# The Oxygen Cascade

CRFS Workshop Part 1, Canberra 2012

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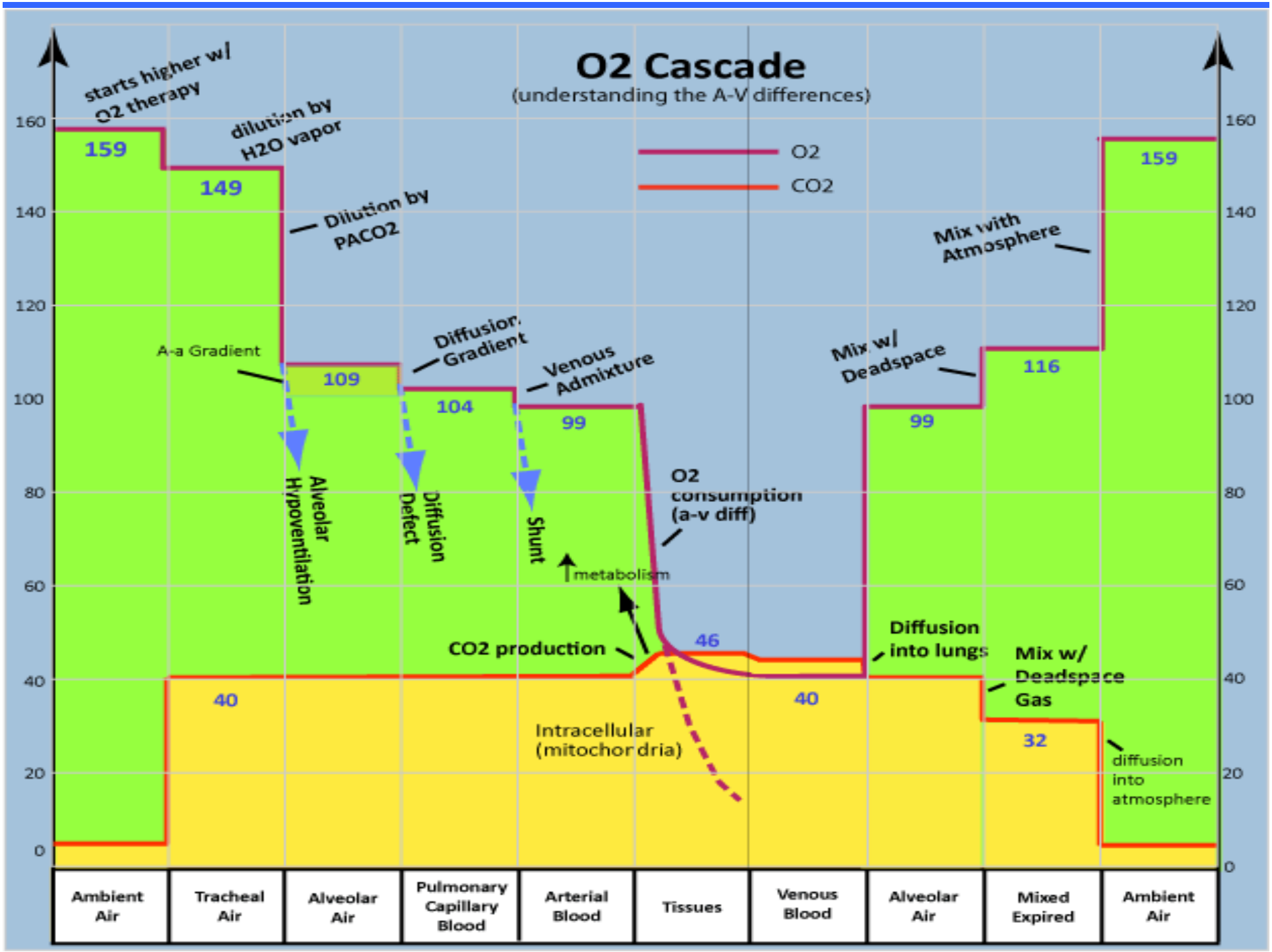
Government of Western Australia
Department of Health
