oncotic pressure

Def'n: ***haem*** = iron porphyrin compound, tetrapyrrole ring, joined to protein
globin = 4 polypeptide chains, each of which has a haem moiety

Adult Hb (Hb_A)	2 alpha chains	141 AA residues	Haem → 87^{His}
	2 beta chains	146 AA residues	Haem → 92^{His}
	Total MW **64,458.5**		
Foetal Hb (Hb_F)	2 alpha chains		
	2 gamma chains		

* increased O_2 affinity due to decreased binding of 2,3-DPG by gamma chains

• the reaction $Hb + 4O_2 \rightarrow$ ***oxygenation***, not oxidation as Fe^{++} stays in the reduced form
• the reaction is rapid (≤ 0.01 sec), and results in movement of the peptide chains, with an associated positional change of the haem moiety,

1. R = ***relaxed state*** → ↑ affinity for O_2
2. T = ***tense state*** → ↓ affinity for O_2

• the conformational changes are due to the formation and breaking of salt bridges
• as Hb takes up O_2, the β-chains move closer together favouring the R-state & ↑ O_2 affinity
• ↑ affinity during oxygenation → the ***sigmoid*** shape of Hb-O_2 dissociation curve
• during saturation of the last 25% of reduced Hb, the last reaction will predominate,

$$Hb_4O_6 + O_2 \xleftrightarrow{k_4'} Hb_4O_8$$

• the higher forward velocity constant for this reaction, (k_4'), counteracts the decreased number of O_2 sites which would otherwise slow the reaction rate by the ***Law of Mass Action***
• the net result is that the reaction proceeds at much the same rate until full saturation
• for each reaction, the ***dissociation*** rate constants are ***slower*** than the association constants
• the association constant for CO is approximately the same as that for O_2, but the dissociation constant is considerably slower
• at full saturation 1gm of pure Hb can carry 1.39 ml of O_2, however *in vivo* some Hb is in other forms, eg. met-Hb, and cannot contribute to O_2 uptake
• thus, the physiological value ~ 1.34 to 1.37 ml.O_2/gm.Hb,

15 g.Hb/100 ml.blood → 20.1 to 20.4 ml.O_2/100 ml.blood

Methaemoglobin

- normal adult Hb_A has iron in the Fe^{++}, or ***ferrous state***
- this may be ***oxidised*** to Fe^{+++} forming methaemoglobin, and may be due to either,

    a. hereditary - met-Hb reductase deficiency

    b. acquired - drugs (nitrites, nitrates, prilocaine)

- met-Hb does not participate in O_2 exchange
- patients appear clinically cyanosed at levels **> 1.5 gm%**
- in otherwise healthy patients, this has little effect on the oxygen carrying capacity
- however, may be corrected by the administration of reducing agents

(***methylene blue*** 1-2 mg/kg IV)

Carboxyhaemoglobin COHb

- CO has greater affinity for Hb, ~ 210 times that for O_2
- CO-Hb produces a ***left*** shift of the Hb-O_2 curve, partly by decreasing 2,3-DPG
- also, its formation decreases the remaining amount of useable Hb_A

Haemoglobinopathies

- these are usually only minor abnormalities in the AA sequence, or composition of α/β chains
- however, may lead to,

    a. decreased O_2 affinity

    b. increased O_2 affinity

    c. unstable haemoglobins

    d. aggregating haemoglobins - eg. Hb_S at low P_{O2}

Thallassaemias

- partial or complete defect in the synthesis of one of the normal Hb peptide chains
- ie. the defect is the ***rate*** of synthesis of Hb

Sulfhaemoglobin

- Hb derivative of unknown composition
- irreversible change usually induced by drugs, eg. phenacitin

OXYGEN FLUX

Def'n: the quantity of oxygen transported by the circulation in one minute

= CO × arterial O_2 content
~ 5000 ml/min × (20 ml O_2/100 ml blood)
~ **1000 ml/min** (at rest in a 70 kg man)

- as the MRO_2 ~ 250 ml/min, so venous blood is ~ 75% saturated
- thus, three factors can decrease the O_2 flux,

i. cardiac output → stagnant hypoxia
ii. O_2 saturation → hypoxic hypoxia
iii. [Hb] → anaemic hypoxia

- the fourth type of hypoxia is ***histotoxic***, as in CN^- poisoning, however this is usually associated with a normal or increased O_2 flux
- the minimum O_2 flux compatible with life is ***~ 400 ml/min*** at rest, but this is quite variable
- metabolic indicators, eg. lactate production, are more useful than attempts to measure tissue P_{O2}

Partial Pressure Gradients					
	Air	Lung	Blood	Tissue	Mitochondria
P_{O2} mmHg	149	101	95	~ 30	~ 1-3
P_{CO2} mmHg	0	39	40	46	??

- tissue P_{O2} depends upon,

1. the rate of O_2 delivery
   - capillary blood flow
   - capillary CO_2
   - position of Hb-O_2 dissociation curve
   - capillary/tissue P_{O2} gradient
   - capillary/tissue diffusion distance
2. rate of tissue usage
   - basal metabolic rate
   - temperature, physical activity, rate of O_2 usage, pH
   - hormones (thyroxine, catecholamines)
   - drugs (CN^-)

- active tissues have low P_{O2}, low pH, high T, and high P_{CO2}, all of which dilate arterioles locally, increasing the number of open capillaries and reducing the intercapillary distance
- P_{cO2} must be high enough to establish diffusion gradient to cells
- C_{cO2} must be high enough to supply O_2 requirements of active tissues
- increased requirements of the tissues may be met by,

a. increased extraction ratio of O_2 from blood
b. increased tissue blood flow

CARBON DIOXIDE TRANSPORT

Carriage in Blood		
Form	Arterial %	Venous %
Dissolved	5	10
Bicarbonate	90	60
Carbamino	5	***30***

• of the CO_2 added to the circulation in the tissues and carried to the lung,

a. 65% is carried in plasma

b. 35% is carried in RBC's

NB: however, the proportion carried in the RBC's increases due to the increased basic nature of deoxy-Hb

▪ ***Dissolved***

• obeys ***Henry's Law***, as does O_2, but CO_2 is ~ 24x more soluble than O_2
• 5-10% of the CO_2 liberated by the lung comes from the dissolved fraction
• the solubility coefficient (α), is temperature dependent (Nunn table 9.1)

i. O_2 solubility is expressed in $ml.O_2/mmHg/100\ ml$

ii. CO_2 solubility (α) is usually expressed as $mmol/l/mmHg$

at 37°C, a_{CO2} **~ 0.0308 mmol/l/mmHg**

▪ ***Bicarbonate***

$$CO_2 + H_2O \xleftrightarrow[CA]{} H_2CO_3 \longleftrightarrow H^+ + HCO_3^- \longleftrightarrow 2H^+ + CO_3^{=}$$

• the first forward reaction occurs very slowly in plasma but rapidly in RBC's due to the presence of ***carbonic anhydrase*** (CA - Zn enzyme)
• the carbonic acid formed is only a small percentage (~ 1%) and frequently both this and dissolved CO_2 are referred to as H_2CO_3
• therefore, in the various equations, the term a$\mathbf{P_{CO2}}$ is preferable
• these should really be expressed as thermodynamic activities, rather than concentrations, but for very dilute solutions the ***activity coefficient***,

$$AC = \text{activity} / []n \sim 1.0$$

• therefore, the equilibrium constants are apparent constants, *K'*
• the second reaction occurs quickly with a *pKa' = 6.1*

• the third reaction occurs with a *pKa' > 9.0*, therefore is not an issue in the physiological range
• the HCO_3^- formed diffuses from cell due to a large concentration gradient but H^+ cannot follow due to the relative membrane impermeability
• Cl^- therefore diffuses into the cells → the ***chloride shift***
• deoxy-Hb is more ***basic*** than oxy-Hb and accepts H^+ ions more readily
• therefore, reducing the P_{O2} and Hb saturation increases the CO_2 carrying capacity of the blood

→ the ***Haldane Effect***

• as the osmolality of RBC's increases with CO_2 uptake, water enters cells with subsequent swelling, the process being reversed in lung

■ ***Carbamino***

• formed from the combination of CO_2 with terminal amine groups of blood proteins,

$$Hb\text{-}NH_2 + CO_2 \longleftrightarrow Hb\text{-}NH\text{-}COOH$$

• quantitatively ***Hb*** is the most important
• the carboxyl and amino groups of peptide linkages have no functional effect
• most side chains, such as glutamic acid and lysine, have pK's well outside the physiological range
• the imadazole groups of ***histidine*** are the only effective protein buffer
• the buffering effect of plasma proteins is relatively low and directly proportional to their histidine content
• Hb has 38 histidine residues and is thus quantitatively the most important
• deoxy-Hb is more basic than oxy-Hb and accepts H^+ ions more readily
• therefore, reducing the P_{O2} and Hb saturation increases the CO_2 carrying capacity of the blood,

→ the ***Haldane Effect***

Buffering Capacity of Hb

• the titration curves for Hb and HbO_2 are parallel over the physiological range, Hb being more basic than HbO_2
• delivery of O_2 and uptake of CO_2 are therefore mutually helpful in the tissues,

a. the addition of H^+ & CO_2 shifts the HbO_2 curve to the ***right***

→ the ***Bohr Effect***

b. the formation of deoxy-Hb adds buffer, allowing addition of H^+ without a significant change in pH

• this effectively prevents the large decrease in blood pH which would follow CO_2 uptake,

NB: 1mmol of HbO_2 → Hb, allows 0.7 mmol H^+ addition *without* a change of pH

• these effects are exaggerated in exercise due to greater CO_2 production and the shift of the HbO_2 curve to the right

Carbon Dioxide Dissociation Curve

- in the physiological range the curve is almost ***linear***
- therefore, changes in P_{CO2} are accompanied by corresponding changes in C_{CO2},

  → compensation of regional V/Q imbalance

- the position of the dissociation curve is dependent upon HbO_2 saturation,

  → the ***Haldane effect***

- the slope of the CO_2 curve is much steeper in the physiological range than that for O_2

▪ *Haldane Effect*

Def'n: for a given P_{CO2}, C_{CO2} increases as P_{O2} decreases,

ie., shifts the CO_2-blood curve to the ***left***

- this is due to,
  a. the greater affinity of deoxy-Hb for H^+, and
  b. the greater ability of deoxy-Hb to form carbamino compounds

NB: the major effect being (b)

▪ *Bohr Effect*

Def'n: at a given P_{O2}, increases in $[H^+]$, P_{CO2}, and temperature decrease the C_{O2},

ie., shift the HbO_2 curve to the ***right***

- composite O_2-CO_2 diagrams are used to obtain HbO_2 saturation when P_{CO2} deviates from 40 mmHg
- the slopes of the respective concentration lines, ***isopleths***, representing the above two effects (West 6.7)

Body Stores of CO_2

- body fluids contain ~ 50 ml% CO_2
- bone contains greater than 100 ml% CO_2

- therefore, the mythical 70 kg man contains ~ 35 l of stored CO_2
- of this ~ 20 l is readily exchangeable
- with complete ***apnoea***, rate of rise of P_{aCO2} ***~ 3 mmHg/min***, which is a balance between the rate of metabolic production and the ability of the tissues to store CO_2
- significance to anaesthesia,

    a. hypoventilation following prolonged hypocapnia

    b. apnoeic oxygenation (mass movement oxygenation)

Important Effects of Carbon Dioxide **(G&G 7th Ed.)**

- ***Respiration***

- CO_2 is a potent stimulus to respiration
- inhalation of 2% CO_2 produces a marked increase in rate and depth of respiration
- 10% CO_2 produces minute volumes up to 75 l/min in normal individuals
- there are at least two sites where CO_2 acts to increase respiration,

    a. the integrating areas in the brain stem in response to stimulation from ***medullary chemoreceptors***

    b. peripheral ***arterial chemoreceptors***

- the mechanism by which CO_2 acts at these sites is by reducing ***local pH***
- elevated P_{aCO2} causes bronchodilatation while hypocarbia produces constriction of airway smooth muscle, thus, helping match ventilation to local perfusion

- ***Cardiovascular***

NB: the circulatory effects of CO_2 are the result of,

1. direct ***local effects*** and
2. centrally mediated ***autonomic effects***

• the direct effect on the heart results from decreased local pH, reducing contractile force and slowing the rate of contraction
• rhythm is usually unaffected
• the direct effect on systemic blood vessels is vasodilatation

• the autonomic effects of CO_2 result in widespread activation of the SNS
• this results in an increased concentration of catecholamines, angiotensin and other vasoactive peptides
• the results of SNS activation are, in general, opposite to the local effects of CO_2
• this results in increased force and rate of cardiac contraction and vasoconstriction of many vascular beds

• the overall effects of ***hypercarbia*** in normal man are,

a. an increase in cardiac output and heart rate
b. elevation of systolic and diastolic blood pressures
c. an increase in pulse pressure
d. a decrease in TPR (local effects dominating)
e. cerebral vasculature dilates due to minimal SNS supply
f. increased ICP from increased BP plus cerebral vasodilatation
g. renal and splanchnic flow is not significantly altered

• in the isolated myocardium, the threshold for catecholamine induced arrhythmias is increased
• however, in vivo, this effect is overwhelmed by the release of large amounts of CA's

NB: arrhythmias are likely to occur with a coexisting factor, eg. Halothane

• the circulatory effects of ***hypocarbia*** include,

a. decreased blood pressure
b. vasoconstriction in skin, brain, renal, cardiac and most vascular beds
c. vasodilatation in skeletal muscle

• if hypocarbia results from voluntary hyperventilation, then CO and HR increase due to increased venous return and the demands of respiratory muscles
• in contrast, hypocarbia resulting from mechanical hyperventilation reduces CO and HR, probably due to increased intrathoracic pressure

- ***CNS***

• low concentrations of inspired CO_2 → moderate hypercarbia,

a. decrease neuronal excitability

b. raise the seizure threshold

c. increases the cutaneous pain threshold (central mechanism)

• therefore, can cause further depression of the already depressed CNS
• still higher concentrations, 25-30%, → increased cortical excitability and convulsions
• $FiCO_2$ ~ 50% → marked cortical and subcortical depression

- ***Miscellaneous***

• increases in the P_{aCO2} produce,

a. shifts the HbO_2 curve → ***right***

b. placental vasoconstriction

c. respiratory acidosis

d. hyperkalaemia

e. increased plasma HCO_3^- by the kidney, enhanced H^+ secretion

f. increases in ionised Ca^{++} due to decreased binding

g. alterations in drug solubility, binding, distribution etc.

h. decreased neuronal excitability

NB: Reference range (Nunn): **38.3 ± 7.5 mmHg**

Hypocapnia $P_{aCO2} < 31$ mmHg Causes

1. excessive IPPV
2. voluntary hyperventilation
3. hypoxaemia
4. metabolic acidosis
5. mechanical abnormalities of the lung
   → increase drive through vagal stimulation
6. hypotension - may drive respiration directly
   - metabolic acidosis is usually more important
7. hysteria
8. head injuries
9. pain
10. pregnancy

Hypercapnia $P_{aCO2} > 46$ mmHg Causes

a.	inadequate IPPV	
b.	depression of the medullary respiratory centre	
c.	UMN lesions	- trauma
d.	anterior horn cell lesions	- polio
e.	LMN lesions	- trauma, Guillian-Barre, M-N disease
f.	NMJ	- myasthenia gravis, botulin toxin
g.	muscles	- diaphragmatic splinting (obesity, pregnancy, ascites) - fatigue 2° workload (resistance/compliance)
h.	decreased compliance	- lung causes (H-R syndrome, fibrosis, ARDS) - pleura (empyema, haemothorax, mesothelioma, Ca) - chest wall (kyphoscoliosis) - skin (extensive burns in children) - external pressure
i.	loss of integrity of chest wall	- open pneumothorax - tension pneumothorax - flail chest
j.	increased airways resistance	= the ***commonest cause***

Measurement of P_{aCO2}

1. Direct Microtonometry
2. Solution of Henderson-Hasselbach Equation
3. Interpolation (micro-Astrup)
4. CO_2 Electrode
5. Rebreathing Method

Measurement of CO_2 in Gas Mixtures

1. Chemical absorption (Haldane)
2. IR absorption analysis - at 4.28 μm wavelength, end-tidal CO_2
3. Raman spectroscopy
4. Photoacoustic spectroscopy
5. Gas chromatography
6. Mass spectrophotometry

ACID-BASE BALANCE

- the principal acid product of metabolism is CO_2, equivalent to potential carbonic acid
- the lungs excrete **~ *15,000 mmol*** of CO_2 per day (R:15-20,000)
- fixed acid excreted by the kidney ~ 70 mmol (<100 mmol)
- ECF pH is set within the limits 7.35 to 7.45, being equivalent to $[H^+]$ = 45 to 35 nmol/l
- ICF pH is difficult to determine and varies from one organelle to another, a mean value pH ~ 6.9
- the normal $[CO_2]$ in body fluids is fixed at 1.2 mmol/l, P_{CO2} = 40 mmHg
- the total buffer capacity of body fluids is ~ 15 mEq/kg body weight
- because intracellular and extracellular buffers are functionally linked, the ***isohydric principal***, measurement of the plasma bicarbonate system provides information about total body buffers
- from the dissociation of carbonic acid,

$$H_2CO_3 \longleftrightarrow HCO_3^- + H^+$$

$$K_A = \frac{[HCO_3^-] \,.\, [H^+]}{[H_2CO_3]}$$ by the law of mass action

- but as K_A only applies to infinitely dilute solutions with negligible interionic forces, the ***apparent dissociation constant***, $\mathbf{K_A'}$, is used
- this may be rewritten for hydrogen ion, viz.

$$[H^+] = \frac{K_A' \times \alpha . P_{CO_2}}{[HCO_3^-]}$$

- K_A' cannot be derived and is determined ***experimentally*** by measuring all three variables under a wide range of physiological conditions
- under normal conditions, using mmHg $\rightarrow$ a $\mathbf{K_A'}$ **~ 24**
- therefore, the equation may be written,

$$[H^+] = \frac{24 \,.\, P_{CO2}}{[HCO_3^-]}$$

so, $P_{CO2} \propto [HCO_3^-].[H^+]$

- and, as $[H_2CO_3]$ is always proportional to $[CO_2]$, which is proportional to P_{aCO2} the equation may be written,

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.0301 \times P_{aCO_2}}$$

- graphical plot of plasma $[HCO_3^-]$ vs. pH = ***Davenport diagram*** (West 6.8)
- also plotted in the log P_{CO2} vs. pH format (Siggaard-Andersen)
- preferred method is nomogram of $[HCO_3^-]_{pl}$ vs. P_{aCO2} (see Harrison's)

Definitions

Acid: a proton, or hydrogen ion donor

Base: a proton, or hydrogen ion receiver

Plasma pH: the negative $\log_{10}$ of the hydrogen ion ***activity*** ~ $[H^+]$

Normal pH = 7.4 ± 0.4 ~ $[H^+]$ ~ 39 nmol/l

Acidosis: an abnormal process or condition which would lead to an acidaemia, if uncompensated

Alkalosis: an abnormal process or condition which would lead to an alkalaemia, if uncompensated

Acidaemia: a plasma pH $\leq$ 7.36

Alkalaemia: a plasma pH $\geq$ 7.44

Respiratory: a disorder those where the primary disorder is a change in the P_{CO2}

Metabolic: a disorder where the primary disturbance is in the $[HCO_3^-]$

Base Excess: the amount of strong acid required to be added to 1.0 l of fully saturated blood, at 37°C, at P_{CO2} = 40 mmHg, to return the pH to 7.4

Normal BE = 0 ± 2.0 mmol/l

Standard Bicarbonate: the HCO_3^- concentration in fully saturated blood, when the P_{CO2} = 40 mmHg at 37°C (** a ***derived variable***)

Normal = 24.0 ± 2.0 mmol/l

Plasma Bicarbonate: the actual HCO_3^- concentration in plasma at that particular point in time; cannot be measured but is calculated from the Henderson-Hasselbalch equation, when the P_{CO2} and pH are known

NB: some laboratories report the plasma bicarbonate as the total CO_2, where this is given by,

Total CO_2 = $[HCO_3^-] + [H_2CO_3]$
~ 24.0 ± 2.0 mmol/l

where, $[H_2CO_3]$ ~ 1.2 mmol/l

Anion Gap: = $[Na^+] - ([Cl^-] + [HCO_3^-])$ ~ 12.0 ± 2.0
or, = $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$ ~ 16.0 ± 2.0

ACID-BASE BALANCE

• the major problem in clinical assessment stems from compensatory processes
• multiple experimental observations of all primary acid-base disturbances is used to produce confidence bands (± 2SD) for assessment of blood gas measurements → ***nomogram***

