By Adam Hollingworth

4.Diffusion

Table of Contents

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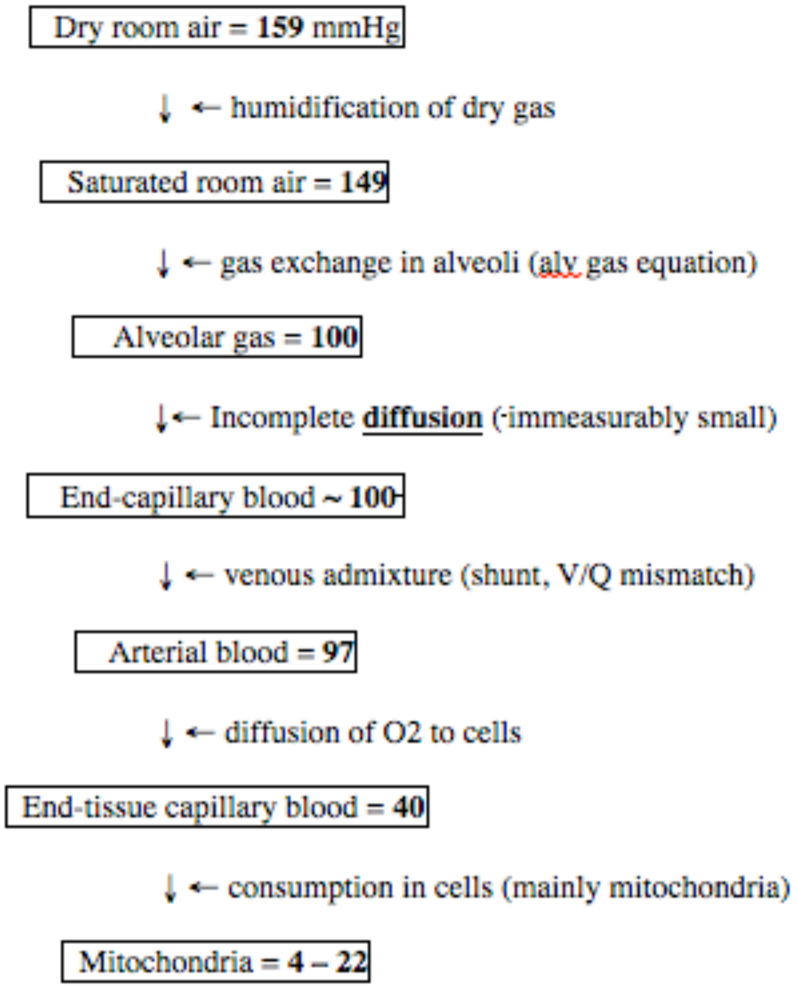
Oxygen Cascade

- = stepwise decrease in PO2 starting from dry room air all the way to the site of consumption (ie mitochondria)
- typical values in a health person on **room air**:



Dry room air = **159** mmHg

↓ ← humidification of dry gas

Saturated room air = **149**

↓ ← gas exchange in alveoli (alv gas equation)

Alveolar gas = **100**

↓← Incomplete **diffusion** (-immeasurably small)

End-capillary blood ~ **100**

↓ ← venous admixture (shunt, V/Q mismatch)

Arterial blood = **97**

↓ ← diffusion of O2 to cells

End-tissue capillary blood = **40**

↓ ← consumption in cells (mainly mitochondria)

Mitochondria = **4 – 22**

Diffusion

Laws of Diffusion

- under norm conditions PO2 difference between alveolar gas and end capillary blood should be immeasurable small.
- Difference is due to incomplete diffusion as defined by Fick: (not same as Fick principle)
- Must diffuse across blood-gas barrier:
  - Alveolar epithelium
  - Interstitial fluid
  - Pulmonary capillary epithelium
- Ficks Law: Diffusion rate is:
  - $\propto$ to the area
  - inversely $\propto$ to the thickness
  - $\propto$ to partial pressure difference
  - $\propto$ to the solubility of the gas in the tissue but inversely proportional to the square root of the molecular weight
    - ↳= the diffusion constant

- Can define Ficks law mathematically:

$$\text{Gas flow} \ \alpha \ \frac{D.A.\ \Delta P}{T}$$

A = area (~300 million alveoli with surface area of 50-100m^2 for the lung)
ΔP = partial pressure difference across membrane (P1 – P2)
T = thickness of blood gas barrier (~0.3um in lung)
D = diffusion constant of gas