Sir Charles Gairdner Hospital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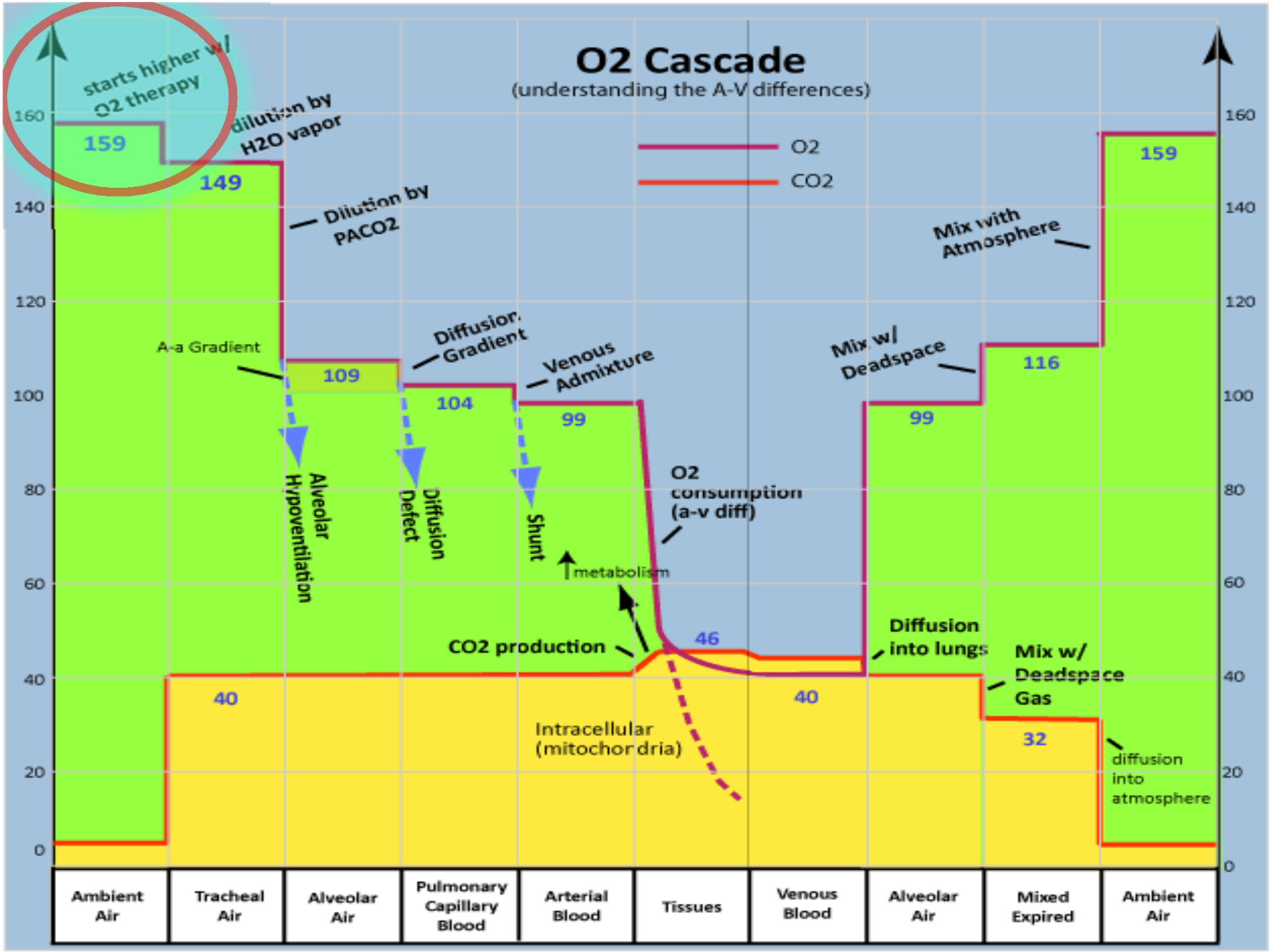
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PO2 = 159 mmHg