NB: given P_{aCO2} is proportional to the ***product*** of $[HCO_3^-].[H^+]$, as P_{aCO2} increases or decreases, so the $[HCO_3^-]$ increases or decreases by dissociation, however, ***not*** to the same degree as it is the product $[HCO_3^-].[H^+]$ which is proportional, therefore, the ratio $[HCO_3^-]/P_{aCO2}$ alters with a resultant change in the pH

▪ ***Respiratory Acidosis***

• caused by hypoventilation, V/Q inequality

- $\mathbf{P_{aCO2}}$ → ↑ $[HCO_3^-]$ by dissociation, but

ratio of $[HCO_3^-] / P_{aCO2}$ falls → ¯ **pH**

• increased P_{aCO2}, and to a lesser extent increased $[H^+]$→ ↑ renal tubular H^+ secretion
• thus, bicarbonate reabsorption is increased and more H^+ ion is excreted with phosphate and ammonium
• the increased $[HCO_3^-]$ compensates for the respiratory acidosis but compensation is ***rarely complete***
• the extent of renal compensation is determined by the ***base excess***

▪ ***Respiratory Alkalosis***

• caused by hyperventilation, eg. altitude, hysteria, mechanical ventilation

¯ $\mathbf{P_{aCO2}}$ → ↓ $[HCO_3^-]$ by association, but

ratio of $[HCO_3^-] / P_{aCO2}$ rises → - **pH**

• decreased P_{aCO2} inhibits renal tubular H^+ secretion
• therefore some bicarbonate escapes reabsorption and less H^+ is available for formation of titratable acid and ammonium, ergo, urine becomes alkaline
• decreased plasma $[HCO_3^-]$ compensates for respiratory alkalosis and may be nearly complete
• extent of renal compensation determined by ***base deficit***, or negative base excess

- ***Metabolic Acidosis***

  - $[H^+]$ or $^-$ $[HCO_3^-]$ → ↓ plasma $[HCO_3^-]$

  ↓ ratio of $[HCO_3^-] / P_{aCO2}$ → $^-$ **pH**

• decreased pH stimulates ventilation, predominantly via peripheral chemoreceptors, decreasing P_{aCO2} and compensating acidosis
• the kidney ***increases*** excretion of ***titratable acid*** despite the decrease in P_{aCO2}
• this occurs as the filtered load of HCO_3^- decreases to a greater extent than the reduction in distal tubular H^+ secretion

→ more H^+ is available for titration against NH_3 and $HPO_4^=$

• the decreased plasma $[HCO_3^-]$ shows as a ***base deficit***

- ***Metabolic Alkalosis***

• loss of gastric acid from, excess alkali added to, or retained by, the body,

$^-$ $[H^+]$ or - $[HCO_3^-]$ → ↑ plasma $[HCO_3^-]$

↑ ratio of $[HCO_3^-] / P_{aCO2}$ → **- pH**

• increased pH inhibits ventilation, predominantly via the peripheral chemoreceptors, increasing P_{aCO2} and compensating for alkalosis
• the excess plasma $[HCO_3^-]$ shows as a ***base excess***

NB: compensation may be small or absent,
this is the least well compensated acid-base disturbance

NEUROGENESIS OF BREATHING

▪ *Medullary Respiratory Centres*

• these lie within the reticular formation of the brainstem
• divisible into two poorly localised groups,

1. dorsal respiratory group (DRG) → inspiration
2. ventral respiratory group (VRG) → expiration ± inspiration

• cells within the DRG are thought (West) to posses inherent ***rhythmicity***, generating bursts of neuronal activity to the diaphragm and respiratory muscles in the absence of any other input
• the DRG is under the control of the ***pneumotaxic centre***

→ termination of the inspiratory "ramp" of action potentials

• input from the vagal and glossopharyngeal nerves via the nearby nucleus of the tractus solitarius modulates activity in the DRG
• the VRG is divided into 2 divisions,

1. cranial division - neurones of the nucleus ambiguus
2. caudal division - neurones of the nucleus retroambiguus

• the cranial division innervates muscles of the ipsilateral accessory muscles of respiration, principally via the vagus
• the caudal division provides inspiratory and expiratory drive to the motor neurones of the intercostal muscles
• the neurones of the expiratory VRG are quiescent during tidal respiration, however become active with forced expiration, exercise, etc.
• all impulses activating respiratory muscles synapse in the respiratory centres of the medulla, ie. CSA, hypothalamus, cortex, RAS

▪ *Apneustic Center*

• situated in the lower pons in the floor of the 4th ventricle, near the middle cerebellar peduncle
• impulses from these neurones → inspiratory DRG and increased "ramp" AP's
• section of the brainstem immediately above this group → ***apneusis***
• prolonged inspiratory gasps interrupted by transient expiratory efforts
• this is restrained by the pneumotaxic centre and the inflation reflex

▪ *Pneumotaxic Centre*

• located in the upper pons, in the nucleus parabrachialis and the Kolliker Fuse nucleus
• acts to limit the activity of the inspiratory DRG
• therefore regulating the inspired volume and rate of respiration
• acts only as a modulator, as normal respiratory rhythm can exist in its absence

Nunn:

• most of the classical studies, based on ***ablation experiments***, are now realised to be rather unpredictable due to unpredictable tissue destruction and interruption of blood supply
• rhythm can be generated in the medulla, in the absence of input from the lungs or elsewhere
• there is no doubt of the existence of pontine neurones firing in synchrony with the different phases of respiration but they are no longer believed to be essential for the generation of the respiratory rhythm
• although the pneumotaxic centre is no longer thought to be the dominant controller of the respiratory rhythm, the pattern of firing of these neurones suggests a modification and fine control of the respiratory rhythm
• the ***dorsal respiratory group*** is probably of paramount importance in driving the inspiratory muscles

• the generation of inherent rhythm is due a "bistable" system, exhibiting reciprocal stimulation / inhibition
• the final integration of respiratory drive occurs in the ***anterior horn cells*** of the spinal cord
• these receive UMN's from three regions,

a. fibres from the inspiratory & expiration medullary centres
   → ventrolateral tracts of the spinal cord

b. fibres carrying voluntary control (singing etc.)
   → dorso-lateral & ventro-lateral cord

c. fibres carrying involuntary, non-rhythmic control
   → diffuse pathways, but not with (a) or (b)

REGULATION OF PULMONARY VENTILATION

- the brain stem respiratory centres are influenced by,

a.	carotid & aortic chemoreceptors	- decreased P_{aO2} - increased P_{aCO2} - increased $[H^+]$
b.	central chemoreceptors	- increased P_{aCO2} - increased $[H^+]_{CSF}$
c.	cerebral blood flow	
d.	reflexes from lungs, inflation reflex, etc.	
e.	muscle spindles in respiratory muscles	
f.	carotid, aortic baroreceptors	
g.	thoracic chemoreceptors	
h.	peripheral	- temperature receptors - pain receptors - mechano-receptors
i.	cerebral cortex	- emotion, breath holding
j.	RAS and higher CNS centres	- ANS, special senses (olfaction) - speaking, swallowing, etc.
k.	hormones	- progesterone increases ventilation

Carotid & Aortic Chemoreceptors

- the ***carotid bodies*** are located at the bifurcation of common carotid artery
- they send afferents in the carotid sinus nerve to the glossopharyngeal nerve (IX)
- the ***aortic bodies*** are located between the arch of aorta and pulmonary artery
- afferents ascend in the recurrent laryngeal nerves to the vagus (X)

- these are small neuro-vascular organs, whose perfusing blood comes in contact with special sensory cells, ***glomus cells*** (SIF), which have a large content of ***dopamine***
- these are actually inhibitory interneurones and impulses are generated in afferent nerve terminals
- these tissues have an extremely high blood supply relative to their size and metabolic needs

→ ~ 20 ml/gm/min, therefore a very low O_2 extraction ratio
they are sensitive to a low P_{aO2}

- stimulation results from a decrease in carotid and aortic body tissue P_{O2} (***tension***, not content)
- a fall in carotid and aortic body tissue P_{O2} will occur with,

1. ***arterial hypoxia*** - decreased P_{aO2}
2. ***ischaemia*** - eg. from marked hypotension

- they are ***not*** stimulated by,

1. anaemia
2. carbon monoxide (CO) poisoning
3. methaemoglobinaemia

- these later conditions produce a decrease in C_{aO2} not P_{aO2}, therefore there is no decrease in carotid and aortic body tissue P_{02}
- they are also stimulated by,

1. an increased tissue P_{CO2} > 10 mmHg
2. decreased tissue pH > 0.1-0.2 units
3. metabolic poisons - eg. cyanide (CN^-) poisoning
4. drugs - eg. nicotine, lobeline

- the effects of chemoreceptor stimulation include,

1. increased respiratory rate and depth
2. bradycardia (carotid body)*
3. tachycardia (aortic bodies)*
4. hypertension, due to peripheral vasoconstriction
5. bronchoconstriction

NB: * the 1° response is ***bradycardia***, increases being 2° to P_{CO2}

- ***Carotid & Aortic Chemoreceptors***

• the response time is very fast and cyclic changes occur with the normal respiratory cycle
• the peripheral chemoreceptors are responsible for ***all*** of the ventilatory response to ***hypoxia***
• in their absence, decreased P_{aO2} depresses respiration due to direct effects on the brain stem
• complete loss of ***hypoxic drive*** has been seen in patients with bilateral carotid body resection
• peripheral responses to increased P_{aCO2} are << those of the CNS
• the carotid, but ***not*** the aortic, bodies respond to increased $[H^+]$, both of respiratory and metabolic origins
• the various stimuli exhibit potentiation in their effects

O_2-Ventilation Response

• the O_2-ventilation response curve describes a rectangular hyperbola, with the point of inflection at ~ 50 mmHg, and the increase in minute ventilation asymptotical to ~ 30 mmHg
• some activity begins at P_{aO2} ~ 500 mmHg, with little response until the P_{aO2} < 100 mmHg and a marked response below 50-60 mmHg
• hence, some chemoreceptor cells are tonically active at the normal P_{aO2}
• the response is enhanced by increased P_{CO2}, conversely the normal hyperventilatory response to hypoxia is limited by concurrent hypocapnia and alkalosis
• the carotid and aortic bodies account for the increased ventilation and hypertension from acute hypoxia
• if hypoxia is severe or prolonged, additional and probably central mechanisms increase breathing, ie. a mild cerebral acidosis

• thus, ventilation is increased when breathing an, F_IO_2 < 10-12%
P_{aO2} < 40-50 mmHg
• TV increases first, then respiratory rate
• there is a wide range of individual response

CO_2-Ventilation Response

• a rise in local tissue P_{CO2}, due to an increased P_{aCO2}, leads to a reflex increase in ventilation
• however, a rise of 10-20 mmHg P_{CO2} is required
• the peripheral chemoreceptors are ***not*** required for the sensitive response of increased ventilation with increased P_{aCO2}
• however, they are important in mediating a rapid respiratory response to a large rise in P_{aCO2}

Hydrogen Ion - Ventilation Response

• increases in $[H^+]$ in arterial blood increase ventilation
• Kussmaul breathing in acidosis $\rightarrow$ deep, labored ventilation
• there is no change in ventilation until pH falls by 0.1 of a unit
• a pH decrease of 0.4 $\rightarrow$ 2-3 fold increase in ventilation
• that is, the peripheral chemoreceptors are relatively ***insensitive***

Respiratory Failure

• respiration is relatively unresponsive to CO_2 following continued hypercapnia
• respiration may then be "driven" by hypoxia, acting via peripheral chemoreceptors
• subsequent increases in F_IO_2 then lead to apnoea and CO_2 narcosis
• there is ***no*** adaptation to continued hypoxia
• peripheral chemoreceptors are therefore responsible for hyperventilation of chronic hypoxia at high altitude, or from cardio-pulmonary disease
• the peripheral chemoreceptors are also responsible for,

a. the hyperpnoea of CN^- poisoning
b. part of the hyperventilation associated with hypotension
c. the action of lobeline in stimulating breathing in new-born
d. pharmacological effects of lowest effective dose of nicotine

Central Chemosensitive Areas (CSA)

• situated near (beneath) the ventral surface of the ***medulla***, near the origins of the vagi and glossopharyngeal nerves
• these are anatomically separate from the respiratory centres, and are bathed in brain ECF, the composition of which is determined by CSF, blood flow and local metabolism
• of these, CSF is the most important due to the effects of the blood-brain barrier
• this is impermeable to both H^+ and HCO_3^-, however CO_2 diffuses readily and decreases pH_{CSF} within a few minutes, which subsequently increases ventilation
• increased P_{aCO2} also causes cerebral vasodilatation which enhances diffusion of CO_2 into the CSF and brain ECF

NB: normal pH_{CSF} ~ 7.32

• there is decreased buffer capability due to the low [protein], therefore, an increased P_{aCO2} causes a greater decrease in pH_{CSF}
• long term alterations of pH_{CSF} → compensatory changes in bicarbonate transport across BBB (24-48 Hrs)
• these occur more rapidly than alterations in renal acid excretion
• thus, patients with chronic lung disease and CO_2 retention may have normal pH_{CSF} and no compensatory hyperventilation
• consequently, pH_{CSF} is held within narrow limits by ventilatory responses, despite pH changes in arterial blood
• the response is limited however, by the associated fall in P_{aCO2},

a. acute acidosis → immediate increase in ventilation due to peripheral chemoreceptor stimulation
b. chronic acidosis → further increase in ventilation due to stimulation of central chemoreceptors (delay imposed by blood/CSF barrier)

NB: the reverse situation occurs on correction of acidosis

CO_2-Ventilation Response

- increasing $FiCO_2$ → increased TV, respiratory rate & minute ventilation
- P_{aCO2} is held within 3 mmHg of normal, though, may rise slightly more during sleep
- a marked linear increase in minute ventilation occurs over wide range
- as for hypoxia, there is individual variation in response,

$$\rightarrow \quad \sim 2.5 \text{ l / min / mmHg-}\delta P_{CO2}$$

- the response curve is usually drawn as respiratory minute volume vs. alveolar or arterial P_{CO2}
- the slope of the curve measures the ***sensitivity*** of the respiratory mechanism to CO_2
- changes are seen due to,

a. drugs - CNS / respiratory depressants → right shift
b. decreased P_{aO2} - left shift & increased slope
c. pH - increasing $[H^+]$ → left shift
d. temperature
e. plasma adrenaline levels
f. conscious state, ARAS activity

- another method of assessing respiratory drive is $\mathbf{P_{0.1}}$, the inspiratory driving pressure generated against a closed airway in the first 0.1 sec
- this is largely unaffected by the mechanical properties of the respiratory system, although it may be influenced by lung volume
- a reduction of arterial CO_2 is very effective in reducing the drive to respiration
- trained athletes and divers tend to have low sensitivities to CO_2
- the ventilatory response to CO_2 is also reduced if the work of breathing is increased
- this is seen in normal subjects breathing through narrow tubes, or in patients with CAL

▪ ***Threshold for CO_2***

- does not exist in conscious man
- apnoea does not follow the decreased P_{aCO2} from hyperventilation, possibly due to ARAS activity
- apnoea readily occurs with a fall in P_{aCO2} in anaesthetised man or animals

- ***Physiological Importance***

1. no longer need to assign the medullary centres with dual excitability to both chemical and neural stimuli
2. respiratory depressant drugs depress CSA rather than medullary respiratory centres, the later still being responsive to afferent nerve stimuli
3. explains the slow increase in ventilation when breathing a CO_2 mixture, and the slow return of ventilation to normal when inhalation stopped
4. explains the hyper and hypo-ventilation seen at times when blood gas analysis would lead to expectation of the opposite response, eg.
   i. continued hyperventilation after return to sea level after spending days to weeks at high altitude, or after continued hyperventilation on a ventilator
   ii. explains the relatively small rise in ventilation with non-respiratory acidosis, or the continued hyperventilation after correction of blood pH with HCO_3^- after sustained non-respiratory acidosis, eg. diabetic keto-acidosis
5. explains why chronic hypoxia produces a further increase in ventilation, compared with acute hypoxia at same P_{aO2}

Cerebral Blood Flow

• decrease in CBF, eg., from severe hypotension or a rise in ICP → ↑ ventilation
• increase in CBF, eg., vasopressor drugs → ↓ ventilation
** these are due to effects on local $[H^+]$ and P_{CO2}

Reflexes from the Lungs

• there are many types of respiratory reflexes from lungs, heart and great vessels

- ***Inflation Reflex Inhibito-Inspiratory Reflex (Hering-Breuer)***

• pulmonary stretch receptors are situated within smooth muscle of bronchi and bronchioles
• these produce sustained discharge on lung inflation (no adaptation)
• afferents travel in large myelinated fibres of the vagus to the medulla
• central pathways are only partly known,

→ decreased respiratory frequency due to increased expiratory time

• the receptors are stimulated by the ***rate*** as well as ***extent*** of inflation, and are sensitised by reduced compliance, such as with trilene
• stimulation leads to a decrease, or cessation, of inspiratory muscle activity
• the physiological role in man is unknown
• the reflex is largely inactive at tidal volumes less than 1.0 l
• it has been demonstrated that transient bilateral vagal blockade in awake man does not alter the rate or rhythm of respiration
• may possibly be of some importance in the newborn

- the reflex is, however, well-developed in animals in which it may be associated with,
    a. termination of inspiration
    b. tonic inhibition of the respiratory centres throughout the respiratory cycle
    eg. in breath holding experiments, the breath may be held longer if lung is inflated than if deflated
    c. regulation of the work of breathing

▪ ***Paradoxical Reflex of Head***

- lung inflation produces a paradoxical further increase in inspiration
- possibly related to the ***sigh*** mechanism
- seen with "triggering" of respiration under spontaneous ventilation during anaesthesia

▪ ***Deflation Reflex***

- opposite of the Hering-Breuer reflex
- lung deflation leads to increased frequency and force of respiratory effort
- possibly related to the sigh mechanism
- produces an increase in ventilation with a reduction in FRC below normal

▪ ***J-Receptors***

- ***"juxta-capillary" receptors***, believed to be the in alveolar walls, close to capillaries
- respond very quickly to chemicals injected into the ***pulmonary circulation***
- may also possibly respond to chemicals in ***alveolar air***
- impulses travel in slow, non-myelinated ***vagal fibres***,

    → rapid, shallow breathing (intense stimulation → apnoea)

- some evidence that pulmonary capillary engorgement and interstitial oedema may cause stimulation
- these may be responsible for the hyperpnoea and dyspnoea of CCF and interstitial lung disease

▪ ***Irritant Receptors***

- believed to reside between airway epithelial cells
- discharge in response to ***nociception***, impulses travel in myelinated vagal fibres,

    → bronchoconstriction and hyperpnoea

- these show rapid adaptation and are involved with mechanoreception

- ***Gamma Efferent System Reflexes From Respiratory Muscles***

• these provide information about the relationship between inspiratory volume change and required muscle effort
• ensure adequate inspiratory muscle activity for given ventilation, allowing stabilisation of ventilation even in the face of changing mechanical conditions
• probably determine the optimal combination of frequency and tidal volume required to achieve this ventilation with minimal effort (work of breathing)
• compared to healthy subjects, patients with restrictive lung disease breathe rapidly with relatively small tidal volumes, whilst those with obstructive lung disease breathe more slowly with large tidal volumes ** P/V curves !