- Can define diffusion constant mathematically also:

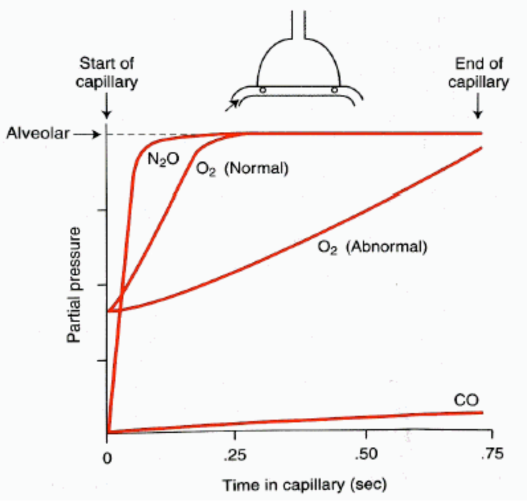
$$D_{Gas} \ \alpha \ \frac{\text{solubility}}{\sqrt{MW}}$$

Dgas = diffusion constant
MW = molecular weight = Grahams Law

- Figures for both equations as prev:
  - D_{CO2} ~ x20 that of D_{O2}
    ↳ means CO2 diffuses 20x faster than o2 because Co2 highly soluble but with same molecular weight
  - ΔP for:
    - O2 = PAo2 – PvO2 = 100mmhg – 40mmHg = 60mmHg
    - CO2 = PvCO2 – PACO2 = 46 – 40mmHg = 6mmHg
- Overall diffusion:
  - O2 = ~ 250mlO2/min
  - CO2 = ~ 200ml CO2/min
    ↳ because of the power of solubility stronger that ΔP difference or MW

Diffusion & Perfusion Limitations

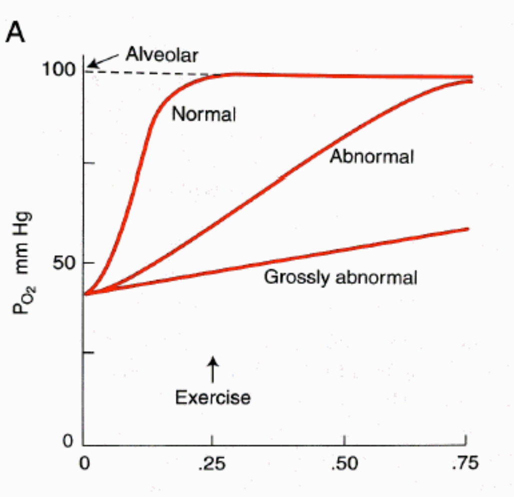
- At resting cardiac output rbc spends ~0.75secs in pulmonary capillary
  ↳ during exercise transit time ↓to ~0.25secs
- Equilibrium of partial pressures occurs within 0.25secs ie 1/3 transit time



- Carbon Monoxide = diffusion limited
  - CO rapid across blood-gas barrier ⇒ ↑CO content of rbc

  - But CO binds so tightly to Hb that it leads to hardly any ↑ in pp of CO
    ↳ affinity for Hb x250 that of O2 & rate of combination is faster
  - ∴ pp gradient remains (∴ ΔP remains high) & CO can continue to rapidly diffuse across alveolar wall
  - ∴ amount of CO that gets into blood is limited by diffusion properties of barrier and not amount blood available
- Nitrous Oxide = perfusion (or flow) limited
  - Into blood, no reaction with Hb ⇒ ↑ppN2O rapidly
  - eg pp N20 in blood same as alveolar gas within 0.10 secs (∴ΔP = 0)
  - ∴ amount N20 taken up depends on blood flow
- O2 = usually perfusion limited under norm circumstances:
  - O2 combines with Hb but not as strong as CO
  - Resting condition : Po2 of blood reach alveolar level ~1/3 through cap transit time
    ↳∴ perfusion limited
  - Abnormal conditions eg damage/thickening of blood gas barrier ∴ equilibrium not obtained in transit time
    ↳∴ diffusion limitation
- Diffusion vs perfusion limitation depends on comparison of solubility of gas in the:
  - blood-gas barrier compared with blood ↳= dissociation curve
    ↳eg N20 = same; CO = very different