# Ambient Air
# Partial Pressures Dalton's Law

**Dalton's law of partial pressures states that the total pressure exerted by the mixture of non-reactive gases is equal to the sum of the partial pressures of individual gases.**

- pTotal = pX + pY + pZ

The total concentration is the sum of the all the component concentrations

- cX + cY +cZ = 1

Therefore pX = cX * pTotal for IDEAL gas mixtures

E.G.:

If pTotal = 100 mmHg and the Oxygen concentration is 50%

then $pO_2$ = 50 mmHg

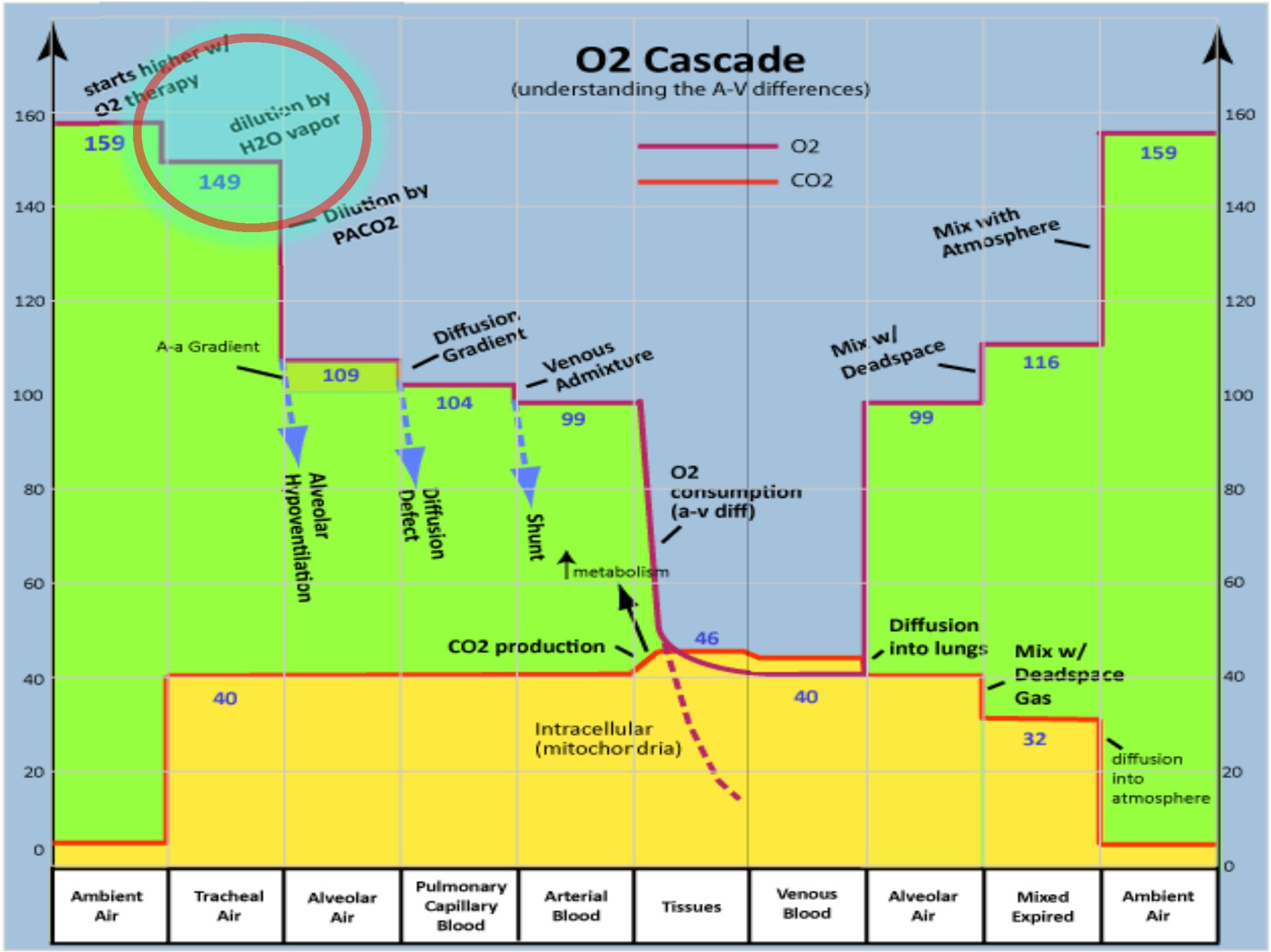
If pTotal = 760 mmHg and the Oxygen concentration is 20.9%

then $pO_2$ = 158.8 mmHg

# Room air at sea level

- The average barometric pressure at sea level is 760mmHg.
- Composition is;

| *Component* | *Room air [%]* | *Pressure [mmHg]* |
|---|---|---|
| $N_2$ | 78.08 | 593.4 |
| $O_2$ | 20.95 | 159.2 |
| Ar | 0.93 | 7.0 |
| $CO_2$ | 0.04 | 0.3 |
| Total | 100.00 | 713.0 |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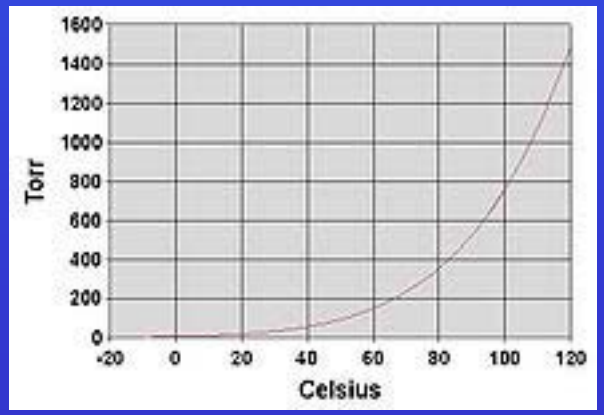
# Ambient Air → Tracheal Air