- ***Carotid & Aortic Baroreceptors***

• ↑ BP → ↓ ventilation
• ↓ BP → ↑ ventilation

- ***Atrial & Venous Baroreceptors***

• ↑ CVP → ↑ ventilation
• ↓ CVP → ↓ ventilation

- ***Thoracic Chemoreflexes***

• producing bradycardia, hypotension, apnoea

- ***Reflexes From Somatic & Visceral Tissues***

• ventilation increases with stimulation of

a. temperature- cold water on skin
b. pain - surgical stimuli
c. mechanical - passive movements of joints/exercise

• probably acting via RAS, both in anaesthetised & non-anaesthetised subjects

ARAS & Higher CNS Control

- higher CNS control is involved in talking, singing, whistling, etc.

a. wakefulness & sleep
   - during sleep ventilation decreases → $\mathbf{P_{aCO2}}$ **~ 46 mmHg**
   - this may be involved in immediate awakening from sleep with respiratory obstruction

b. emotions
   - respiration affected by a variety of emotional states
   - eg., anticipation of physical activity, crying, anxiety depression

Hormones - Progesterone

- probably responsible for the hyperventilation of pregnancy
- in late pregnancy the mean P_{aCO2} ~ 32-34 mmHg
- however, the pH is normal due to decreased plasma [HCO_3^-]

MECHANICS OF RESPIRATION

- inspiration occurs when the alveolar pressure < atmospheric pressure, and may be due to,
    a. lowering alveolar pressure below atmospheric pressure,
        → negative pressure respiration
    b. raising atmospheric pressure above alveolar,
        → positive pressure respiration

- expiration occurs when the alveolar pressure > atmospheric

Normal Breathing

- commences with active contraction of inspiratory muscles, which,
    a. enlarges the thorax
    b. lowers intrathoracic and intrapleural pressures
    c. enlarges alveoli, bronchioles, bronchi
    d. lowers the alveolar pressure below atmospheric pressure

        → air flows from mouth and nose to alveoli

- inspiratory muscles provide the force necessary to overcome,
    a. ***elastic recoil*** of the lungs and chest wall
    b. ***frictional resistance***
        i. caused by deformation of lung tissue and thoracic cage
            = ***tissue resistance***
        ii. to air flow in the conducting airways
            = ***airway resistance***

Respiratory Muscles Inspiration

■ ***Diaphragm***

• innervated by the ***phrenic nerve***, from cervical segments $C_{3,4,5}$
• the principal muscle of inspiration → "piston-like" activity, causing,

a. enlargement of the thoracic cavity

b. elevation of ribs, especially when diaphragmatic descent is restricted

• in health, the visceral pleura slides easily over the parietal pleura, so descent of the diaphragm enlarges all lobes of lung
• during tidal breathing the diaphragm descends ~ 1.5 cm, and with forced inspiration ~ 10 cm
• unilateral paralysis produces little decrease in ventilatory capacity
• bilateral paralysis does not cause hypoventilation, but does produce paradoxical upward movement on inspiration
• with hyperinflation, eg. emphysema, the flattened diaphragm acts at a mechanical disadvantage
• the diaphragm still works when the abdominal contents are increased, as the diaphragm is centrally "fixed" under these conditions

■ ***External Intercostal Muscles***

• these slope downwards and forwards → elevation of ribs in upward, outward direction enlarging the A-P diameter of chest, in a "bucket-handle" fashion
• these also tense the intercostal spaces, preventing indrawing during descent of the diaphragm and enlargement of the thorax
• innervated by intercostal nerves from adjacent spinal levels

■ ***Accessory Muscles***

• active only in hyperpnoea or dyspnoea, when the minute volume is ≥ 40-50 l/min
• not normally active in tidal breathing
• scaleni, sternomastoid, posterior neck, trapezius and back muscles

→ help raise the thoracic cage

• muscles of the nose, mouth, and larynx act to reduce upper airway resistance
• maximum reduction in intrapleural pressure ~ 60-100 mmHg subatmospheric

Muscles of Expiration

• expiration normally occurs due to the elastic recoil of the pulmonary and thoracic tissues stretched during inspiration
• with hyperpnoea or dyspnoea, especially from airways obstruction, expiratory muscles contract actively ($V_M \geq 40$ l/min)
• they are also active during coughing, straining, vomiting, etc.

■ *Abdominal Muscles*

• these are the most important of the expiratory muscles (Nunn)
• they act to force the diaphragm upward and depress the lower ribs

■ *Internal Intercostal Muscles*

• these tense the intercostal spaces during coughing, straining etc.
• depress the ribs in downward & inward in direction

NB: the diaphragm is active during in early expiration, allowing a smoother transition from inspiration to expiration

• vigorous contraction of the expiratory muscles can produce intrapleural pressure,

i. sustained rise ~ 100 mmHg
ii. transient rise ~ 300 mmHg

Effects of Anaesthesia

• with deep anaesthesia a pattern of "abdominal", or "diaphragmatic" respiration develops
• this used to be thought due to intercostal muscle paralysis, however, intercostal muscle activity is maintained
• Nunn talks about the relative loss of intercostal activity being responsible for both,

a. diaphragmatic respiration, and
b. loss of the ventilatory response to CO_2

• the later being predominantly mediated by intercostal activity
• "abdominal" breathing is usually associated with a short duration of inspiration, in which a sharp descent of the diaphragm results is a sharp drop in intrathoracic pressure, and the chest wall is indrawn or fails to expand normally
• a similar situation is seen with respiratory obstruction
• expiratory muscle activity occurs regularly during anaesthesia, with or without an endotracheal tube or pharyngeal airway, especially during light anaesthesia

Resistance to Breathing

1. Elastic resistance **~ 65%**
2. Non-elastic resistance **~ 35%**
   - i. Airflow ~ 80%
   - ii. Viscous ~ 20%

Elastic Resistance to Breathing

▪ *Elastic Recoil of the Lungs*

• the tendency of elastic lung tissue to recoil from the chest wall results in a sub-atmospheric intrapleural pressure
• at FRC, the mean intrapleural pressure ~ 4-5 cmH_20 sub-atmospheric
• the intrapleural pressure is normally estimated by an oesophageal balloon catheter
• this is more accurate in measuring changes rather than absolute pressure, due to interference from the weight of the heart

▪ *Compliance*

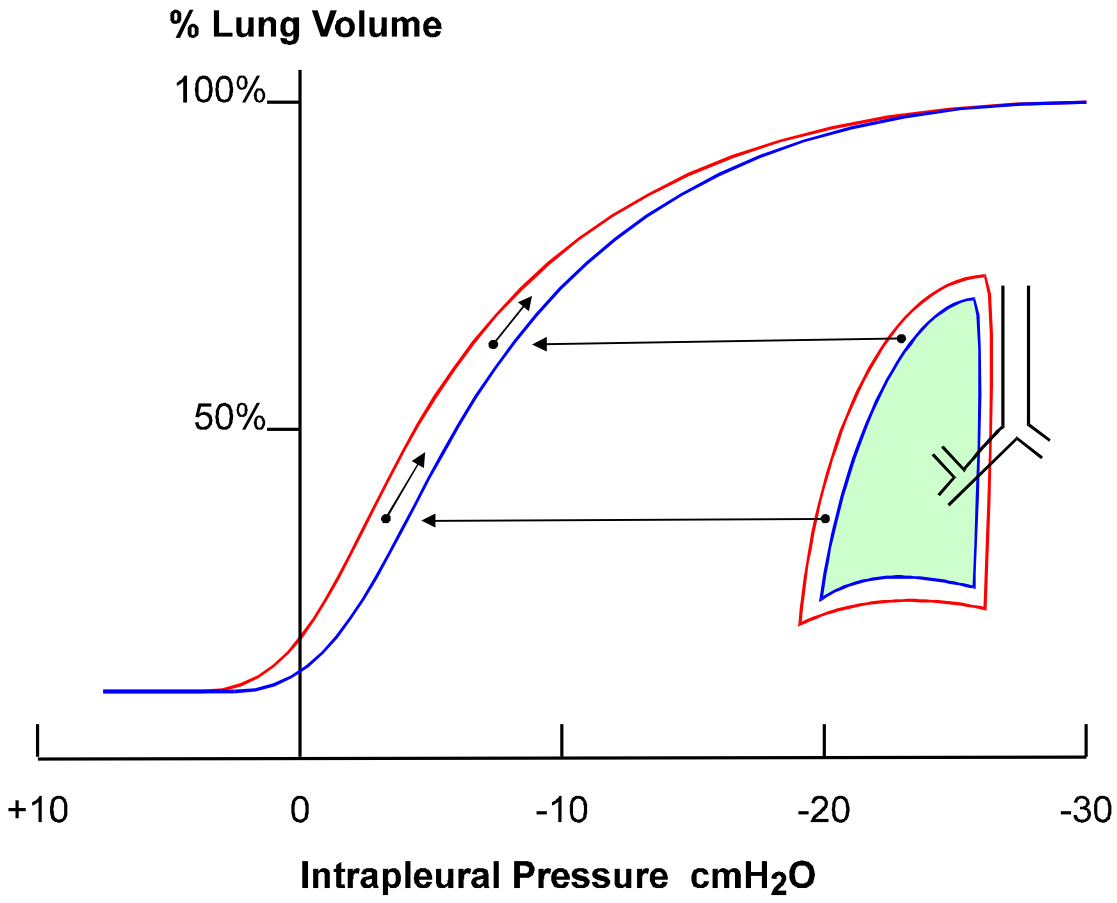
• is a measure of the elasticity, or distensibility, of pulmonary or thoracic tissues
• for an elastic body, this is given by the relation between the distending force and length
• for the lung, this is given by the relationship of pressure and volume
• this may be measured under ***static*** conditions, ie. zero air flow, or under ***dynamic*** conditions
• the units of compliance are $\delta V/\delta P$ = litres/cmH_20

▪ *Respiratory Pressures*

1. Transrespiratory Pressure $P_{RS} = P_A - P_B$
2. Transpulmonary Pressure $P_L = P_A - P_{IP}$
3. Transthoracic Pressure $P_{CW} = P_{IP} - P_B$

Static Lung Compliance

- the relationship between volume change of lung and the transpulmonary pressure change, i.e., ***airway - intrapleural pressure change***, measured under known static conditions (zero airflow)
- the normal value for a 70 kg adult ~ **200 ml/cmH_20**
- the value decreases as lung volume increases, due to the limitations of the non-elastic components of the lung/chest wall system
- static P/V curves for the lung → ***sigmoid*** curve with varying degrees of ***hysteresis***, with the volume at any given pressure being greater during deflation (see below)
- the P/V curve doesn't reach zero volume due to trapping of gas in small airways
- this occurs at a greater volume with increasing age and lung disease



- the varying slope of the curve, and the differential intrapleural pressure down the lung is also partially responsible for the differential ventilation of various lung segments

• compliance is directly related to lung volume, a 1.0 cmH_20 increase in transpulmonary pressure will inflate,

a. two lungs by 0.2 l

b. one lung by 0.1 l

• the ***absolute compliance*** of the lung of a neonate ~ 0.006 l/cmH_20
• however, the ***specific compliance*** ~ 0.067 $l/cmH_20/l.V_L$
• the later being identical to an adult
• ***specific compliance*** is a true measure of the elasticity of lung tissue, defined as,

$$C_S = \frac{\text{Lung Compliance}}{\text{Lung Volume}} = (\delta V/\delta P)/V$$

$$= \frac{\text{Lung Compliance}}{\text{FRC}}$$

• a change in posture, from sitting to the supine position, with a decrease in FRC, will reduce the absolute static compliance but not specific compliance
• in comparison, interstitial fibrosis will reduce specific lung compliance

■ ***Measurement***

• the patient takes a breath from a spirometer and holds it until the transpulmonary pressure difference becomes stable
• this is repeated with different tidal volumes to produce a pressure/volume curve, where

Compliance = the slope of the pressure/volume curve

• this can also be done with the patient apnoeic using PPV
• the patient is inflated with known volumes of gas and the transpulmonary pressure change determined at equilibrium
• this is taken as the mouth - oesophageal balloon gradient

- ***Factors Affecting Static Compliance***

a. FRC ↑ FRC → ↑ C_L
- age
- body size
- posture

b. lung volume ↓ V_L → ↓ C_L
- lobar, lung resection
- collapse or consolidation
- diffuse atelectasis

c. lung elasticity
- increased lung elasticity, eg. emphysema* (see below)
- decreased lung elasticity, eg. pulmonary oedema, congestion, fibrosis

NB: Nunn lists 7 factors,

1. lung volume - the bigger the lungs the larger the compliance
2. posture - due to changes in lung volumes
   - does not affect specific compliance
3. pulmonary blood volume
   - pulmonary venous congestion from any cause will decrease the compliance
4. age
   - many studies have failed to demonstrate any change in compliance when allowing for changes in lung volumes
   - this is consistent with the notion that most of the elastic recoil is due to surface forces
5. restriction of chest expansion
   - causes only temporary changes in compliance
6. recent ventilatory history
7. disease

- ***emphysema*** is unique in that static C_L is increased
- destruction of pulmonary tissue and loss of both elastin and surface retraction increases FRC
- however, the distribution of inspired gas may be grossly abnormal, therefore the dynamic C_L is frequently reduced

- in ***asthma***, the P/V curve is simply displaced upwards without a change in C_L
- the elastic recoil is reduced at normal transmural pressure, thus the FRC is increased
- most other types of pulmonary disease decrease the C_L, both static & dynamic

Dynamic Lung Compliance

- airflow is zero at the point of flow reversal during the normal respiratory cycle
- measurements of lung compliance made using these points reflect dynamic compliance
- in normal lungs at low and moderate frequencies, dynamic and static lung compliance are about the same value
- however, at higher frequencies in normal lungs, and at normal frequencies in abnormal lungs, dynamic compliance is ***less than*** static compliance
- this is due to incomplete filling of alveoli in the time available
- true pressure equilibrium between applied pressure and alveolar pressure is not obtained, and the lung appears to be stiffer than it actually is
- the time to fill an alveolus depends on the product of ***airway resistance*** and the ***compliance*** of the alveolus = the exponential ***time constant***
- the higher the airway resistance, or regional lung compliance, the longer a given alveolus will take to fill
- slow alveoli will not fill in the time available, especially in emphysema

- taken from the slope of the transpulmonary pressure/volume loops recorded during tidal ventilation
- using a differential pressure transducer, from an oesophageal balloon to the airway, and a pneumotachograph
- the ***pneumotachograph*** measures instantaneous flow, however, this may be electronically integrated over time to give volume
- thus, the pressure difference at the no flow points of the P/V loop can be established

Factors Affecting Dynamic Compliance

- decreased dynamic lung compliance is seen especially with increased airways resistance, eg. asthma, chronic bronchitis and emphysema
- this is principally due to the prolonged time constants
- emphysema increases specific lung compliance but, due to its effect on the time constant,

$$\tau\,(\text{tau}) = C_L \times R_A$$

produces the phenomenon of ***frequency dependent compliance***

- dynamic C_L decreases as the respiratory frequency increases, as slower alveoli fail to fill
- numerically, the ***time constant*** is the time which would be taken to reach 63% of the final δV
- stated another way, the time which would be taken to full volume change, if the initial rate of change of volume ($\delta V/\delta t$), were maintained

Surface Forces and Lung Recoil

- elastic lung recoil is dependent on,
    a. ***surface tension*** → produces > 50% of normal lung recoil
    b. tissue elastic fibres

- filling the lung with fluid eliminates the liquid/gas interface and allow assessment of the tissue factors
- the recoil pressure of a saline filled lung is lower, determined only by the elastic recoil of pulmonary tissue → ***tissue recoil ~ 20%***
- ***surface tension*** is the force in dynes acting on an imaginary line 1.0 cm long within the liquid surface (dynes/cm, SI units = N/m)
- as the intermolecular forces between liquid molecules are greater within the liquid than at the liquid/air interface,

fluids → minimum surface area possible

- for liquid spheres, using ***Laplace's Law***,

$P = 4 \times T_s/r$ where T_s is ***surface tension***

- however, the liquid lined alveoli have only 1 liquid/air interface, therefore,

$$P = 2T_s/r$$

- surface active agents exert smaller attracting forces for other molecules
- therefore, when concentrated at the surface they dilute the molecules of the liquid and hence lower its surface tension

NB: Laplace's' Law actually states: $P = T(1/r_1 + 1/r_2)$

Pulmonary Surfactant

• all alveoli experience some transpulmonary pressure regardless, of their size
• Laplace's law would suggest that small alveoli should tend to empty into large alveoli and collapse, however, this does not occur!
• pulmonary surfactant in the alveolar lining fluid alters the surface tension as alveolar volume changes
• ***dipalmitoyl phosphatidyl choline*** (DPPC), a phospholipid, is the main component
• synthesised in ***type II alveolar cells***, granular pneumocytes
• the elimination half life, t½ ~ 14 hrs
• ordinary detergents lower the surface tension, but surface tension does not alter with changes in the area of the surface
• with pulmonary surfactant, as the surface area decreases, so surface tension also decreases
• conversely, an increase in surface area leads to an increase in surface tension (see West 7.7)
• DPPC has hydrophilic and hydrophobic ends, therefore forms a ***lipid monolayer***
• as the area of the surface decreases, the $[DPPC]_s$ increases, and due to repulsive forces between molecules decreases the surface tension
• these curves differ during contraction and expansion of the liquid surface, contributing to the observed hysteresis of the P/V loops
• this is probably the major factor in the hysteresis seen in static P/V loops

• alveoli are also held patent by ***tissue interdependence***, due to the expansive forces of surrounding alveoli
• due to the weight of lung tissue, P_{IP} is more negative at apices and alveoli are more expanded,

a. apices ~ - 10.0 cmH_2O
b. bases ~ - 2.5 cmH_2O
c. mean value ~ - 4.0 to 5.0 cmH_2O

• therefore, different portions of the lung reside on different portions of the P/V curve and have different compliances
• this is the cause of the greater ventilation of the bases during tidal respiration, the apices residing on the stiffer "shoulder" of curve are less compliant
• at very low volumes, the apex may be better ventilated due to decreases in C_L at low lung volumes and small airways closure

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NB: these theories regarding alveoli and surfactant are attractive, however, Hills (1982) displayed that alveoli are dry, with surfactant acting as a "wetting agent", thus contradicting much of the above theory

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- ***Physiological Importance of Pulmonary Surfactant***

a. reduces T_s in alveoli
   - cf. water or plasma, reducing lung recoil and the work of breathing

b. stabilises alveoli of variable size
   - as surface tension is proportional to surface area
   - preventing small alveoli tending to "fill" larger ones

c. promotes alveolar dryness
   - a high T_s tending to draw fluid into alveoli as well as promoting collapse

NB: Deficiency of Surfactant → decreased compliance
segmental atelectasis
pulmonary oedema
V/Q imbalance

- interference with production, or increased inactivation occurs with,

a. IRDS of new-born

b. pulmonary lavage

c. hyperoxia - O_2 toxicity of lung

d. pulmonary oedema, atelectasis, embolism

e. hypoxia, acidosis

f. gross overdistension of alveoli

g. ARDS

- other factors preventing collapse of alveoli include,

a. tissue interdependence

b. collateral ventilation

c. the "sigh" mechanism → ~ 2-3 × tidal V

Elastic Recoil of the Thoracic Cage

• resting volume for thoracic cage ~ FRC + 600-700 ml
• thoracic cage compliance is calculated from total compliance of the thoracic cage + the lungs, and from pulmonary compliance when measured simultaneously, where,

$$1/C_{TOT} = 1/C_L + 1/C_{CW}$$

- ***Normal Values***

1. Total thoracic compliance C_{TOT} ~ 0.1 l/cmH_20
   ($\delta P = P_A - P_B$) ~ 85 ml/cmH_2O*
2. Compliance of lung C_L ~ 0.2 l/cmH_20
   ($\delta P = P_A - P_{IP}$) ~ 150 ml/cmH_2O*
3. Compliance of chest wall C_{CW} ~ 0.2 l/cmH_20
   ~ 200 ml/cmH_2O*

NB: * figures are from Nunn, anaesthetised patient, supine, IPPV

• total thoracic compliance is calculated from the volume change in relation to the ***transrespiratory*** pressure change → $\delta P_R = P_A - P_B$
• compliance of the thoracic cage may be measured directly using the ***transmural*** pressure change
→ $\delta P_{CW} = P_{IP} - P_B$

• thoracic cage compliance is decreased in,

a. kyphoscoliosis
b. scleroderma
c. muscle spasticity
d. abdominal distension, obesity - especially when supine

• chest wall elastic recoil is outward at FRC, FRC being the equilibrium point of the recoil forces of both systems, therefore,

1. V_L > FRC → expiration passive
2. V_L < FRC → inspiration passive

• this is not quite true, as FRC is 400-500 ml ***above*** the equilibrium point due to the tonic activity of the diaphragm
• since the pressure, at any given volume, is inversely proportional to the compliance, so the total compliance of the lung and chest wall must be the sum of the ***reciprocals*** of each system measured separately,

$$1/C_T = 1/C_L + 1/C_{CW} \qquad (C \propto 1/R)$$

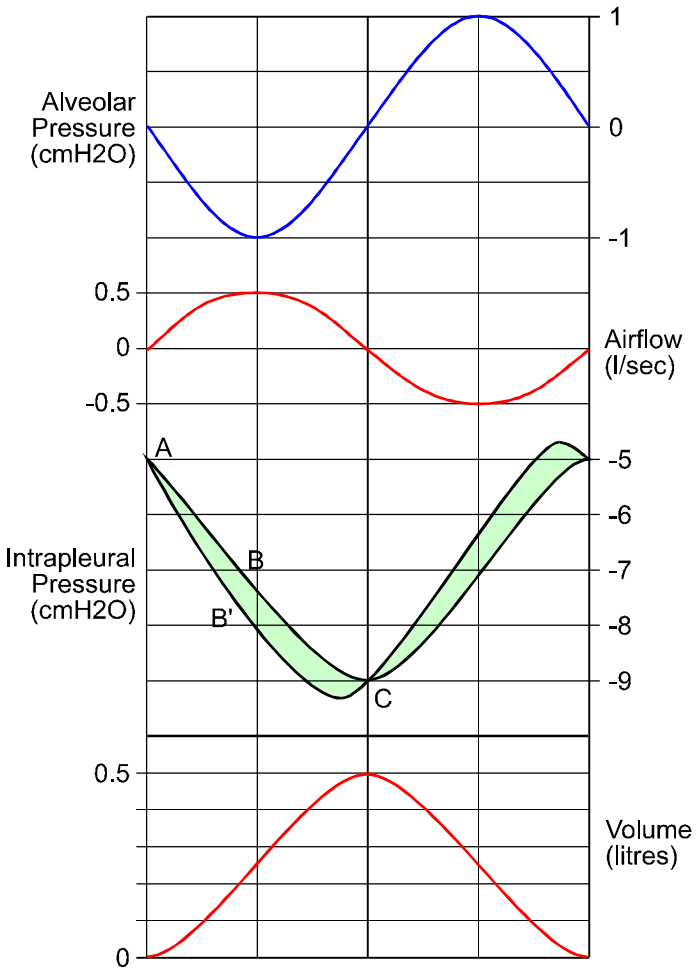
Non-Elastic Resistance to Breathing

- this is composed of,
  a. airway ***flow resistance*** **~ 80%**
  b. pulmonary tissue resistance, or ***viscous resistance*** **~ 20%**

■ ***Resistance to Air Flow***

- the work of breathing during tidal respiration,
  a. elastic recoil of lungs and thorax ~ 65%
  b. airway and tissue resistance ~ 35%

- the work to overcome non-elastic resistance increases markedly with rapid respiration, or narrowing of the airways
- during airflow, the pressure to produce a unit increase in lung volume is greater than when there is no flow (see below)
- the pressure required to produce a given airflow depends upon whether the flow is ***laminar***, or ***turbulent***



Respiratory Cycle Pressures

If airway resistance were zero;

- there would be no mouth-to-alveolar gradient and alveolar pressure would remain zero

- intrapleural pressure would be determined by ***elastic resistance*** alone, and would follow the line ABC; the shaded area representing the added pressure to overcome airflow resistance

Note the diagram in West (7.13) is slightly inaccurate, as it indicates that for a given tidal volume, peak intrapleural pressure would be the same with or without added airflow resistance.