Oxygen Uptake Along Pulmon Capillary



- PO2 of blood in pulmon art entering alveoli = 40mmHg
- Alveolar PO2 = 100mmHg
- Diffusion across large pressure gradient; equilibrium within ~1/3 cap transit time
- ∴Diffusion reserves of normal lung are enormous
- with severe exercise:
  - ↓↓cap transit time of blood
  - in normal people – equilibrium still achieved
- grossly abnormal blood-gas barrier:
  - thickened barrier
  - rise in Po2 in blood much slower & equilibrium ± not achieved
- alveolar hypoxia:
  - marked ↓in pressure gradient ∴ slower diffusion
  - also influenced by o2 dissociation curve as at low Po2 have hit steep slope
  ↳ eg diseased lung or high altitude
- ∴ diffusion process is challenged by:
  - exercise

  - alveolar hypoxia – eg high altitude/lung disease
  - thickened blood-gas barrier

Measurement of Diffusing Capacity

- Carbon monoxide (CO) is gas of choice for measuring diffusion properties as is entirely diffusion limited
- In living person the area & thickness of blood/gas barrier cannot be measured
  ↳∴ Fick equation can be re-written

  Gas flow = D_L x ΔP

- D_L =
  - the diffusing capacity of the lung ie:
    - area
    - thickness
    - diffusion properties of b/g barrier & gas involved

- thus rearrange above equation to find D_L =

$$D_L = \frac{V_{CO}}{\Delta P}$$

V_{CO} = gas flow for CO

- because PaCO is so small it can be ignored leaving PACO2 only:

$$D_L = \frac{V_{CO}}{P_ACO}$$

↳ VCO and PaCO can both be measured

- ∴ diffusing capacity of the lung for CO = volume CO transferred in ml/min/mmHg of alveolar partial pressure
-
- Single breath method:
  - Single insp of dilute CO
  - Rate of disappearance of CO from alveolar gas during 10second breath hold is calculated
  - Measure inspired & expired conc of CO before & after breath hold
  - Helium is added to give measurement of lung volume by dilation
- Norm value @ rest = 25ml/min/mmHg
  ↳this ↑s 50-70ml/min/mmHg on exercise due to ↑ed recruitment & distension of pulmon capillaries

Factors Affecting Diffusion Capacity for CO

- measured diffusion capacity for CO depends on
  - lung surface area – most common
    - body size: ↑height ⇒ ↑lung volume ⇒ ↑ D_L
    - V/Q mismatch: ↓interface for transfer ⇒ ↓ D_L
    - Posture: ↑ D_L in supine
    - Pathology: eg emphysema ⇒ ↓alveolar septae ⇒ ↓interface ⇒ ↓ D_L
  - blood gas barrier changes:
    - APO: 2 methods of disruption:
      - ↑length of diffusion pathway through plasma or interstitial oedema

    - ↑ed capillary pressure ⇒ damaged epithelium & endothelial cells ⇒ prolif of type II alveolar cells ⇒ thickened membrane
- factors affecting uptake of gases by Hb:
  - Hb concentration – influences rate & amount of O2 uptake
  - ↓ed capillary transit time eg exercise:
    - causes capillary recruitment ∴ ↑ D_L
    - causes ↓transit time: if <0.25secs
- other causes of ↓ D_L :
  - ↑ing age
  - women
  - black Americans
  - smoking
- exercise can double D_L
- in diseased lung also:
  - diffusion properties
  - alveolar volume
  - capillary blood

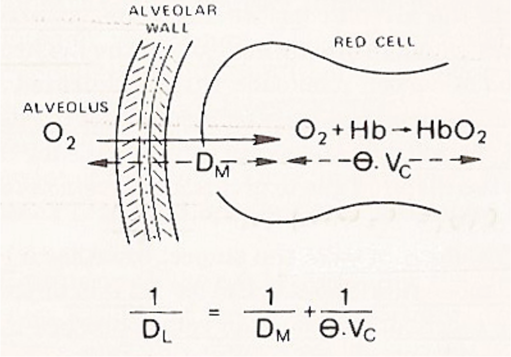
Overall Diffusion Resistance

- Ficks law assumes all resistance to movement of O2 & Co2 resides in the alveolar wall
  ↳ 2 other factors exist:
    - Distance from alveolar wall to centre of rbc
    - Reaction rate of O2 with Hb inside rbc
      ↳ = a finite rate (for O2 & CO2 = 0.2 secs)
- ∴ uptake of gas effectively in 2 stages:
  - diffusion of gas – through blood gas barrier, plasma and rbc membrane
  - reaction of O2 with Hb
    ↳ known as θ**,**
    = mlO_2/min that combine with 1ml of blood per mmHg of PO_2
- the 2 stages can be added together = overall diffusion resistance
- MATHS:

Ohm equation for resistance : $R = \frac{\Delta P}{Q}$

inverse of resistance is known as **conductivity** $\frac{1}{R} = \frac{Q}{\Delta P}$

diffusion capacity actually = conductivity: $D_L = \frac{\text{Gas flow}}{\Delta P}$



∴ inverse of D_L ($1/D_L$) = total resistance:

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta . V_C}$$

1/Dm = resistance of b/g barrier ie incl plasma & distance to centre of rbc

θ = reaction rate of O2 with Hb analogue to diffusing capacity of 1ml of blood ∴ multiply it with total volume of pulm capillary blood (Vc) = effective diffusing capacity of rate of reaction with Hb

↳ ∴ $1/V_C . \theta$ describes the *resistance* of this reaction

CO$_2$ Transfer Across Pulmon Capillary

- CO2 diffusion being x20 faster than o2 means (due to ↑ed solubility)
- ∴ any ↓in transfer of CO2 v unlikely will be a diffusion problem
- But reaction of CO2 with blood is complex ∴ it is possible any difference between end capillary blood and PACO2 can develop if b/g barrier is diseased
- Norm conditions: time for PaCO2 = PACO2 (40mmHg) ~ 0.25 secs (similar to O2)
  - ↳ ∴ good reserves for diffusion
  - ↳ ∴ need diffusing capacity ↓1/4 of normal value to see non equilibrium PACO2:PaCO2

Different O2 Cascades –

Partial Pressure cascade:

FiO2 21%		**FiO2 100%**
Dry room air = **159** mmHg		Dry room Air = **760**
↓	← humidification of dry gas →	↓
Saturated room air = **149**		Saturated room air = **711**
↓	← gas exchange in alveoli (alv gas equation)→	↓
Alveolar gas = **100**		Alveolar Gas **661**
↓	← Incomplete **diffusion** (immeasurably small)→	↓
End-capillary blood **~ 100**		End capillary blood ~ 661
↓	← venous admixture (shunt, V/Q mismatch) →	↓
Arterial blood = **97**		Arterial blood **~ 600**
↓	← diffusion of O2 to cells →	↓
End-tissue capillary blood = **40**		**End-tissue capillary blood ~48-50‡**
↓	← consumption in cells(mainly mitochondria)→	↓
Mitochondria = **4 – 22**		Mitochondria **~4-22**

O2 content (concentration) cascade for Hb 14g/dl:

FiO2 21%		**FiO2 100%**
Dry room air = **159** mmHg		Dry room Air = **760**
↓	← humidification of dry gas →	↓
Saturated room air = **149**		Saturated room air = **711**
↓	← gas exchange in alveoli (alv gas equation)→	↓
Alveolar gas = **100**		Alveolar Gas **661**
↓	← Incomplete **diffusion** (immeasurably small)→	↓
End-capillary blood **~ 20**	**(mlO2/dl for Hb14g/dl)**	End capillary blood ~ **21,5**
↓	← venous admixture (shunt, V/Q mismatch) →	↓
Arterial blood = **20**		Arterial blood **~ 21,3**
↓	← diffusion of O2 to cells →	↓
End-tissue capillary blood = **15**		End-tissue capillary blood **~16,3**
↓	← consumption in cells(mainly mitochondria)→	↓
Mitochondria = 4 – 22mmHg		Mitochondria ~4-22mmHg

- Nb:
  - A-a difference is different on RA compared to 100% O2:
    - 21% = ~4mmHg
    - 100% = ~61mmHg

    ↳ this is due to shape of OHDC – see VQ mismatching

Summary

- Ficks law
- Diffusion & perfusion limited gases
- O2 transfer normally perfusion limited but may become diffusion limited under some circumstances
- Diffusing capacity of lung measured using inhaled CO. Value ↑↑ on exercise
- Finite reaction of rate of O2 with Hb ⇒↓transfer rate into blood