- ***Laminar Flow***

$$\dot{Q} = \frac{\pi r^4 . \delta P}{8 \eta l}$$

where	r	=	radius of a tube
	l	=	length of the tube
	(P_1-P_2)	=	the pressure gradient (δP)
	η	=	gas viscosity

- since resistance, R = δP/V, by rearrangement,

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

- therefore, if the radius is halved, resistance to flow increases ~ 16 times!
- laminar flow → ***velocity profile***, where the velocity at the center ~ twice the average velocity
- other factors remaining constant, flow rate is directly proportional to the driving pressure,

$$\delta P = K_1 \times V$$

Turbulent Flow

• the likelihood of flow becoming turbulent is predicted by the,

Reynold's Number $(Re) = \frac{\rho v d}{\eta}$

• the gas ***viscosity*** (η-eta) becomes relatively less important, c.f. ***density*** (ρ-rho) which decreases flow proportionately
• the viscosities of respirable gasses do not vary greatly, however their densities may vary considerably
• when **Re > 2000**, turbulent flow becomes increasingly more likely, and the driving pressure becomes proportional to the ***square*** of the flow rate,

$\delta P = K_2 \times V^2$ the constant K_2 incorporating gas density

• theoretically, the required driving pressure becomes inversely proportional to the fifth power of the tube radius (***Fanning equation***)
• Nunn states when Re < 1000 flow is laminar and when Re > 1500 flow is almost entirely turbulent
• with both laminar and turbulent flow, the driving pressure becomes proportional to both the rate of flow and to its square

• quantification represents only an approximate statement for airway resistance
• methods of approximation of airway resistance include,

1. the two constants method $\delta P = K1.V + K_2.V^2$
   $\sim 2.4 \times V + 0.3 \times V^2$
2. the exponent n, where (1 < n < 2) $\delta P = K.V^n$
   $\sim 2.4 \times V^{1.3}$ cmH_2O

• another approach is the graphical method, where δP is plotted against log V, and the slope of the line indicates the value of "n" above

- ***Turbulent Flow***

• the conditions of flow at the entrance to tube are also important, ***eddies*** being carried distally
• branching points with different airway ***impedances*** also disrupts laminar flow, due to ***reflection*** of the pressure wavefront
• airways are not smooth, cylindrical, rigid tubes
• the upper airway has two irregular nasal passages in parallel, followed by the pharynx, larynx and trachea in series
• the net effect is such that flow probably only becomes laminar in the small terminal bronchioles, where Re ~ 1
• for the majority of the bronchial tree, flow → ***transitional***
• as airways become smaller, the total resistance would rise tremendously except for bronchiolar subdivision,

a. as each bronchiole divides into two the subdivisions have only a slightly smaller radius than the parent airway, and are also shorter in length

b. the gas flow rate decreases with each subdivision

• gas flow is largely laminar during quiet breathing
• increased flow rates readily produce turbulence in the larynx, trachea, pharynx and major bronchi

Measurement of Airway Resistance

- normal value for a healthy adult **~ 0.5-1.5 $cmH_20/l/s$**
  - body plethysmograph
  - at 0.5 l/s flow rate (quiet breathing)

- another source → 1.0-3.0 $cmH_2O/l/s$
- 50 to 75% of this is in the nose (less resistance through mouth)
- most of the remaining resistance in larynx and bronchial tree

■ ***Airway Resistance***

- as $R = \delta P/\delta V$, simultaneously measure the rate of air flow and the alveolar-to-mouth pressure gradient,

$$R_{AW} = \frac{\text{mouth - alveolar pressure}}{\text{flow } (\delta V)}$$

- alveolar pressure is measured in a ***body plethysmograph***
- making use of Boyle's Law relating pressure and volume of gases to measure alveolar pressure directly during inspiration and expiration
- in normal tidal breathing $\delta P \sim 1.0\ cmH_2O$ but may be much higher in patients with obstructive airways disease
- thus, during tidal breathing,

i.	δP	~ 1.0 cmH_2O
ii.	$\delta V/\delta t$	~ 0.5 l/s
iii.	R_{AW}	~ 2.0 $cmH_2O/l/s$

■ ***Non-Elastic Resistance***

$$R_{NE} = \frac{\text{mouth - intrapleural pressure}}{\text{flow } (\delta V)}$$

- effectively, $(P_M\text{-}P_{IP}) = (P_M\text{-}P_A) + (P_A\text{-}P_{IP})$, where $(P_A\text{-}P_{IP})$ is represented by the shaded portion of fig. 7.13
- a differential pressure transducer instantaneously measures $P_M\text{-}P_{IP}$ gradient
- a pneumotachograph measures the instantaneous flow rate, which may be integrated to give respired volumes
- at points of ***zero flow***, the pressure gradient is opposed only by elastic forces
- it is then possible to construct the dotted line in the pressure trace, representing the pressure gradient to overcome elastic forces alone
- the difference between this and the observed pressure gradient (shaded zone) is the flow resistance component (Nunn fig. 3.15)
- the total non-elastic resistance = ***airway resistance + tissue resistance***, where,

i.	airway resistance	~ 80%
ii.	pulmonary tissue resistance	~ 20%

Factors Affecting Airway Resistance

- ***Aetiology of Small Airway Obstruction***

  a. constriction of bronchiolar smooth muscle
  b. mucosal congestion, inflammation
  c. oedema of bronchiolar tissues
  d. plugging of the lumen by mucus, oedema fluid, exudate, or foreign bodies
  e. cohesion of mucosal surfaces by surface tension forces
  f. infiltration, compression, or fibrosis of bronchioles
  g. collapse, or kinking of bronchioles due to loss of normal traction by alveolar elastic fibres, or to loss of structural, supporting tissues (cartilage) of bronchi

  NB: physical, nervous and chemical factors influence airway size and therefore resistance,

- ***Physical Factors***

  1. lung volume
  2. closing volume
  3. respiratory cycle - inspiration versus expiration
  4. forced expiration
  5. coughing
  6. fixed obstructive lesions

- ***Nervous Factors***

  1. cholinergic
  2. adrenergic
  3. non-cholinergic - nonadrenergic

- ***Chemical Factors***

  a. endogenous - CA's, histamine, 5HT, bradykinin
  b. exogenous - sympathomimetics, anticholinergics, steroids
     - irritant chemicals, particulates

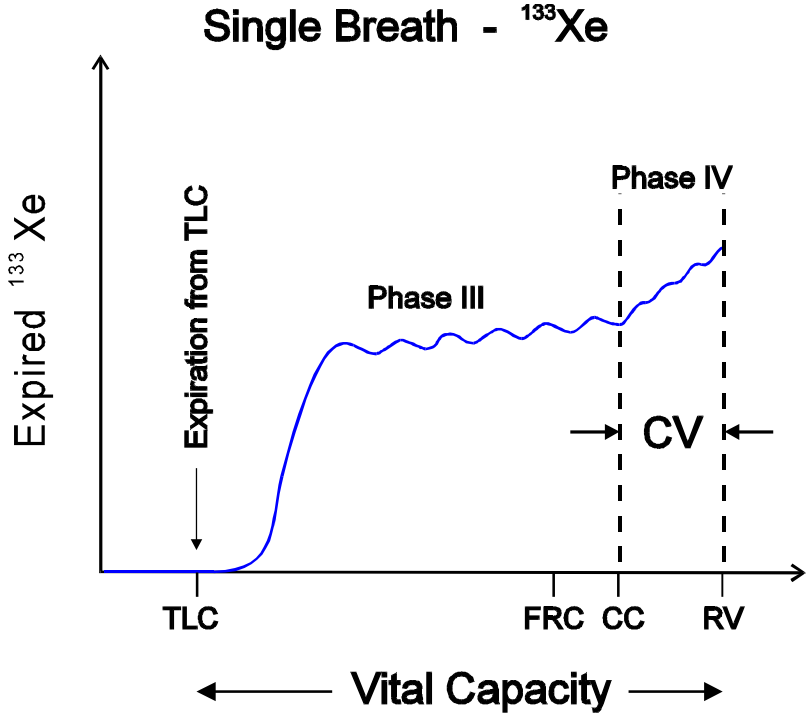
■ ***Physical Factors***

- airway resistance decreases as lung ***volume*** is increased
- increased stretch of elastic fibres causes distension of the small airways, widening their lumen
- a decrease in lung volume narrows airways, increasing airways resistance
- this effect is maximal in the dependent parts of lung due to the weight of supported lung tissue
- small airway closure and V/Q imbalance may follow

Def'n: ***closing volume*** is that volume in which closure of dependent airways begins, or the volume in which dependent lung units cease to contribute to expired gas, ie.,the beginning of ***phase IV*** of the washout curve to RV

normal values ~ 15-20% of VC, ie. a part of the VC manoeuvre

this is distinct from ***closing capacity***, which is the difference between the onset of ***phase IV*** and zero lung volume = CV + RV, expressed at a % of TLC



- measured by either a ***bolus*** or ***resident gas*** technique

1. ***bolus technique***
   - originally xenon or argon, usually now ***helium***
   - inspiration from RV to TLC creating differential tracer gas composition
   - as dependent portions of lung have "closed units", the inspired tracer is preferentially distributed to the apical segments

     → apical areas contain more tracer gas cf. bases
   - during slow controlled expiration, as dependent units again start to close, the expired concentration of tracer gas rises abruptly (see above)

2. ***resident gas technique***
   - as for the above, depends upon a pre-expiration concentration gradient
   - however there is normally little difference in $[N_2]$ between apex & base at TLC
   - therefore, inspiration of **100% O_2** is used to dilute the already present N_2

     → apex to base concentration difference **~ 2x**
   - the $[N_2]_{Exp.}$ is then plotted against expired volume, and with the onset of dependent lung closure, the $[N_2]_{Exp.}$ ***decreases*** (Anthonisen *et al.* 1969)

NB: may result in smaller values cf. the bolus technique in the presence of asthma or bronchoconstriction, probably due to air trapping (??)

- as CV represents a portion of the VC manoeuvre, it is usually expressed as a percentage of such
- expiration must be performed slowly to prevent ***dynamic*** airways collapse, ~ 0.5 l/sec
- changes in CV may represent small airways disease, or loss of elastic recoil and parenchymal supportive tissue
- with advancing age there is an increased tendency toward airway closure, with an increase in closing volume, Nunn

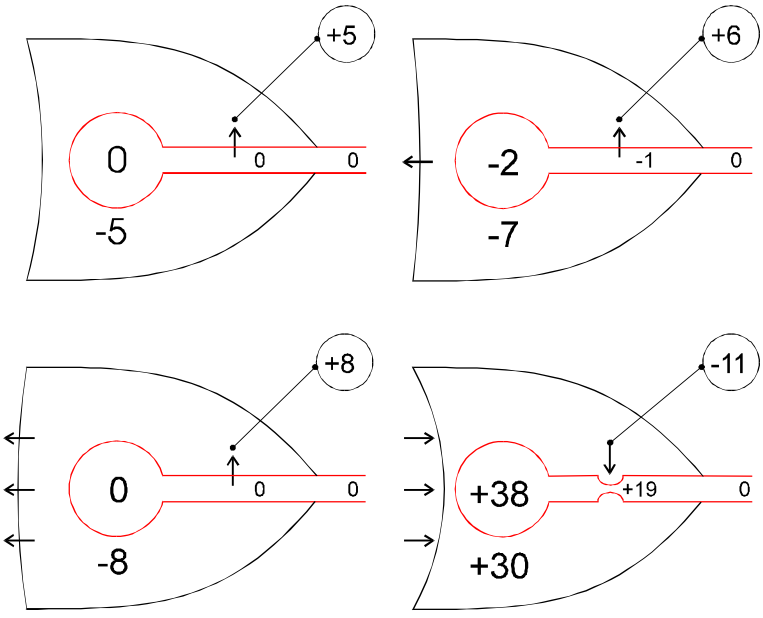
a. at ~ 65 years → CV ~ FRC ***erect***

b. at ~ 45 years → CV ~ FRC ***supine***

- presumably this is due to a progressive decrease in lung elastic recoil
- this contributes to the decrease in P_{aO2} with advancing age (maximal in supine position)
- young children similarly have decreased elastic recoil & relatively increased CC's

  → minimal values for CV/CC are seen in late the late ***second decade***
- CV is a sensitive marker of early dysfunction, but difficulty defining normal limits

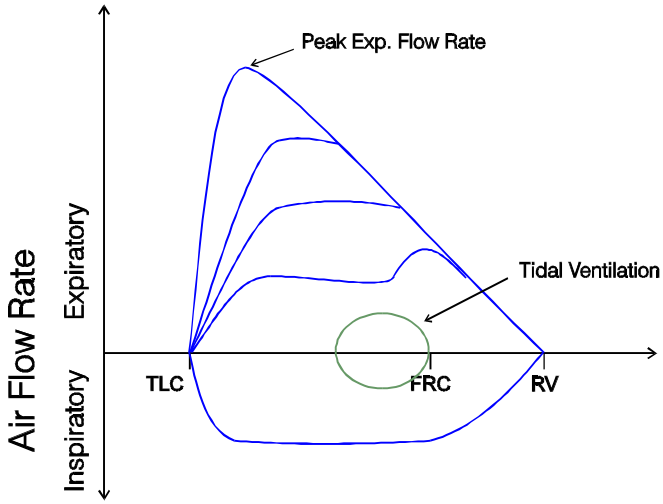
- ***respiratory cycle*** → resistance is less during inspiration than during expiration
- airways widen and lengthen during inspiration / narrow and shorten during expiration
- changes in ***diameter*** are of greater significance, cf. changes in length
- however, these changes are not significant with quiet breathing



- ***forced expiration*** results in flaccid airways collapse when the pressure outside their walls exceeds the intraluminal pressure

- intrapleural pressure is applied to alveoli, bronchioles and bronchi
- the air pressure in bronchioles is less than that in alveoli, due to the pressure drop along the airway secondary to flow resistance

• when this pressure drop is great, due to increased airways resistance or forced expiration, and when there is reduced elastic recoil, as with age/emphysema, the extramural pressure can exceed intraluminal pressure and airway collapse occurs
• greater effort ***cannot*** increase flow under these conditions, the greater pressure gradient simply shifting the point of collapse closer to the alveoli



• thus, ***flow-volume curves*** → an ***envelope*** which cannot be exceeded irrespective of driving pressure (opposite)
• within limits the PEFR is dependent upon effort, but the later portions of the curve approach an identical ***effort-independent*** part

• isovolume pressure flow curves show ***effort independent flow*** at low and mid lung volumes (see West 7.17)
• under these conditions driving pressure becomes (P_A - P_{IP}), not (P_A - P_B), similar to the ***Starling resistor*** mechanism limiting blood flow in Zone 2

• as P_{IP} is increased, the driving pressure is unaltered, the point of ***airway collapse*** merely moves closer to alveoli
• bronchioles are, in general, the most collapsible as,

a. their size depends upon elastic fibres of the lung radially distending their walls, and
b. they have no cartilaginous support

• in chronic bronchitis large bronchi may lose cartilage and collapse readily during forced expiration
• once collapsed additional force is needed to open airways
• ***flow limitation*** is increased by,

a. low lung volumes → decreased (P_A - P_{IP})
b. increased lung compliance → decreased (P_A - P_{IP})
   • eg. emphysema
c. increased airways resistance → increased δP

▪ ***Coughing***

• forced expiratory effort against a closed glottis
• the glottis then opens suddenly with rapid expulsion of gas producing very high expiratory flow
• this is coupled with tracheal narrowing and inversion of the non-cartilaginous part of intrathoracic trachea

▪ ***Nervous Factors***

• the ***parasympathetic*** nervous system is of major importance in the control of bronchomotor tone
• ***afferents*** arise from receptors under the tight junctions of the bronchial epithelium and pass centrally in the ***vagus***
• these respond to a wide variety of noxious stimuli
• ***histamine*** sensitises these endings, in addition to its direct effects
• ***efferent*** fibres run in the vagus and terminate on ganglia located in the walls of the small bronchi
• short postganglionic fibres release **ACh**, which acts on ***muscarinic receptors*** on smooth muscle
• smooth muscle is present in the trachea, bronchi, and alveolar ducts
• some degree of resting tone is usually present
• airways constrict reflexly with,

a. inhalation of smoke, dust, chemical irritants
b. arterial hypercapnia - cf. alveolar hypocapnia ?CNS/PNS
c. cold
d. pulmonary emboli

• airways dilated reflexly,

a. during inspiration
b. arterial hypertension - carotid sinus reflex

• the ***sympathetic*** nervous system is poorly represented in the lung and its functional significance questioned
• bronchial smooth muscle has b_2 ***receptors*** on which NA has little effect

NB: β-blockers cause minimal constriction in normal subjects,
however may cause marked bronchospasm in asthmatics

• in addition, there is a ***non-adrenergic non-cholinergic*** system also running in the vagus nerve
• the neurotransmitter is probably ***VIP*** (28 AA)
• stimulation of these fibres, or the administration of VIP results in prolonged dilatation but the significance is uncertain
• other neurotransmitters present include,

a. PHI - peptide histidine isoleucine (27 AA)
b. substance P - (11 AA)
c. CGRP - calcitonin gene related peptide

Chemical Factors

- isoprenaline, adrenaline, salbutamol, and other β_2-adrenergic agonists cause bronchodilatation
- β_2 adrenergic antagonists, acetylcholine, and anticholinesterases cause bronchoconstriction
- histamine (**H_1**) constricts bronchioles and alveolar duct sphincters
- alveolar hypocapnia causes regional bronchoconstriction, thereby tending to correct V/Q imbalance resulting from regional decreases in perfusion

Effects of Increased Airways Resistance

1. lung hyper-inflation → increased FRC and residual volume
2. dyspnoea
3. decrease in respiratory rate
4. mechanical disadvantage of respiratory muscles
5. prolongation of the time constant → V/Q mismatch

- the differential diagnosis of types of increased airway resistance,
  a. increased airway resistance in expiration only → airway collapse
  b. airway obstruction rapidly reversed by therapy → bronchoconstriction, ±
     i. mucosal congestion, oedema
     ii. mucus, exudate, etc., in the lumen

Pulmonary Tissue Viscous Resistance

- due mainly to the movement of pleural layers between lobes, and between the lungs and chest wall during inspiration & expiration
- accounts for < 20% of the total non-elastic resistance in health
- increased in ***pulmonary fibrosis***, carcinomatosis, etc., but rarely to significant or limiting values
- measurements of thoracic cage viscous resistance, rib cage & abdominal contents, is difficult
- there is also the inertia of lung/thorax system and the air mass, however, this is very small

WORK OF BREATHING

Def'n: mechanical work of breathing = **F** × ***s*** (Force × distance)
= **P** × **V** (Pressure × Volume)

thus, the work of breathing = the cumulative product of ***pressure*** × ***volume*** of air moved each instant,

= $\int P.dV/dt$

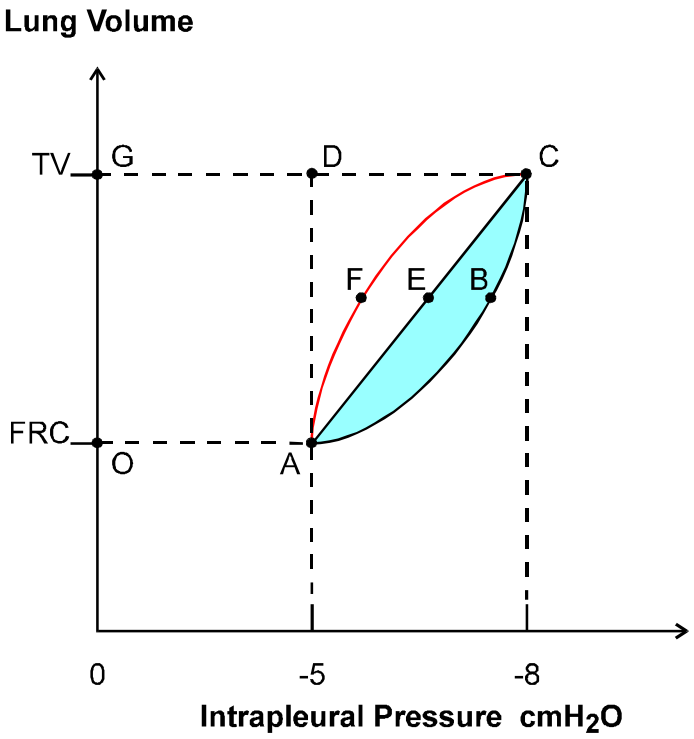
• this is required to overcome,

1. ***elastic*** resistance ~ 65%
2. ***non-elastic*** resistance ~ 35% → 80% airflow
   20% viscous

• frequently expressed in ***Watts***, which is in fact work/time, hence the correct term should be the ***power*** of breathing, viz.

$$Work = \int_0^t \delta V.\delta P\, dt$$

~ 0.5 l × 3.0 cmH_2O
~ 0.5 l × 0.3 kPa
~ **150 mJ**



• West (fig. 7.20) describes the ***total work*** required to move the lung as OABCGO
• with the work to overcome ***elastic resistance*** given by the trapezoid OAECGO
• the difference between these representing the ***non-elastic resistance***, given by the shaded area ABCEA
• ***NB:*** this is ***not*** the work of "breathing", as some work is performed by the stored elastic potential energy of the thoracic cage, (see Ganong fig. 34-9 and below)
• the true ***work of inspiration*** is given by **ABCDA**, with the elastic component being AECDA

• as airway resistance, or inspiratory flow rate is increased, so would δP_{IP}, effectively sloping the curve to right, increasing total and viscous work
• on expiration, the work to overcome non-elastic forces (AECFA), falls within work trapezoid and can be accomplished with the stored energy in elastic structures

• the difference between AECDA - AECFA represents the energy expenditure with which no external work is done → ***heat***

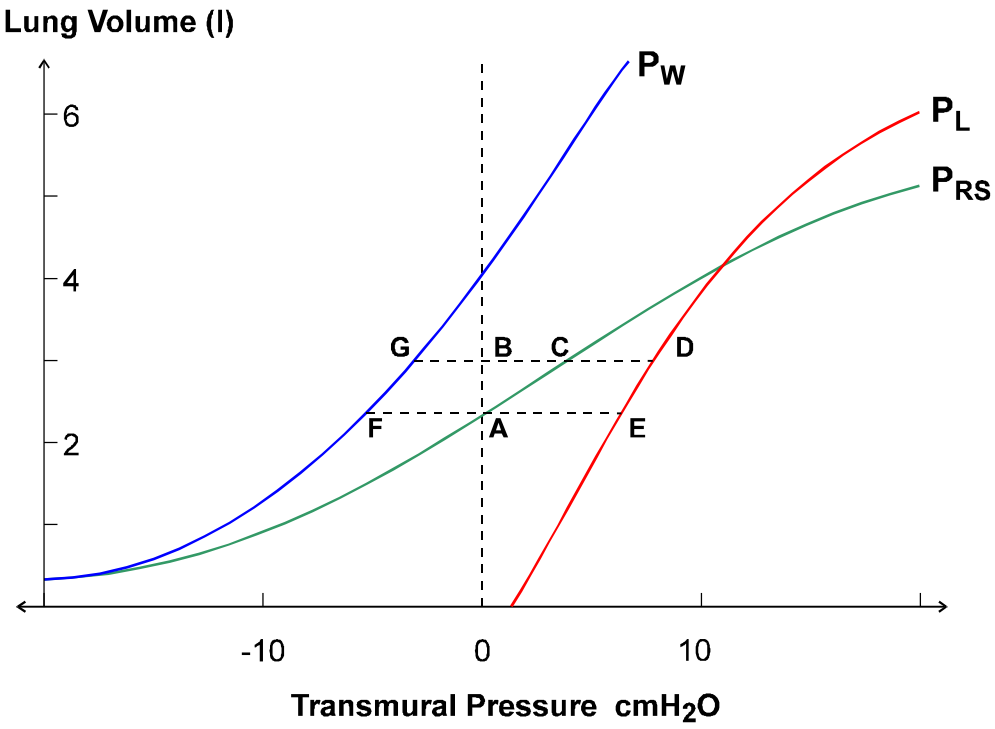
- ***Ventilatory Pattern***

a. as respiratory ***frequency*** increases,
→ flow rates increase and the ***non-elastic*** area ABCEA increases

b. as tidal ***volume*** increases,
→ the ***elastic*** work area OAECGO increases

NB: therefore, patients with stiff lungs → small shallow breaths
patients with airways obstruction → long deep breaths

as both of these patterns tend to decrease the work of breathing



NB: The total ***elastic work*** required for inspiration is the area **ABCA**.

The elastic work to inflate the lungs alone is ABDEA; however, part of this work is performed by the elastic energy stored in the thoracic cage AFGBA. The elastic energy gained by the lungs (AEDCA) is equal to that lost by the thoracic cage (AFGBA)

Metabolic Work of Breathing (Oxygen cost of breathing)

• usually expressed as ml.O_2 (additional O_2 consumption)/l ventilation
• this is low during quiet breathing, but increases with increasing ventilation, especially in the presence of pulmonary disease
• in severe cases of obstructive lung disease, the O_2 cost of additional ventilation may exceed the additional O_2 provided by that increased effort

O_2 cost of quiet breathing ~ 0.5 to 1.0 ml.O_2/l ventilation
~ 1-2% of basal MRO_2 (250 ml/min)

• mechanical ***efficiency*** of respiratory muscles, E,

$$E = \frac{\text{useful work}}{\text{total energy expended } (O_2 \text{ used})} \times 100 \quad \sim \mathbf{5 - 10\%}$$

Hyperpnoea of Exercise

• the aetiology is largely unknown, but multiple factors are involved
• a fit young male may increase V_M to 120 l/min, with a MRO_2 ~ 4.0 l/min
• in steady state, exercise ventilation correlates closely with the increase in metabolic rate

NB: that is there is ***no*** appreciable change in P_{aO2} or P_{aCO2}

• however, there is an abrupt increase in ventilation at the onset of exercise, and an abrupt decrease toward resting values at the end of exercise
• possible factors involved,

a. P_{aCO2} & P_{aO2} - unchanged with exercise unless extreme
- therefore are not a major factor

b. arterial pH - falls only with very severe exercise

c. unknown chemical stimulus - oscillations in P_{aO2} or P_{aCO2}
- the additional CO_2 load presented to lungs

d. temperature- rises only slowly with exercise
- may produce a delayed increase in ventilation
- but there is no temperature sensitive mechanism in muscle for the stimulation of ventilation

e. mechano receptors in muscles & joints

f. impulses from the motor cortex

g. psychogenic factors - increased ventilation in anticipation of exercise

Abnormal Breathing Patterns

Cheyne-Stokes Breathing

• periodic breathing, characterised by periods of apnoea lasting 15-20 secs, alternating with crescendo-decrescendo pattern of ventilation of approximately equal duration
• usually seen in patients with severe ***hypoxaemia***,

a. brain damage
b. overdose of respiratory depressant drugs
c. increased circulation time, e.g., cardiac failure
d. occasionally seen in healthy individuals and infants, during sleep
e. frequently seen at high altitude, especially during sleep

• can be induced in experimental animals by lengthening the lung/brain circulation time

Respiration at High Altitude

• normal barometric pressure is ***halved*** at 18,000 ft (5500 m), thus

1. P_IO_2 = (380-47) × 0.2093 **~ 70 mmHg**
2. P_aO_2 **~ 40 mmHg**

• > 15 million people reside at altitudes over 10,000 ft.
• there are permanent residents in the Andes at over 16,000 ft.

Hyperventilation

• typically residence at over 15,000 ft. → P_{aCO2} ~ 33 mmHg
• driven by ***hypoxic*** stimulation of the peripheral chemoreceptors
• the resulting ***alkalosis*** and hypocapnia work against this increase
• after a day or so the pH_{CSF} is returned to normal by removal of HCO_3^- from the CSF
• after several days the arterial pH is returned to near normal by renal excretion of bicarbonate
• these two restrictions on ventilation are then removed and the minute volume increases further
• people born at high altitudes have a diminished response to hypoxia, which is only slowly corrected on descent to sea level
• in contrast, lowlanders ascending to altitude retain the high respiratory drive for an extended period

▪ ***Polycythemia***

• hypoxia stimulates release of ***erythropoietin*** from the kidney which stimulates RBC synthesis by the bone marrow with a subsequent rise in the haematocrit

→ although P_{aO2} & O_2 saturation are decreased, CaO_2 may actually be ***increased***

• similarly, polycythaemia is seen in patients with chronic hypoxia from lung or heart disease
• a detrimental effect of increased haematocrit is raised blood ***viscosity***
• other factors compensating for hypoxia include,

a. hypoxic pulmonary vasoconstriction → decreased V/Q mismatch
b. ↑ CO & regional blood flow, especially brain
c. ↑ anaerobic metabolism
d. ↑ 2,3-DPG and ***right*** shift HbO_2 curve
e. ↑ SNS outflow

▪ ***Other Features of Acclimatisation***

• HbO_2 dissociation curve is shifted to the ***right***, resulting in increased tissue availability of O_2
• this is caused by a rise in the [2,3-DPG] which is the result of the alkalosis and hypoxia
• some argue that the right shift is deleterious due to reduced loading of O_2 in the lungs and that a shift to the left would be more advantageous
• the number of capillaries increases, reducing the intercapillary diffusion distance
• also, there are changes in the oxidative enzymes inside the mitochondria
• the ***maximum breathing capacity*** MBC is increased due to the lower density of air and the minute ventilation may reach 200 l/min with exercise
• however, the VO_2^{max} is dramatically reduced at elevations > 15,000 ft.
• alveolar hypoxia → ***pulmonary vasoconstriction*** with subsequent increased right atrial pressure, stroke work and hypertrophy
• the pulmonary hypertension is occasionally associated with oedema, even in the absence of elevated pulmonary venous pressure ?? mechanism
• ascent to altitude frequently → headache, dizziness, nausea, palpitations and insomnia

→ ***acute mountain sickness***, and is attributable to the hypoxaemia and alkalosis

NB: the theoretical maximum achievable altitude is ~ 69,000 ft.,
at which the atmospheric pressure equals the vapour pressure of water and body fluids boil

OXYGEN TOXICITY

• in the course of evolution of the earth, the atmospheric [O_2] has increased and organisms have had to develop defence mechanisms against oxidative damage
• these consist of,

a. enzymes - eg. superoxide dismutases
b. reducing agents - eg. glutathione and ascorbate
c. scavenger compounds - which combine with free radicals

• these normal defenses become overwhelmed when high a [O_2] is inspired
• at high O_2 tensions, highly reactive forms of oxygen are present in abnormal concentrations,

a. free radicals - .OH, $.O^-$
b. activated molecular oxygen - H_2O_2

• some workers believe the effects are due partly to O_2 itself, possessing 2 pairs of unpaired electrons
• damage at the cellular level includes,

a. enzyme inhibition - flavoproteins and oxidative-phosphorylation
b. membrane lipid damage
c. destruction of nucleic and thioamino acids
d. ? chromosomal damage in long term

• peculiar effects seen in neonates are ***retrolental fibroplasia*** and ***bronchopulmonary dysplasia***
• the later being determined by the pattern of IPPV

■ ***Central Nervous System***

• F_IO_2 = ***100% > 2 bar*** $\rightarrow$ mood changes, nausea, vertigo, muscular twitching, convulsions and loss of consciousness

• this syndrome is related to both the ***duration*** and ***PiO_2*** but is rarely seen at < 2 bar
• possibly due to inactivation of certain enzymes, particularly dehydrogenases containing sulfhydryl groups
• following a period of post-ictal depression, recovery of normal function is complete and relatively rapid

- ***Respiratory System***

• the first pathological changes are seen in pulmonary endothelial and ***type I alveolar cells***
• clinically seen in patients breathing F_IO_2 > 80% for longer than 12 hours
• the symptom complex begins with substernal discomfort, nasal stuffiness, coughing and diminished vital capacity (500-800 ml) $\rightarrow$ $\uparrow$ RR
• continued exposure results in tracheobronchitis, pulmonary congestion with transudation and exudation, finally atelectasis (predominantly in areas with low V/Q)
• oxygen also depresses the ***mucociliary transport*** mechanism after several hours of increased concentration
• pulmonary toxicity is ***not*** seen in subjects breathing F_IO_2 < 50%, nor those breathing 100% O_2 at 0.5 bar pressure for periods of 24 hours or more

NB: thus, it is the PiO_2 which is the determining factor

- ***Absorption Atelectasis***

• when breathing 100% O_2, if the airway is obstructed for any reason, the absence of a high [N_2] to effectively "splint" the alveoli leads to absorption of the alveolar gases and atelectasis
• even breathing 100% O_2 the PvO_2 remains fairly low, providing a large gradient for the diffusion of oxygen
• absorption still occurs breathing air, however the process is much slower, the rate of collapse being determined by the rate of absorption of N_2
• this is particularly likely to occur at the bases of the lung, where the parenchyma is less well expanded

Hyperbaric Oxygen Therapy

• useful in some clinical situations,

a. carbon monoxide poisoning
b. rarely in anaemic crisis
c. gas gangrene
d. ? MS

NON-RESPIRATORY LUNG FUNCTION

• such functions include,

1. blood reservoir and filter
2. immunological and mechanical defence
3. heat exchanger
4. metabolism
5. substrate synthesis
6. substrate modification

▪ ***Blood Reservoir and Filter***

• acts as a reservoir for blood, holding ~ 20% of the blood volume, or 1000 ml of which < 100 ml is in capillary bed
• acts as a particulate filter for blood-borne particles ^{3} **10 µm**
• the capillary diameter being ~ 7 µm
• however, some particles ≤ 500 µm may traverse the lung

▪ ***Immunological & Mechanical Defence***

1. secretory IgA
2. macrophages < 2 µm
3. mucociliary escalator ~ 2-10 µm
4. mucous lining airways > 10 µm
5. cough and sneeze reflexes

▪ ***Heat Exchanger***

• acts as a source for considerable heat exchange and results in the insensible loss of water
• especially for ***neonates*** and small children

▪ ***Metabolism***

• uses 1-2% of the basal O_2 consumption
• however this may be dramatically increased in ARDS/IRDS

- ***Substrate Synthesis***

1. surfactant
2. prostaglandins
3. histamine and heparin from mast cells
4. VIP, CCK*
5. somatostatin* *from ***APUD cells***
6. endorphins*
7. kallikrien
8. mucopolysaccharides from CHO

- ***Substrate Modification***

1. activation - angiotensin I $\rightarrow$ angiotensin II
   - ACE / calveoli
2. inactivation
   - i. bradykinin ~ 80% by ACE
   - ii. serotonin ~ 98% $\rightarrow$ MAO
   - iii. PGE_2, $PGF_{2\alpha}$ - not PGA
   - iv. noradrenaline ~ 30% uptake[1]
   - v. fibrinolysis
   - vi. acetylcholine
   - vii. tricyclic antidepressants
   - viii. drugs[2] - fentanyl, propofol, propranolol, lignocaine
     - imipramine, nortryptyline
3. unaffected
   - ADH
   - Adrenaline, Dopamine, Isoproterenol
   - PGA_2
   - angiotensin II, ?III
   - histamine

NB: 1. uptake and removal is not inhibited by MAOI's
2. mostly basic drugs, as acids $\rightarrow$ plasma proteins

RESPIRATORY EFFECTS OF ANAESTHESIA

Control of Breathing

▪ *PCO2 - Ventilation Response Curve*

• deepening anaesthesia is associated with decreasing ventilation and an increasing P_{aCO2}
• progressive increases in the alveolar concentration of all of the inhalational agents is associated with a decrease in the ***slope*** of the curve
• at deep levels there may be no response at all
• as opposed to the awake subject, apnoea supervenes if the P_{aCO2} is lowered below the ***apnoeic threshold***
• this appears to be in part attributable to the effects on respiratory muscle activity (see below)
• the halogenated agents differ little, but ***ether*** is exceptional in having little effect ≤ 1 MAC
• thereafter, depression occurs progressively until at 2.5 MAC the depression is comparable to the halogenated agents
• this may be related to increased levels of circulating catecholamines with ether
• surgical stimulation antagonises this effect
• the level of depression is relatively greater in patients with ***chronic airways obstruction***
• ***barbiturates*** have little effect in sedative or light sleep dosage, however are similar to the inhalational agents at anaesthetic doses
• ***ketamine*** has little effect, and this again may be related to circulating NA
• ***opiates*** are well known respiratory depressants
• small doses may simply displace the curve to the right, but larger doses also decrease the slope

▪ *PO2-Ventilation Response Curve*

• long believed that this reflex was the *ultima moriens* and relatively unaffected by anaesthesia
• however, observed by Gordh (1945) that ether abolished the response to O_2 while the response to CO_2 was still intact
• the hypoxic response is actually extremely sensitive to the inhalational anaesthetics, being markedly attenuated at **0.1 MAC**
• this is also seen with N_2O and would clearly persist well into the recovery period
• it appears that the effect is due to action on the ***carotid chemoreceptors***
• partial reversal can be attained with ***almitrine***
• there are 4 important aspects of this effect,

1. the patient will lose their hyperventilatory response to hypoxia
2. CO_2 retainers may cease breathing on induction
3. anaesthesia may be dangerous at high altitude, where survival depends on (a)
4. the effect is still present after apparent "recovery"

▪ *Metabolic Acidaemia - Ventilation Response Curve*

• this response is also obtunded at subanaesthetic levels of anaesthesia
• the degree of suppression is comparable to that seen with ***hypoxia***

Response to Increased Resistance

• anaesthetised patients retain a remarkable ability to compensate for increases in airflow resistance
• following increases in inspiratory resistance, there is an instantaneous augmentation of the force of contraction of the diaphragm
• this is consistent with muscle spindle activity
• there is a delayed response which displays "overshoot" when the resistance is withdrawn
• the time course for this response is such that P_{aCO2} appears to be the likely mediator
• in combination these allow the anaesthetised patient to compensate for inspiratory loading of the order of ~ 8.0 cmH_2O
• there is even greater ability to compensate for increases in expiratory resistance
• up to 10 cmH_2O there is no activation of the expiratory muscles, awake or anaesthetised
• the additional work is performed by the inspiratory muscles, shifting the tidal loop further up the compliance curve, allowing the increased elastic recoil to overcome the increased resistance

Pattern of Contraction of the Respiratory Muscles

Inspiratory Muscles

• realised as early as John Snow (1858) that deepening anaesthesia was associated with decreased ***thoracic excursion*** and that abdominal excursion was well maintained
• this is due to progressive failure of the ***intercostal muscles*** with preservation of diaphragm
• in contrast, there is an increase in the thoracic component during IPPV in the anaesthetised paralysed patient
• Bryan & Froese (1977) demonstrated that most of the ventilatory response to ***hypercapnia*** was due to the rib cage, rather than the abdominal component of total respiratory excursion
• this is the basis of the statement that the reduction in the CO_2 response is due to inhibition of intercostal muscle activity
• this loss of intercostal activity may be detrimental in patients with compromised abdominal excursion, or with hyperinflated lungs and flattened diaphragms
• the other major change is the loss of the tonic activity of the diaphragm, with the resultant decrease in the FRC

Expiratory and Other Muscles

• GA results in phasic activity of the expiratory group which are normally silent during the respiratory cycle
• this appears to serve no useful purpose and is unrelated to the decrease in FRC
• this increases abdominal muscle tone in the absence of paralysis
• the genioglossus normally rhythmically contracts with respiration
• loss of tone to this may result in upper airway obstruction

Alterations to Lung & Trunk Volumes

▪ ***Function Residual Capacity***

• the following points are relevant,

a. ¯ **FRC ~ 16-20%** (R: +19 to -50)

b. the decrease occurs early, within minutes, then FRC stabilises

c. a high F_IO_2 is not a factor

d. the reduction is the same paralysed or not

e. the reduction has a weak correlation with age

f. expiratory muscle activity ***does not*** play a part

g. anaesthesia ***does not*** alter FRC in the sitting position

• demonstrated by Froese & Bryan with lateral radiographs that the diaphragm ascends ~ 2 cm into the thorax during anaesthesia, with or without paralysis
• this is complicated by,

a. a decrease in the thoracic volume of ~ 250 ml

b. redistribution of blood volume from the thorax to the abdomen

→ ~ 300 ml increase

c. elevation of the diaphragm ~ 500 ml

→ ¯ **FRC ~ 450 ml**

▪ ***Consequences of the Decrease in FRC***

• in the supine position, the ***ERV*** is only ~ 1.0 l for males and ~ 600 ml for females
• thus, the reduction in FRC will reduce this reserve further

• ***closing capacity*** decreases in parallel with the reduction in FRC, possibly due to the bronchodilatation caused by inhalational agents
• thus, the tendency to airway closure ***is not*** increased during anaesthesia
• this was thought to be a cause for the increase in V/Q mismatch and impaired gaseous exchange

• other factors being equal, as lung volume decreases, airways ***resistance*** increases
• the shape of this curve is hyperbolic, and FRC resides on the steep part of the curve
• therefore, the decrease in FRC would be expected to increase airways resistance
• however, this is also largely offset by the bronchodilator effect of the GA's
• there are, however, other causes for increased airways resistance, relating to breathing circuits, valves, connectors and tracheal tubes etc.

• ***compliance*** is significantly decreased, with little difference with or without paralysis
• the majority of the change occurs in the lung, there being little alteration of chest wall compliance
• pressures ≤ 30 cmH_2O inflate the lung to only 70% of the preoperative total lung capacity
• this reduction occurs early in anaesthesia and is not progressive

• there is no general agreement on a direct effect of anaesthetics on pulmonary ***surfactant***, some studies have shown a decreased activity
• alternative explanations include,

a. breathing at a reduced lung volume
b. pulmonary collapse in the dependent regions*
c. the reduced compliance is a cause of the decreased FRC

NB: *the later is unlikely given volume changes and the second has definitely now been shown to occur

Metabolic Rate

• the MRO_2 is reduced by ~ 15% during anaesthesia
• there are major reductions in the cerebral and cardiac oxygen consumptions

Gas Exchange

• except in the very young, anaesthesia produces abnormalities in gas exchange
• the major adverse changes being,

1. reduced minute volume of ventilation
2. increased dead space
3. increased shunt

▪ ***Minute Volume***

• during spontaneous respiration the minute volume may remain normal but is usually decreased
• this results from decrease in the MRO_2 and depression of the chemical control of breathing
• some workers with closed circuit halothane anaesthesia have reported P_{aCO2} ≤ 150 mmHg !
• multiple studies of this insult have failed to shown any adverse long term effect
• many anaesthetists believe transient hypercapnia is without consequence in a healthy patient
• with artificial ventilation there is a natural tendency to hyperventilate the patient
• studies have recorded P_{aCO2} values down to 18 mmHg
• similarly no specific adverse effects have been demonstrated
• most anaesthetists tend to avoid extreme hypocapnia due to the adverse effects on cerebral blood flow, aiming for values ~ 34 mmHg
• hypothermia, intentional or accidental, may result in severe hypocapnia unless the ventilation is reduced to match the decrease in MRO_2

▪ ***Physiological Dead Space***

• the V_D/V_T ratio, from the carina downwards, is ~ 32% during anaesthesia with both spontaneous and artificial ventilation
• this corresponds closely to the ratio for the normal conscious subject, including the mouth, pharynx and trachea which are ~ 70 ml
• therefore, ***subcarinal*** $\mathbf{V_D}$ must increase by ~ 70 ml during anaesthesia, and this occurs in the ***alveolar*** component
• anatomical V_D is always less than physiological, reaching a maximum of ~ 70 ml at tidal volumes above 350 ml
• this value corresponds to the expected geometric volume of the lower respiratory tract
• at smaller tidal volumes anatomical V_D is less than the expected geometric volume, due to,

1. the mixing effect of the heart beat
2. axial streaming in laminar flow

• ***apparatus*** $\mathbf{V_D}$ increases the V_D/V_T ratio to ~ 50%
• if the patient is not intubated and a facemask is being used this increases further to ~ 70%
• under these conditions an apparent ventilation of 6 l/min will only achieve an alveolar ventilation of 2 l/min
• however, this is usually compensated for by the decreased MRO_2 and high ventilation rates
• there is no evidence that pulmonary hypotension results in the development of "zone 1" ????

▪ ***Shunt***

• in the conscious healthy subject shunt ~ 1-2% of the CO
• the $P_{A-a}O_2$ gradient is ~ 7.5 mmHg but increases with age
• during anaesthesia the shunt increases to **~ 10%**
• referring to an iso-shunt diagram → required F_IO_2 ~ 30-40%
• the cause of the venous admixture is due to,

1. pulmonary collapse in the dependent regions
2. impairment of hypoxic pulmonary vasoconstriction
3. distortion of the pattern of ventilation-perfusion ratios

• there is only minimal change in the degree of shunt and the $P_{A-a}O_2$ gradient in young adults
• progressively larger changes occur as ***age*** increases and this is possibly related to the increase in ***closing capacity***

• PEEP does little to improve the P_{aO2} during anaesthesia
• although the shunt may be reduced, the decrease in CO reduces the mean PvO_2 traversing the remaining shunt with little change in the P_{aO2}
• this contrasts the effect seen in ITU, where the stiff lungs of most of these patients "protects" them from increases in intrathoracic pressure and subsequent reductions in CO

- ***Summary:***

1. changes in the $P_{A-a}O_2$ gradient are markedly affected by ***age***
2. the increase in the $P_{A-a}O_2$ gradient is due partly to an increase in the true pulmonary ***shunt*** and partly to an increased distribution of perfusion to areas of low (but not zero) V/Q ratios
3. the increase in ***alveolar*** $\mathbf{V_D}$ is due to ventilation of areas of high (but usually not infinite) V/Q ratios
4. the major difference is between the awake and anaesthetised states, paralysis and artificial ventilation having little effect on gas exchange parameters, despite the quite different spatial distribution of ventilation
5. PEEP reduces the level of shunt, but the beneficial effect is offset by the decrease in CO and mean PvO_2

- ***Hypoxic Pulmonary Vasoconstriction***

• HPV is an important mechanism for reducing the perfusion of inadequately ventilated lung
• multiple studies with some conflicting results due to failure to account for the reduction in CO seen with anaesthesia
• inhalational agents depress HPV provided that allowance is made for concomitant changes in CO
• the decrease in CO reduces the mean PvO_2 with ensuing generalised pulmonary vasoconstriction
• intravenous agents have been clearly demonstrated ***not*** to affect HPV

- ***The Lateral Position***

• there is a preferential distribution of inspired gas flow to the lower lung and this accords approximately with the distribution of blood flow
• this favourable distribution of gas flow is disturbed by anaesthesia, with or without artificial ventilation
• the dependent lung volume is much reduced and often below closing capacity

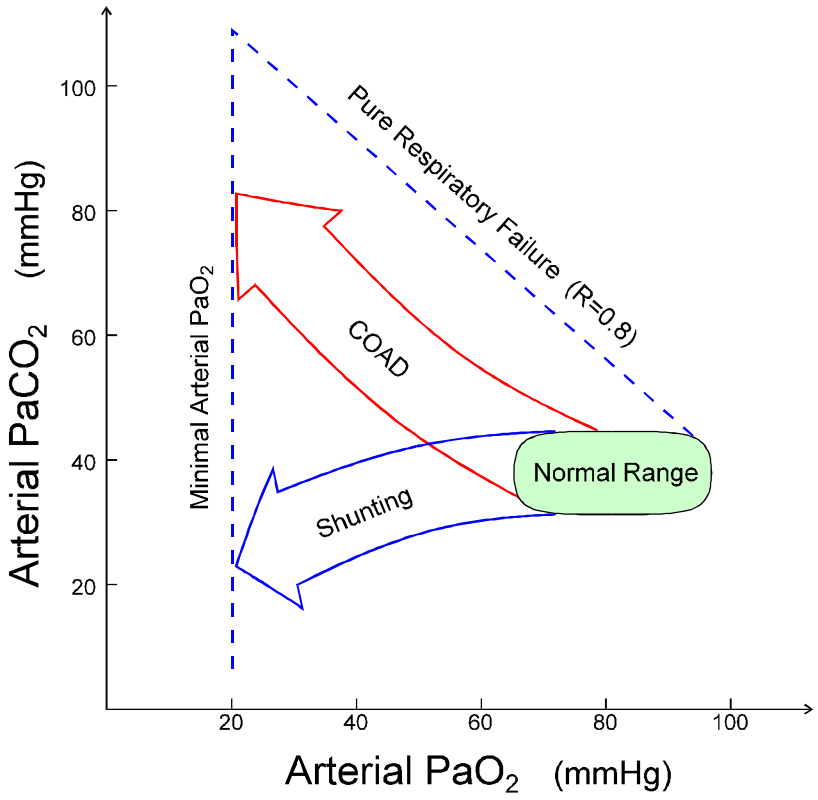
- ***Haemorrhagic Hypotension***

• physiological V_D is increased by haemorrhagic hypotension, or with induced hypotension
• this is most easily explained by the development of "zone 1"
• shunt, however, ***is not*** increased due to the direct relationship between shunt and CO

VENTILATORY FAILURE

Def'n: a ***pathological*** reduction in ***alveolar ventilation*** below the level required for the maintenance of "normal" arterial blood gas tensions

- as the normal P_{aO2} varies considerably with age, F_IO_2 and pulmonary shunt, the adequacy of ventilation is best defined by the P_{aCO2} ~ 38.3 ± 7.5 mmHg
- the survival limit, while breathing air, is reached at a P_{aO2} ~ 20 mmHg and a P_{aCO2} ~ 83 mmHg
- the limiting factor is not CO_2 but O_2, as further rise is not possible unless the F_IO_2 is increased
- in general, the P_{aO2} indicates the severity of failure, while the P_{aCO2} differentiates between ventilatory failure and shunt
- these may of course coexist (see Nunn fig. 20.1)



The oblique broken line represents the changes in alveolar gasses which would result from pure ventilatory failure.

The two large arrows represent the directional changes seen in pure chronic respiratory failure and shunting, in a patient breathing room air.

In COAD, the arterial P_{aO2} is always ***less than*** that expected due to pure ventilatory failure alone

■ *Time Course of Changes in Arterial Blood Gases*

- body stores of **O_2** are small, being **~ 1550 ml** on air, which corresponds to only 6 mins consumption at a basal MRO_2
- thus, with changes in V_A the P_{aO2} rapidly assumes its new value, the ***half time*** of change **~ 30s**
- in contrast the body stores of **CO_2** are large, being **~ 120 l**, or 600 mins of the basal output
- the time course of change for P_{aCO2} is slower for a reduction of V_A than for an increase
- the ***half time*** of rise for P_{aCO2} **~ 16 mins**

- thus, during the acute phase of hypoventilation, the P_{aO2} may be low while the P_{aCO2} is still within the normal range
- during acute hypoventilation, the ***respiratory exchange ratio*** may fall far below the ***respiratory quotient***, which it equals at steady state, as CO_2 production is partly diverted to the body stores

Causes of Ventilatory Failure

- ***Respiratory Centres of the Medulla***

a.	hypoxia	
b.	marked hypercapnia	- probably ≥ 300 mmHg healthy subject
c.	drugs	- barbiturates - opiates - all anaesthetic agents
d.	impaired medullary blood flow	- pressure, trauma - neoplasia - vascular catastrophe

• reduction of P_{aCO2} below the "apnoeic threshold" results in apnoea in the unconscious or anaesthetised patient, but not in the conscious subject
• a loss of sensitivity to P_{aCO2} is seen in various types of chronic ventilatory failure, particularly chronic bronchitis and obstructive sleep apnoea syndrome

- ***Upper Motor Neurones***

a.	fracture/dislocations above C_{3-4}	- affect the phrenic nerve $\rightarrow$ total apnoea
b.	fracture/dislocations below C_{3-4}	- loss of intercostal muscle activity
c.	tumours	
d.	demyelination syndromes	
e.	occasionally syringomyelia	

- ***Anterior Horn Cells***

a.	poliomyelitis	- though, this is now rare
b.	tetanus	- undamped function may result in ventilatory failure

- ***Lower Motor Neurones***

a. traumatic interruption
b. inappropriately placed local anaesthetic
   - interscalene brachial plexus blockade
   - stellate ganglion blockade
c. motor neurone disease
d. Guillain-Barré

- ***Neuromuscular Junction***

  a. myasthenia gravis

  b. botulism

  c. neuromuscular blocking drugs
     - anaesthetic agents
     - organophosphorus insecticides
     - nerve gases

  d. procaine (inhibits synthesis of ACh)

- ***Respiratory Muscles***

  a. diaphragmatic splinting
     - obesity
     - pregnancy
     - ascites
     - intestinal obstruction & distension
     - tension pneumothorax/haemothorax

  b. muscle fatigue
     - increased work of breathing/impedance
     - endotoxin
     - hypoperfusion/shock
     - malnutrition, wasting diseases
     - myopathic diseases

- ***Decreased Compliance - Lung/Chest Wall***

  a. intrapulmonary disorders
     - pulmonary fibrosis, Hamman-Rich syndrome
     - neoplastic infiltration
     - ARDS
     - pulmonary oedema

  b. intrapleural disorders
     - empyema with fibrosis
     - carcinomatosis
     - mesothelioma
     - tension pneumothorax/haemothorax

  c. chest wall disorders
     - kyphoscoliosis
     - extensive burns in children
     - external compression

- ***Integrity of Chest Wall***

  a. closed disorders - flail chest

  b. open disorders - open pneumothorax

- ***Airway Resistance***

a.	upper airway	- foreign body - epiglottitis/croup - laryngospasm - tumour - anaesthetic apparatus
b.	intraluminal	- foreign body - sputum retention - severe pulmonary oedema
c.	bronchial wall	- hyperreactivity - noxious stimuli - tumour - drugs
d.	extraluminal	- dynamic airway obstruction - tumour

Ventilatory Capacity vs. Ventilatory Failure

• a reduction in ventilatory capacity does necessarily imply ventilatory failure
• data from Nunn shows no correlation between P_{aCO2} and FEV1.0 over the range 0.3 to 1.0 l
• COAD patients tend toward one of two groups, either retaining or losing their respiratory centre sensitivity to CO_2
• the later group, relying on hypoxic drive to respiration, often appear less distressed than the former, however decompensate more readily
• asthmatic patients behave similarly to the former group, tending to maintain a normal, or even subnormal P_{aCO2} until they are no longer able to compensate for the increased work of breathing

• in chronic ventilatory insufficiency, the onset of acute failure is dependent upon the MRO_2
• thus these patients tend to self limit their exercise and automatically "tune" their ventilatory pattern to minimise their work of breathing
• as respiratory insufficiency progresses, the maximum ventilatory capacity decreases and the minute ventilation for any given MRO_2 increases
• this is the result of,

a. an increase in ***dead space*** ventilation

b. an increased ***oxygen cost*** of breathing → decreased ***efficiency***

• thus the patient is caught between a decreased MBC and increasing work of breathing
• the untrained individual can sustain a minute volume of **~ 30%** of MBC before dyspnoea occurs
• initially these two result in a decrease in ventilatory reserve and exercise tolerance
• eventually, the work requirement at rest represents > 30% MBC and the patient become progressively ***dyspnoeic***

Breathlessness

Def'n: "an undue ***awareness*** of breathing, or awareness of difficulty in breathing", Campbell & Guz (1981)

• both hypoxia and hypercapnia may force the patient to breath more deeply, however, neither *per se* is responsible for the sensation of dyspnoea
• this arises from the ***ventilatory response*** rather than the stimulus itself
• thus, dyspnoea is usually more prominent in the "pink puffer" group, who retain their responsiveness to CO_2, than in those who have reduced CO_2 response curves
• though, the later usually have more profound hypoxia and hypercapnia
• Campbell and Howell (1963) suggested that a major factor in dyspnoea was an "inappropriateness" between respiratory muscle tension and fibre shortening

• similarly, ***breath holding*** is not limited but is affected by arterial gas tensions
• the sensation terminating breath holding can be relieved by ventilation without an alteration in ABG's
• though, P_{aO2} has a more profound effect than P_{aCO2}
• diaphragmatic afferent traffic appears to be more important than that from the intercostal group

Management of Ventilatory Failure

• many patients survive with P_{aCO2} values ~ 60 mmHg
• above this there is significant impairment of cerebral function, mainly due to the mandatory reduction in P_{aO2} which accompanies any further increase whilst breathing air
• treatment of chronic insufficiency may be roughly divided into two areas

Improvement of PAO2

• an increase in F_IO_2 usually does little to improve ventilation or reduce the P_{aCO2}, which may in fact rise further
• thus it is important to ensure that relief of hypoxaemia, important though this is, does not result in significant hypercapnia
• other factors remaining constant, an increase in F_IO_2 will result in an equal rise in P_{aO2}
• therefore, only small increases in F_IO_2 are required to treat hypoxaemia due to hypoventilation
• hypoventilation sufficient to result in a P_{aCO2} ~ 100 mmHg only requires an $F_IO_2 = 0.3$ to attain a normal P_{aO2} (see Nunn fig. 20.6)
• at this level of hypercapnia, active intervention to increase ***alveolar ventilation*** is required
• an $\mathbf{F_IO_2 = 0.3}$ may therefore be regarded as the upper limit of palliative oxygen therapy

▪ ***Improvement of Alveolar Ventilation***

• this is the only means of decreasing the P_{aCO2}
• the ***first line*** of therapy includes,

i. bronchodilatation
ii. control of infection and secretions
iii. relief of pain
iv. stabilisation of the chest wall
v. correction of gross pathology, eg. open/closed pneumothorax
vi. optimisation of O_2 therapy
vii. avoidance of respiratory depressant drugs

• the ***second line*** includes chemical stimulation of breathing, agents available including,

i. theophylline
ii. doxapram
iii. medroxyprogesterone
iv. acetazolamide (indirect action via pH)

• the third line includes,

i. endotracheal intubation |
ii. tracheostomy | $\downarrow V_D$ and better control of secretions
iii. artificial ventilation

• there are no absolute criteria for artificial ventilation and many factors need to be considered
• even so, a $\mathbf{P_{aCO2}}$ ³ **75 mmHg**, which cannot be reduced by other means, in a patient who is deemed recoverable is generally considered a firm indication
• artificial ventilation may be required at much lower P_{aCO2}'s if there is significant muscle fatigue secondary to the increased work of breathing
• this is frequently difficult to predict
• with intense activity the respiratory muscles suffer low frequency fatigue, as is the case for other skeletal muscles

NB: muscle response to high frequency stimulation is unaltered, however, the CNS is unable to maintain high frequency output for extended periods (? why)

• discoordinated breathing, with thoracic and diaphragmatic movements out of phase is as early indicator of impending failure

ARTIFICIAL VENTILATION

Def'n: the provision of the minute volume of respiration by external forces, when there is impaired function of the patient's respiratory muscles

Resuscitation

▪ *Mechanical Artificial Ventilation*

• until about 1960 most methods involved rescuer manipulation of the arms or trunk of the victim
• these are classified into those with,

a. active expiratory phase
b. active inspiratory phase
c. both, or push-pull

• active expiratory phase ventilation may be attained by direct pressure to either the trunk or abdomen
• inspiration then results from the elastic stored energy of the lung and chest wall
• such ventilation is below FRC, and as such cannot be relied upon to guarantee adequate minute ventilation, even in the absence of respiratory obstruction
• tidal exchange takes place in the ERV, which is considerable reduced in the supine position

• active inspiratory phase ventilation involves techniques to expand the chest by traction on the arms or hips
• like the above, it cannot be relied upon to maintain an adequate minute ventilation

• push-pull ventilation is clearly more effective than either of the above
• due to the effects of posture, a rocking stretcher using phasic tilting 40° either side of the horizontal can achieve a satisfactory minute volume

• virtually all unconscious patients will have some degree of airway obstruction
• most of the above techniques require the use of both hands of the rescuer and studies have confirmed that these techniques can only be guaranteed when the trachea is intubated
• even if minute volume is satisfactory, there is no guarantee P_{aO2} will be maintained with ventilation below FRC, due to small airways closure and appreciable shunting

Expired Air Resuscitation

- some references in the Bible, though, the first clear account appeared in 1796 (Herholdt & Rafn)
- relies on the rescuer ***doubling*** his own minute ventilation
- the effectiveness is improved by the rescuer's ***dead space***
- if V_D is artificially increased by apparatus dead space, this will improve the composition of "expired air", and help prevent hypocapnia in the rescuer
- this method has virtually completely replaced manual methods, and its success depends upon,

    a. adequate ventilation for long periods with little fatigue

    b. the hands of the rescuer are free to control the airway

    c. the rescuer can visually monitor chest expansion

    d. the method is extremely adaptable

    e. requires minimal expertise and is easily taught

- the essential features of the technique include,

    a. the airway must be cleared

    b. the rescuer should ~ double his minute volume

    c. the first few breaths should be given rapidly

    d. alternative variants should be taught (mouth-nose)

    e. ancillary apparatus are ***not*** essential - though desirable

Intermittent Positive Pressure Ventilation (IPPV)

Inspiration

• mouth pressure is transiently raised above ambient pressure and the lung is inflated in accordance with its compliance and resistance
• if inspiration is slow then the distribution is governed solely by regional ***compliance***
• if fast, then the regional ***time constants*** become the major factor
• the distribution differs from spontaneous ventilation, in that there is a relatively greater expansion of the rib cage

Expiration

• expiration is passive and differs from spontaneous ventilation only by the absence of residual diaphragmatic tone
• this may be retarded by the application of positive end-expiratory pressure, PEEP, or by the addition of external resistance to gas flow
• expiration may be accelerated by the application of a subatmospheric airway pressure = NEEP
• if the inflation pressure is constant and applied for several seconds, then the tidal volume will be given by,

$$V_T = P_{mouth} \times C_T$$

eg. 500 ml = 1.0 kPa × 0.5 l/kPa

Time Course of Inflation & Deflation

• equilibration in the above equation will usually take several seconds
• the rise of mouth pressure is opposed by two forms of impedance,

a. elastic resistance of the lungs and chest wall
where, $P = \delta V \times C_T$

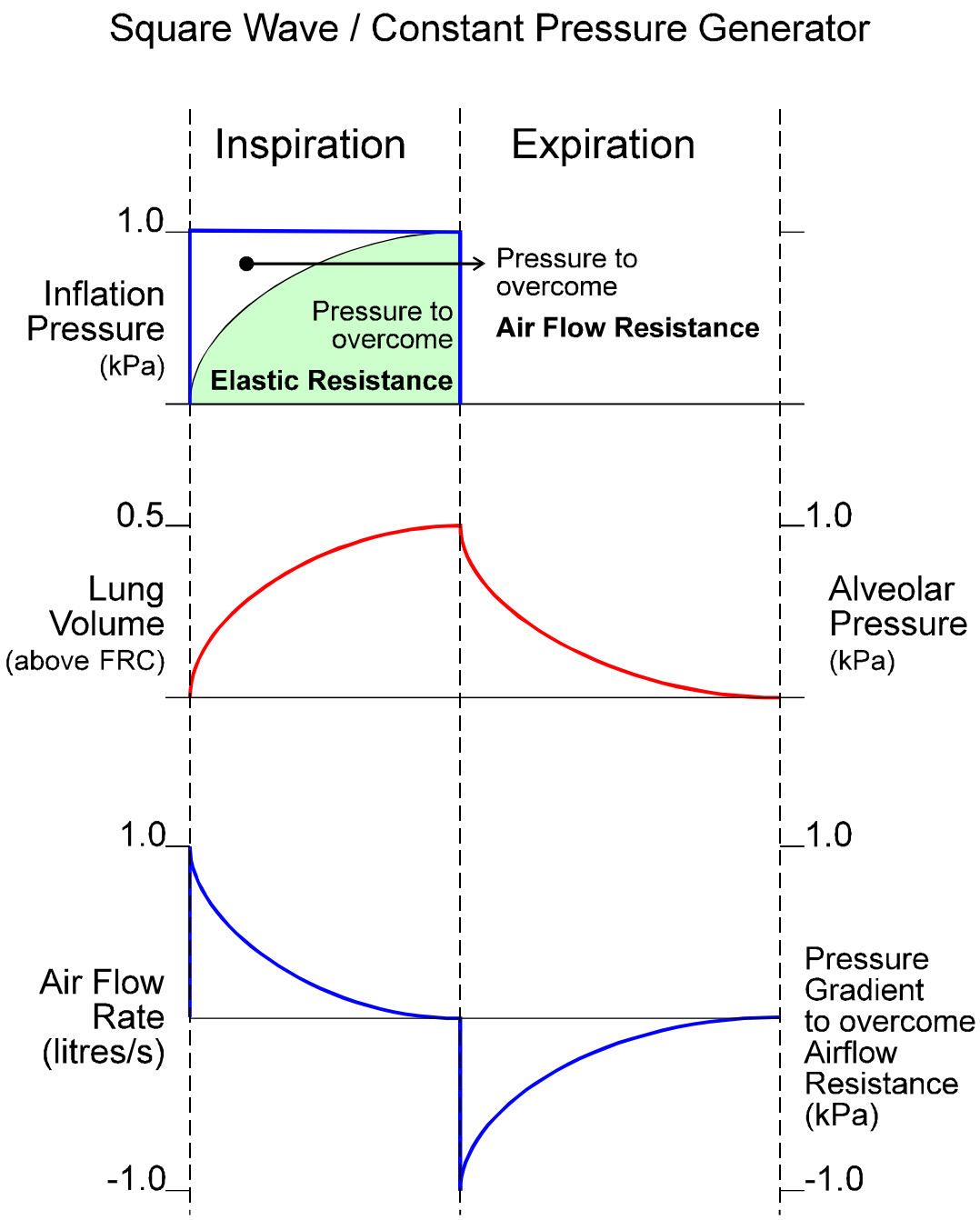
b. resistance to airflow
where, $P = Q_{instantaneous\ airflow} \times R_{airway}$

• at any instant the inflation pressure equals the sum of the pressures required to overcome these two forms of impedance
• resistance to airflow assumes ***laminar*** flow and a constant airways resistance
• with a constant inflation pressure (square wave), the two components vary during inspiration, while their sum remains constant (Nunn 21.1- over page)
• with normal respiratory mechanics in an unconscious patient, inspiration should be 95% complete in ~ 1.5 s
• the increase in lung volume following an exponential wash-in curve, where the ***time constant*** is described by,

τ (tau) = resistance × compliance
~ 1 kPa/l/s × 0.5 l/kPa
~ 10 cmH_2O/l/s × 0.05 l/cmH_2O
~ 0.5 s

- this equates to the time taken to reach 63% of the final volume change
- may use the ***half time*** = 0.69 × time constant

NB: clearly, it is unusual for equilibrium of lung volume to occur during IPPV, and it is common for inspiration to be terminated after 1-2 s, when the lung volume will still be increasing



▪ ***Effects of Inflation Pressure, Resistance and Compliance***

• these are most easily studied in relation to the effects on a constant pressure curve (Nunn 21.2)
• the changes in volume per time constant are as follows,

1. time constant → 63%
2. time constants → 86.5%
3. time constants → 95%
4. time constants → 98%
5. time constants → 99%

• changes in the inflation pressure ***do not*** alter the time constant
• thus, the half time will be unaltered, only the final ***volume*** change will alter, in direct proportion to the change in pressure

• changes in ***compliance*** result in directly proportional changes in both final volume change and the time constant
• thus, if the compliance is doubled, so the final volume change will also double, but the time taken to equilibration will also double

• changes in ***resistance*** do not affect the final volume change, but have direct effects on the time constant
• changes either directly increase, or decrease the time to equilibrium without altering the final volume change

NB: these effect apply not only to the lung as a whole, but to ***regional ventilation***

• increasing inflation pressure has a considerable effect on the time taken to achieve a given δV above FRC
• this effect is used in the application of an ***overpressure***, to increase the inspiratory flow rate and permit a shorter duration of inspiration

▪ ***Deviations from the True Exponential Function***

• airflow is normally partly ***turbulent***, therefore resistance ***does not*** remain constant but varies with flow rate
• furthermore, as expiration proceeds the calibre of the airways decreases and there is also a transition from turbulent to more laminar flow as the flow rate decreases
• approximation to a single exponential function is usually adequate for practical purposes

■ ***Patterns of Inflation Pressure***

• there is ***no*** convincing evidence of the superiority of any one method, except that the distribution of the inspired gas is improved if there is prolongation of the period during which the applied pressure is maximal
• this allows better ventilation of "slower" alveoli but is relatively unimportant in healthy lungs
• the normal means of achieving this is by the addition of an ***inspiratory pause***
• the two other forms commonly seen are,

a. constant flow generators - usually electrical
b. sine wave generators - usually mechanical

■ ***Control of Inspiration***

• this may be achieved by one of three methods,

1. time cycling
2. volume cycling
3. pressure cycling

• limitations on the inspiratory duration are usually a safety precaution
• the usual insp./expiration ratio varies from 1:1-4, with respiratory frequencies from 12-20 bpm
• it has been demonstrated that there is a substantial increase in the $\mathbf{V_D/V_T}$ ***ratio*** if the duration of inspiration is reduced below 1.0 s
• there is no evidence that there is any appreciable effect on the $\mathbf{P_{A\text{-}aO2}}$ ***gradient*** with inspiration in the range 0.5-3.0 seconds

■ ***Methods of Ventilatory Support***

1.	controlled mechanical ventilation	CMV
2.	assisted mechanical ventilation	AMV
3.	inverse ratio ventilation	IRV
4.	intermittent mandatory ventilation	IMV/SIMV
5.	pressure support ventilation	PSV
6.	proportional assist ventilation	PAV
7.	airway pressure release ventilation	APRV

Positive End-Expiratory Pressure (PEEP)

• a great number of pathological conditions, and anaesthesia, result in a reduction in FRC with concomitant disturbance of gas exchange
• increasing the FRC by the administration of PEEP was first described by Hill *et al.* in 1965
• similar effect are obtained by continuous positive airways pressure CPAP, though, this is technically more difficult to achieve
• the simplest technique is to exhale through a preset depth of water, but more convenient techniques involve spring loaded valves, or pressure loaded diaphragms

▪ ***Respiratory Effects***

1. ***lung volumes***
   - the end-expiratory alveolar pressure will equal the applied PEEP, and the FRC will be reset in accordance with the total system compliance
   - in many patients this will shift the tidal range above the ***closing capacity***
   - due to the inverse relationship to lung volume, airways resistance will be reduced
   - the alteration in the relative compliances of the upper and lower regions of the lung may result in a reduction in V/Q mismatch
2. ***dead space***
   - acute application of PEEP does ***not*** alter the V_D/V_T ratio
   - long term application may increase V_D due to bronchiolar dilatation
3. ***arterial*** $\mathbf{P_{O2}}$
   - it is unlikely that PEEP improves arterial oxygenation in patients with healthy lungs
   - in abnormal lungs, the reduction in pulmonary shunting which is observed in a large number of conditions is clearly beneficial,

   i. pulmonary oedema
   ii. pulmonary collapse
   iii. ARDS
      - some researchers have suggested that the reduction in shunt seen with ARDS is secondary to the reduction in CO resulting from the PEEP
4. ***lung water***
   - there is now good evidence that there is ***no*** reduction in lung water
   - the improvement in P_{aO2} is more likely to be due to,

   i. opening of closed alveoli
   ii. movement of water into the interstitial compartment / service side of the alveoli
   iii. the reduction in CO and pulmonary shunt

5. ***intrapleural pressure***
   - P_{IP} is effectively shielded from the applied PEEP by the transmural pressure gradient of the lungs
   - where transmural pressure = transpulmonary = $P_{IP} - P_A$
   - patients with diseased lungs tend to have higher transmural gradients and are therefore better protected against the adverse cardiovascular effects of PEEP
6. ***permeability***
   - PEEP ***increases*** the permeability of the lung to DTPA, a tracer normally unable to traverse the alveolar-capillary membrane
   - this is probably related to volume changes, rather than membrane damage
7. ***barotrauma***
   - the commonest forms attributable to PEEP include,

   i. subcutaneous emphysema

   ii. pneumomediastinum

   iii. pneumothorax
   - modest levels of PEEP result in a negligible increase in the incidence of barotrauma
   - the incidence rises substantially at PEEP ≥ 20 cmH_2O

- during anaesthesia, the application of PEEP to healthy patients is of little value, though the level of shunt is reduced
- the concomitant fall in cardiac output, with reduction in the $Pv'O_2$ offsets the reduction in shunt

Cardiovascular Effects

1. ***cardiac output***
   - modest levels of PEEP result in a negligible decrease in CO
   - in patients with diseased lungs there is similarly little decrease up to the level of "best PEEP", ie. that level which maximises the O_2 flux
   - higher levels of PEEP result in substantial reductions of CO
   - the predominant cause being a reduction in right atrial filling, due to the rise in intrathoracic pressure
   - other contributing factors include,

   i. increased pulmonary capillary resistance (RV afterload)

   ii. decreased left ventricular compliance

   iii. decreased myocardial contractility
   - plasma from patients receiving PEEP will decrease the contractility of isolated myocardial preparations, suggesting the release of some negative inotrope
2. ***oxygen flux***
   - initially PEEP improves the P_{aO2} but as the CO falls, so O_2 flux also falls
   - the maximum point in the O_2 flux curve = ***best PEEP***
   - this point may be extended by enhancement of CO with fluid replacement or positive inotropes

3. ***arterial blood pressure***
   - in a number of studies, the compensatory response of the peripheral vascular bed has been found to be only about a half of that required to maintain the BP
   - some suggest that this failure of compensation is the result of inhibition of the cardiac regulatory centres in the midbrain (?? how)
4. interpretation of ***vascular pressures***
   - atrial pressures are normally read relative to ambient pressure, and these will be increased by PEEP
   - however, relative to intrathoracic pressure they are reduced at higher levels of PEEP, and it is the transmural pressure which determines atrial filling
   - a further problem arises when the tip of the Swan-Ganz catheter lies in the upper regions of the lung
   - the application of PEEP increases zone 1 and the absence of blood flow results is artefactual readings

- ***Renal Effects***

- patients undergoing IPPV frequently become oedematous
- among other factors, PEEP itself may reduce ***glomerular filtration***
- this may result from the reduction in arterial and increase in central venous pressures
- alternatively the reduction in atrial transmural pressure may decrease ANF release
- ?? PEEP does result in an increased secretion of ADH

PULMONARY OEDEMA

Def'n: an increase in pulmonary ***extravascular*** water, which occurs when transudation or exudation exceeds the capacity of lymphatic drainage

▪ *Anatomical Aspects*

• the ***pulmonary capillary*** endothelial cells abut one another in a fairly loose fashion
• gap junctions are **~ 5 nm** wide, and permit the passage of moderately large protein molecules
• consequently, the pulmonary interstitial lymph [albumin] ~ 50-70% of plasma
• the ***alveolar epithelial*** cells meet at tight junctions **~ 1 nm** wide, and are virtually impermeable to protein (values from DeFouw, 1983)

• the lungs have a well developed lymphatic system
• lymphatics cannot be defined at an alveolar level, but are first seen in relation to bronchioles
• until generation 11, these lie in the potential space around air passages and vessels, separating them from the lung parenchyma
• at the hilum these drain into several groups of tracheobronchial lymph nodes
• virtually all of the drainage from the left, and a significant proportion of that from the right enters the ***thoracic duct***
• the remainder from the right lung enters the right lymphatic duct
• the pulmonary lymphatics often cross the midline and pass independently into the junctions of the IJ & SC veins
• the normal lymphatic drainage from human lungs is **~ 10 ml/hr**

Stages of Pulmonary Oedema

• irrespective of the aetiology of pulmonary oedema, it is possible to recognise four stages
• with gradual onset these may be identifiable clinically, however, with fulminate disease progression may be obscured
• there is usually prodromal stage in which lymphatic drainage is increased, though there is no detectable increase in lung water

▪ *Interstitial Pulmonary Oedema*

• interstitial lung water is increased but there is no passage of fluid into the alveoli
• microscopically this is detected as cuffing of distended lymphatics around branches of the bronchi and larger pulmonary vessels
• this produces the "butterfly" shadow on CXR
• EM shows fluid accumulation in the alveolar septa, but this is confined the "service" side of the capillary, leaving the "active" geometry unchanged
• consequently gaseous exchange is better preserved than might be expected from the increase in lung water
• physical signs are generally absent and the PA-aO_2 gradient small
• diagnosis is by PAOP (?? how this is done, stated in Nunn) and CXR

Crescentic Alveolar Filling

- interstitial oedema increases and there is passage of fluid into the alveoli
- this first appears as crescents in the angles between adjacent septa
- the centre of the alveoli and most of the alveolar walls remain clear
- gas exchange remains little affected and the PA-aO_2 gradient remains small

Alveolar Flooding

- in the third stage there is quantal alveolar flooding
- some alveoli are totally flooded, while others, frequently adjacent show only crescentic filling
- fluid enters the alveoli in a crescentic fashion until a ***critical radius*** of curvature is reached
- surface tension then rises sharply and further fluid is drawn into the alveolus as the transudation pressure gradient rises exponentially
- this phenomenon is believed responsible for the ***"all-or-none"*** filling of individual alveoli
- clearly no gas exchange can occur in flooded alveoli, blood flow to these regions adding to ***venous admixture***

> ***NB:*** quantitatively there is no requirement to consider altered diffusing capacity, the entire PA-aO_2 gradient can be attributed to shunt

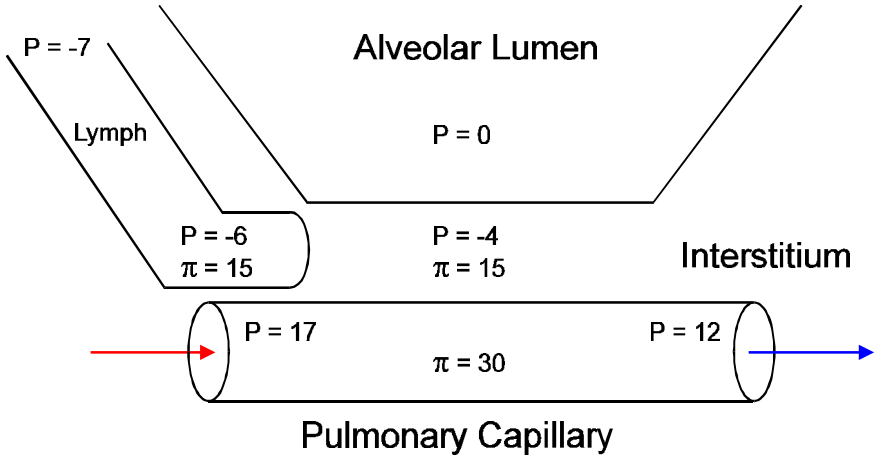
- clinically rales are heard, the CXR shows a butterfly pattern with interstitial markings and overall opacity
- alveolar flooding tends to occur in the dependent regions of the lung

Airway Flooding

- this follows extreme alveolar flooding, effectively blocks air passages preventing any meaningful gas exchange and is rapidly fatal unless treated

Mechanism of Pulmonary Oedema

- transudation of intravascular fluid must be considered in two stages
- first from the microcirculation into the interstitial space, then into the alveoli
- the values for Starling's equation for the lung are difficult to measure and there are a wide range of reported values



P = pressure in cmH_2O relative to atmosphere

(Staub, 1984)

■ ***Transudation Across the Vascular Endothelium***

- under normal circumstances the pulmonary lymph flow **Q_L ~ 10 ml/hr**
- the protein content is ~ ½ plasma
- the pulmonary ***capillary hydrostatic pressure***, P_{pc} ~ 0-15 mmHg, depending upon the vertical height within the lung field
- further there is a progressive decrease in P_{pc} from the arterial to the venous end, as approximately ½ of the pulmonary vascular resistance lies with the microvascular circulation
- the above interstitial pressures are those from the dog, with the lung held at an inflation pressure of 5 cmH_2O
- there is a gradient from the lung interstitium to the hilum
- however, there was no vertical gradient within the lung field
- the interstitial space and lymphatics can accommodate an increase in water of **~ 500 ml** with an increase of pressure of only **~ 1.5 mmHg**
- the interstitial space compliance increases with larger lung volumes
- this is considered to be one of the mechanisms by which PEEP or CPAP improve gas exchange in pulmonary oedema, as they do not decrease the total amount of lung water
- the ***reflection coefficient*** for healthy lung, **σ ~ 0.5**
- the capillary to interstitium osmotic pressure gradient, **π_{pc}-π_i ~ 11.5 mmHg**
- thus, there is a small balance favouring transudation
- this is greater in the dependent regions of the lung, and the safety margin for the formation of oedema is considerably less

- ***Transudation Across the Alveolar Epithelium***

• the alveoli are freely permeable to gases, water and hydrophobic substances
• they are virtually impermeable to albumin and small solutes
• there are considerable uncertainties about the osmotic pressure of the alveolar lining fluid
• it has been suggested by Hills (1982) that the alveolar lining is largely dry
• thus analysis of transudation in terms of a Starling equation is meaningless
• however, it does appear that transudation across this membrane is essentially zero, unless

a. the integrity of the barrier is in someway damaged

b. interstitial pressure exceeds some critical value

- ***Pathophysiology***

• the most important physiological abnormality is venous admixture or ***shunt***
• this results in an increased PA-aO_2 gradient and arterial hypoxaemia
• hypercapnia is seldom a problem
• in mild to moderate oedema P_{aCO2} may be normal or subnormal due to increased respiratory drive from hypoxia and J-receptor stimulation
• if patients with severe oedema are treated with a high F_IO_2, hypercapnia may result from interference with gas exchange

Aetiology of Pulmonary Oedema

- ***Increased Capillary Pressure (Haemodynamic Pulmonary Oedema)***

a.	absolute hypervolaemia	- overtransfusion - decreased H_2O clearance
b.	relative pulmonary hypervolaemia	- postural - vasopressors
c.	raised pulmonary venous pressure	- LV failure (any) - dysrhythmias - MV disease - atrial myxoma - drugs (histamine) - endotoxin
d.	increased pulmonary blood flow	- left/right shunt - anaemia - rarely exercise
e.	subatmospheric airway pressure	

NB: in this group the oedema fluid has a protein content which is ***less*** than the normal pulmonary lymph (Staub, 1984)

- ***Increased Alveolar/Capillary Permeability***

  a. direct injury

  b. indirect injury

  NB: in this group the oedema fluid has a protein content which is approaches that of plasma (Staub, 1984) *see notes on ARDS

- ***Decreased Plasma Oncotic Pressure***

• this is seldom the primary cause of oedema
• however, is common in seriously ill patients and may contribute significantly to their degree of oedema

- ***Lymphatic Obstruction***

  a. infection

  b. tumour

  c. transplantation / surgical

- ***Miscellaneous***

  a. 'neurogenic' - head injuries, cerebral lesions

  b. re-expansion - probably results from increased permeability

  c. high altitude

  d. diamorphine overdosage

- ***Treatment***

  NB: the single highest priority is to restore the P_{aO2}

  a. oxygen

  b. posture - if feasibly, sitting the patient reduces central blood volume

  c. morphine - reduces anxiety and causes vasodilatation

  d. vasodilators- nitrates, ACE inhibitors, (frusemide)

  e. diuretics - loop agents, thiazides generally useless

  f. positive inotropic agents - AD, DB, DA

  g. CPAP ± mechanical ventilation with PEEP

  h. ventricular assist devices

Clinical Measurement

• the most useful clinical measurements are the,

a. $P_{A-a}O_2$ gradient
b. serial CXR's
c. PAOP by Swan-Ganz catheter
d. cardiac hemodynamics via Swan-Ganz catheter
e. loss of gamma-emitter from lung to circulation - ^{99m}TcDPTA

• the normal half life of removal for ^{99m}TcDPTA is 40-100 minutes in the healthy non-smoker
• this is reduced below 40 mins in a variety of insults, however, it is within the range 10-40 mins in apparently healthy smokers
• measurement of lung water during life is difficult
• the only practical method is the double indicator method, which measures pulmonary, or central blood volume
• one indicator is chosen to remain within the circulation, while the other (usually "coolth"), diffuses freely into the interstitium
• extravascular lung water is then estimated as the difference between these volumes
• there is still widespread agreement that the method is difficult, due to the high level of accuracy required to measure small changes in lung water
• thoracic electrical impedance is an alternative approach

ACUTE RESPIRATORY DISTRESS SYNDROME

▪ ***Definition***

• Ashbaugh *et al*. (1967) described a condition in adults which was similar to the respiratory distress syndrome of infants
• the term ***ARDS*** was coined by Petty & Ashbaugh in 1971
• there is ***no*** universal agreement upon the ***diagnostic criteria***
• actually represents a subset of acute lung injury
• the ***essential features*** include,

1. respiratory failure requiring mechanical ventilation
2. severe hypoxaemia with a high $P_{A\text{-}aO2}$ gradient[1]
3. bilateral diffuse infiltration on CXR[2]
4. stiff lungs with $C_T \leq 50$ ml/cmH_2O
5. pulmonary oedema should not be cardiogenic in origin[3]
   - the PCWP should ***not*** be elevated, definitions → PCWP ≤ 12-18 mmHg
6. presence of a known predisposing condition - sepsis
   - trauma
   - aspiration

NB: [1] there is no agreement on the precise degree of ***hypoxaemia***, values ranging from 50-75 mmHg with a F_IO_2 from 0.5 to 1.0; alternatively, the critical level of hypoxaemia has been defined as 20% of the PiO_2
[2] early in the disease course either lung may be predominantly affected
[3] Lloyd, Newman and Brigham (1984) objected to this as it precluded the diagnosis in patients with pre-existing conditions which raised LAP

• the histology is usually diagnostic, however lung biopsy is seldom indicated or advisable
• there are no diagnostic laboratory tests and the diagnosis is in part by ***exclusion***
• differences in diagnostic criteria have greatly complicated data on morbidity, mortality and therapeutic efficacy

- ***Diagnostic Criteria Petty***

1. ***clinical setting:***
   - i. catastrophic event — - pulmonary; - non-pulmonary
   - ii. exclusions — - chronic respiratory disease; - LV dysfunction
   - iii. respiratory distress — - RR > 20 bpm; - laboured breathing

2. ***CXR:*** * diffuse pulmonary infiltrates
   - i. interstitial — - early
   - ii. alveolar — - late

3. ***physiology:***
   - i. $P_{aO2} \leq 50$ mmHg — * with a $F_IO_2 \geq 0.6$
   - ii. $C_T \leq 50$ ml/cmH_2O — - usually 20-30 ml/cmH_2O
   - iii. Q_S/Q_T increased[§]
   - iv. V_D/V_T increased[§] — [§] increased V/Q anomaly

4. ***pathology:***
   - i. heavy lungs — - usually ≥ 1000 g
   - ii. congestive atelectasis
   - iii. hyaline membranes
   - iv. fibrosis

Clinical Course

- there are four recognisable clinical phases;

1. the patient is dyspnoeic & tachypnoeic
   - CXR & P_{aO2} normal
   - usually lasts ~ 24/24
2. arterial hypoxaemia develops
   - P_{aCO2} remains normal, or subnormal
   - there are only minor abnormalities on CXR
   - the is an increase in lung water & Q_T
   - usually lasts ~ 24-48/24
3. * the above diagnostic criteria are present
   - severe arterial hypoxaemia & a large P_{A-aO2} gradient develops
   - P_{aCO2} becomes slightly elevated
   - CXR shows characteristic bilateral infiltrates
   - CT decreases, the lungs are stiff and PAWP increases
   - artificial ventilation is usually instituted if not already present
4. usually terminal
   - massive bilateral consolidation with unremitting hypoxaemia
   - P_{aO2} is usually ≤ 50 mmHg with a $F_IO_2 = 1.0$
   - V_D increases and normocapnia can only be maintained by a large V_M, often 10-20 l/min

- not all patients progress through all of these stages and the disease may resolve at any stage
- serial observations of the CXR and P_{A-aO2} gradient are the best indicators

Predisposing Conditions

Direct injury	Indirect injury
Pulmonary contusion	Septicaemia
Gastric / other aspiration	Shock / prolonged hypotension
Near-drowning	Non-thoracic major trauma
Toxic gas / vapour inhalation	Cardiopulmonary bypass
Certain infections	Head injury
Fat embolus	Pancreatitis
Amniotic fluid embolus	Diabetic coma
Radiation	Massive blood transfusion
Bleomycin	DIC

Nunn 3rd Ed.

Predisposing Conditions

- Pepe's group found the highest single risk factor was ***sepsis syndrome***,
    1. 38% of patients in this group developing ARDS
    2. 25% of patients with a single risk factor developed ARDS
    3. 42% with 2 risk factors
    4. 85% with 3 risk factors

- Fowler's group found the highest incidence in,
    1. aspiration ~ 35.6%
    2. DIC ~ 22.2%
    3. pneumonia ~ 11.9%

- the major predisposing factors are now agreed to be;
    1. septicaemia - particularly gram (-)'ve
    2. aspiration of gastric contents
    3. DIC
    4. multiple trauma - particularly with pulmonary contusion
    5. massive transfusion

- it is extremely difficult, if not impossible to separate the toxic effects of high F_IO_2's from the pathological conditions requiring their use
- however, it is ***unlikely*** that O_2 plays a significant role in pathogenesis

- there is considerable difference in the reported incidence, probably reflecting the different diagnostic criteria in different studies

- ***T.Oh:*** the true incidence is unknown and may only be ~ 7% of "at risk" patients
- there is, however, good agreement on the overall ***mortality £ 50%***
- this tends to be higher in cases which follow ***septicaemia***, being reported as
    a. 81% by Fein *et al.* (1983), and
    b. 78% by Fowler *et al.* (1983)

Histopathology

NB: three stages described

- ***The Acute Stage Infiltration***

• this is characterised by damage to the integrity of the blood-gas barrier
• the changes are not visible by light microscopy
• EM shows extensive damage to ***type I alveolar epithelial cells***, which may be totally destroyed
• the BM is usually preserved and the epithelial cells form a continuous layer, with cell junctions seemingly intact
• ***endothelial permeability*** is nevertheless increased
• interstitial oedema is found predominantly on the "service" side of the capillary, sparing the "active" side
• this pattern is similar to that observed with cardiogenic oedema
• protein containing fluid leaks into the alveoli, together with rbc's and leucocytes bound in an amorphous material containing fibrous strands
• this exudate may form sheets lining alveoli → ***hyaline membrane formation***
• ***intravascular coagulation*** is common at this stage
• in patients with septicaemia, capillaries may be completely plugged with leucocytes and the underlying endothelium damaged

- ***The Sub-Acute or Chronic Stage Proliferation***

• attempted repair and proliferation predominate at this stage
• there is thickening of the endothelium, epithelium and interstitial space
• type I epithelial cells are destroyed and replaced by type II epithelial cells which proliferate but ***do not*** differentiate to type I cells
• the later are end-cells and cannot divide
• they remain cuboidal and ~ 10x the thickness of the type I cells
• this appears to be a non-specific response, as it also occurs in ***oxygen toxicity***
• fibrosis commences after about a week and ultimately fibrocytes predominate
• extensive fibrosis is seen in resolving cases
• within the alveoli, the protein rich exudate may organise to produce the characteristic 'hyaline membrane', which effectively destroys alveoli

- ***Resolution***

• there is a reduction in the inflammatory infiltrate, alveolar duct and respiratory bronchiole fibrosis

Pathophysiology

• lung ***compliance*** C_L is greatly reduced and is adequately explained by histology
• it is also likely that there is impaired production of ***surfactant*** (Fein *et al*. 1982)
• Petty (1979) using BAL showed abnormally aggregated and inactive surfactant
• FRC is reduced by collapse, tissue proliferation and increased elastic recoil
• alveolar/capillary permeability is increased as demonstrated by studies of transit times with inert tracer molecules
• the concept of "non-cardiogenic" capillary leak is oversimplified, possibilities being,

i. C' activation
ii. fibrinolysis and platelet activation

• Dankzer *et al*. (1979) found a bimodal distribution of perfusion; one fraction to areas of near normal V/Q ratio, and the other to areas of near zero V/Q
• this was sufficient to explain the $P_{A\text{-}aO2}$ gradient without the need to evoke changes in the diffusing capacity DO_2
• ***physiological shunt,*** $\mathbf{Q_S}$ is usually so large (≤ 40%) that a near normal P_{aO2} cannot be achieved even with a $F_IO_2 = 1.0$
• the increase in V_D, which may exceed 70%, requires large minute volumes in an attempt to preserve near normocapnia
• it may be argued that attempting ***normocapnia*** in these patients is inappropriate management
• gaseous exchange is further impaired, in that MRO_2 is usually increased, despite the patient being paralysed and artificially ventilated (Sibbald & Dredger, 1983)

- ***Changes in Respiratory Mechanics (Start In Phase 1)***

1. decreased total pulmonary compliance
2. increased airways resistance
3. increased work of breathing
4. decreased FRC
5. increased respiratory rate & decreased V_T

- ***Changes in Haemodynamics (Sibbald, 1983)***

1. increased PAP
   - increased RV afterload
   - increased RVEDV & RVEDP
   - decreased RVEF ∝ 1/(mean PAP)
   - depression of RV contractility
2. ***normal*** LV function
3. elevation of PCWP
   - without increased in LVEDV
   ? ventricular interdependence
   ? decrease in LV compliance
4. LV dysfunction in later stages

Mechanisms of Causation

• due to the diversity of causes of the condition, it appears there may be several mechanisms of causation, at least in the early stages
• in all cases, initiation seems to occur following damage to the alveolar/capillary membrane with transudation often increased by pulmonary venoconstriction
• thereafter the condition is accelerated by a number of positive feedback mechanisms
• the initial insult may be either direct or indirect (see table above)
• much of the interest is in the indirect causes, which may be mediated either by cellular or humoral elements
• ***cell types*** capable of damaging the membrane include,

a. neutrophils
b. basophils
c. macrophages
d. platelets - through arachidonic acid derivatives

• ***humoral agents*** include,

a. bacterial endotoxin
b. tumour necrosis factor
c. platelet activating factor (PAF)
d. histamine, bradykinin, serotonin, and arachidonic acid metabolites
e. O_2 free radicals
f. proteases
g. thrombin, fibrin and FDP's

• various chemotactic agents, especially C_{5a}, play a major role in the direction of formed elements onto the pulmonary endothelium
• Malik, Selig and Burhop (1985) drew attention to the fact that many of the humoral agents are capable of producing ***pulmonary venoconstriction***
• this facilitates transudation caused from increased permeability
• Seeger *et al*. noted that a number of proteins, including albumin but particularly ***fibrin monomer***, antagonise the effects of surfactant

• ***T.Oh:*** two possible mechanisms of causation,

1. C' activation
2. fibrinolysis and platelet activation

NB: however, both suffer from sparse clinical evidence,
C' activation has nonpredictive value and is non-specific
FDP-D 'antigen' identified in patients with ARDS and may be a marker of mediator injury (represents thrombosis preceding fibrinolysis)

Neutrophil Mediated Injury

• the postulated sequence begins with activation of C_{5a}, which results in ***margination*** of neutrophils on vascular endothelium
• this is known to be activated in ***sepsis*** and during ***cardiopulmonary bypass***
• significant margination is seen in many cases of ARDS
• however, margination can occur ***without*** significant lung injury, as occurs during haemodialysis with a cellophane membrane
• the postulate is that the neutrophils are somehow primed prior to margination
• this may occur with ***endotoxin***, which results in firm adherence of neutrophils to the endothelium
• C_{5a} results in temporary adherence but more importantly triggers inappropriate release of lysosomal contents to the cell exterior, cf. into phagocytic vesicles
• four groups of substances released in this way may potentially damage the endothelium;

1.	O_2 derived free radicals	→	lipid peroxidation inactivate α_1-antitrypsin
2.	proteolytic enzymes (esp. elastase)	→	direct endothelial damage monocyte/macrophage chemotaxis (elastin fragments)
3.	arachidonic acid metabolites	→	vasoconstriction increased permeability neutrophil chemotaxis
4.	platelet activating factors	→	intravascular coagulation direct tissue damage

• the role of neutrophils has been studied in depleted animals with conflicting results
• ARDS does seem less severe in ***neutropaenic patients***, however it still may develop
• while they possess the capability for tissue damage, it seems unlikely they are the sole agent

Macrophages & Basophils

• these have been studied to a far lesser extent
• they contain a similar array of potentially tissue destructive factors and are already present within the alveoli
• there numbers are greatly increased in patients with ARDS

Platelets

• these are also present in large numbers in the capillaries of patients with ARDS
• aggregation at that site is associated with an increase in capillary hydrostatic pressure, possibly due to a release of arachidonic acid metabolites
• they may also play a role in the normal integrity of the capillary endothelium (Malik, Selig & Burhop, 1985)

- ***Mediators***

a. ***prostaglandins*** - $TBXA_2$
- PGI_2

b. ***leukotrienes*** - chemotaxis
- vasoconstriction
- bronchoconstriction

c. ***lymphokines***

i. IL-1 & TNF - widespread immune stimulation
- activation of inflammatory response
- septic syndrome, fever
- vasodilatation
- hyperdynamic circulation
- systemic catabolism, hepatic anabolism
- acute phase response

ii. IL-1 & 2 - T-cell stimulation/activation

iii. IL-3 & CSF's - marrow & specific colony stimulation

iv. IL-4 & 6 - B-cell stimulation

v. interferons - antiviral activity
- T & NK cell stimulation

- IL-1, or ***endogenous pyrogen,*** acts on the pre-optic area of the hypothalamus with subsequent heat production

d. ***complement*** - chemotaxis
- vasodilatation
- increased capillary permeability

e. ***tumour necrosis factor***

f. ***endotoxin***

g. others

i. histamine

ii. serotonin

iii. FDP's

Principals of Management

NB: treatment of ***primary pathology***,
other management is essentially supportive

• no specific therapeutic measure has been shown to significantly reduce the development / progression of the disease
• there are four main objectives of management (Nunn),

1. maintenance of an adequate P_{aO2}
2. minimise pulmonary transudation
3. prevent complications, particularly - sepsis
   - barotrauma
4. maintenance of an adequate circulation

▪ ***T.E. Oh***

1. ventilation - pressure controlled ventilation
2. fluid management
3. cardiac support
4. nutrition
5. physiotherapy
6. other therapies
   i. steroids - short burst therapy, methylprednisolone 1-2g
      ? long-term, see below
   ii. CPAP
   iii. antibiotics * only by M,C&S, not prophylactic
   iv. heparinisation - not useful for ARDS
   v. ECMO
   vi. ultrafiltration - patients unresponsive to diuretics with H_2O retention
      ? clearance of mediators of sepsis, medium MW

▪ ***Ventilation***

• aim to maintain adequate oxygenation and reduce peak and mean airway pressure
• PEEP is almost universally required to maintain an adequate P_{aO2}
• it is of no prophylactic benefit but improves survival
• benefits of PEEP are,

1. reduction in F_IO_2
2. improved DO_2
3. increased compliance
4. reduction in atelectasis

▪ ***Ventilation***

• hazards of PEEP include,

a. ***increase*** in total lung water

b. destruction of surfactant

c. may produce a fall in CO and DO_2

• normocapnia becomes a lower priority as ***barotrauma*** becomes likely
• HFJV & HFPPV provide ***no advantage*** over traditional ventilation, they result in a decrease in mean P_{IP}, but there is no improvement in mortality
• ECMO has shown no proven benefit, mortality remains the same (except in children)
• however, partial ECMO ($ECCO_2R$) may reduce the mortality in the severe group

• ***T.Oh:*** the optimal mode of ventilation is unknown
• the level of ***optimal PEEP*** is described using various end-points,

a. lowest Q_S < 20%

b. maximal DO_2

c. P_{aO2} > 60 mmHg * with lowest $F_IO_2 \geq 30\%$

d. maximal improvement in C_L

▪ ***Pharmacotherapy***

• fluid balance should be adjusted to lessen the formation of oedema
• Fein *et al*. recommend values of **PCWP ~ 5-10 mmHg**
• formation may be further reduced with the administration of NSA-C, as the plasma albumin is frequently reduced

• some early work suggested the administration of massive doses of ***steroids*** may halt the development of the disease, Sibbald *et al*. 1981
• subsequent work has shown ***no benefit***, or an increased incidence of sepsis and a higher mortality, thus the administration of steroids is not recommended
• other pharmacotherapy includes,

a. PG inhibitors

b. anti-TNF

c. anti-LPS Ab

d. antioxidants

e. PG's

NB: these are only of prophylactic benefit in animal studies
Ibuprofen improves early haemodynamic stability but not mortality

- ***Outcome***

a.	mortality	~ 50-70% - unchanged over the last decade
b.	poor prognosis	- severe disease - uncontrolled 1° cause - high PVR - RV dysfunction - impaired DO_2
c.	associated problems	- 70% nosocomial pneumonia - high incidence of sepsis syndrome - MOSF