- $PO_2$ ↑ by Oxygen therapy
- E:G at sea level: 30% O2 = 30% * 760 = 228 mmHg

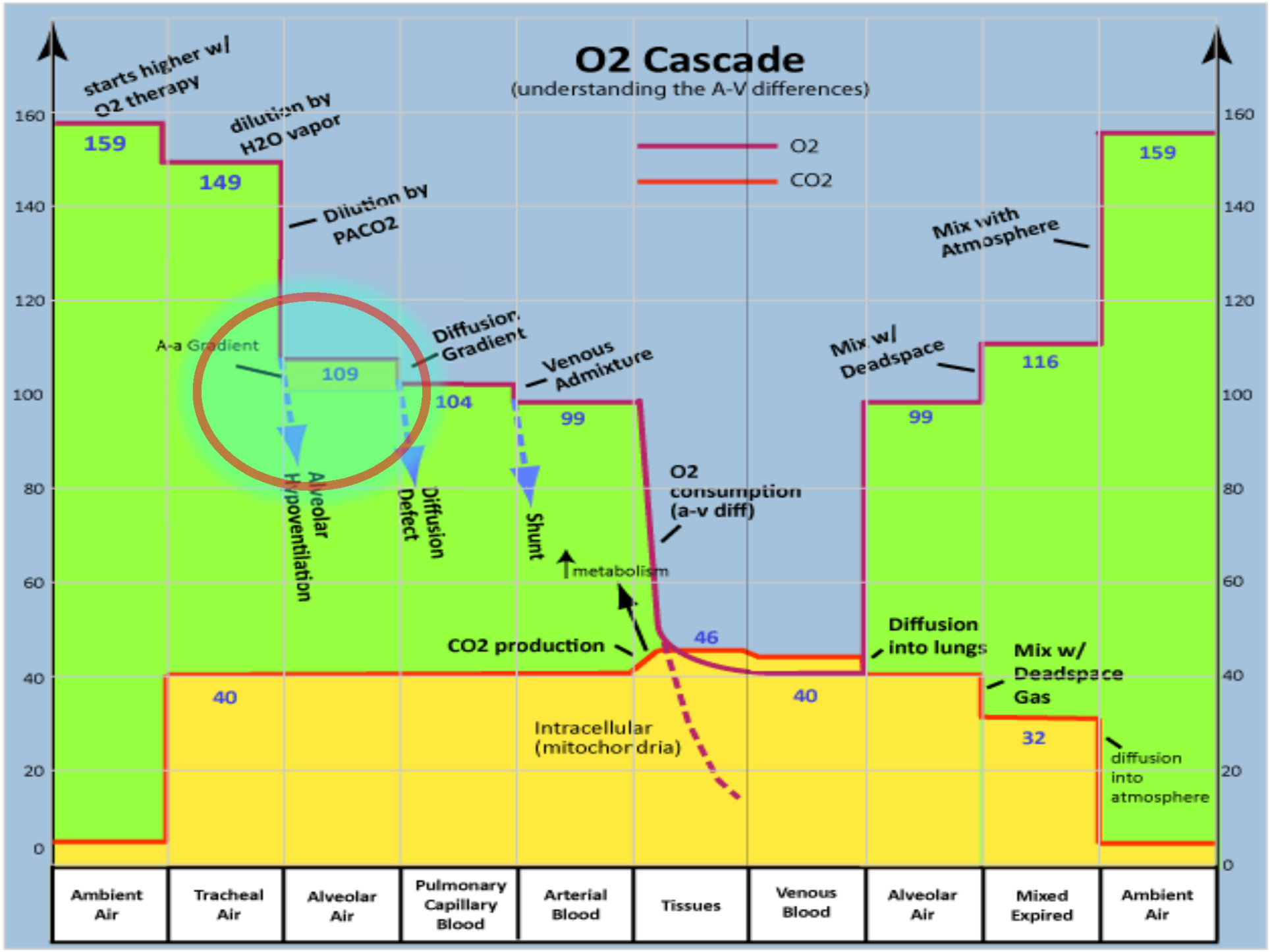
# Ambient Air → Tracheal Air Water Vapour

- Upper Airway warms and humidifies inspired air
- If a liquid is in a closed container the space above the liquid contains a vapor of the liquid.
- The liquid evaporates until the rate of evaporation equals the rate of condensation.
- The partial pressure exerted by the vapor at this equilibrium is the vapour pressure of the liquid.
- Liquids with a higher vapour pressure are said to be more volitile
- Vapour pressure is determined by the liquid and the temperature
- Vapour pressure increases with temperature for water
  - at body temperature 37°C is the vapour pressure is 47 mmHg
  - at 100°C the vapour pressure is 760 mmHg and at sea level water boils.
- Dry gas is 760-47 = 713mmHg



# Saturated vapour pressure

- If a liquid is in a closed container the space above the liquid contains a vapour of the liquid.
- As the vapour becomes more dense the number of molecules returning to there liquid state equals those “evapourating”.
- The particles of this saturated vapour exert a pressure (SVP).
- When saturated this pressure is constant. For water in the atmosphere saturation occurs at 100% humidity and the SVP exerted is 47mmHg.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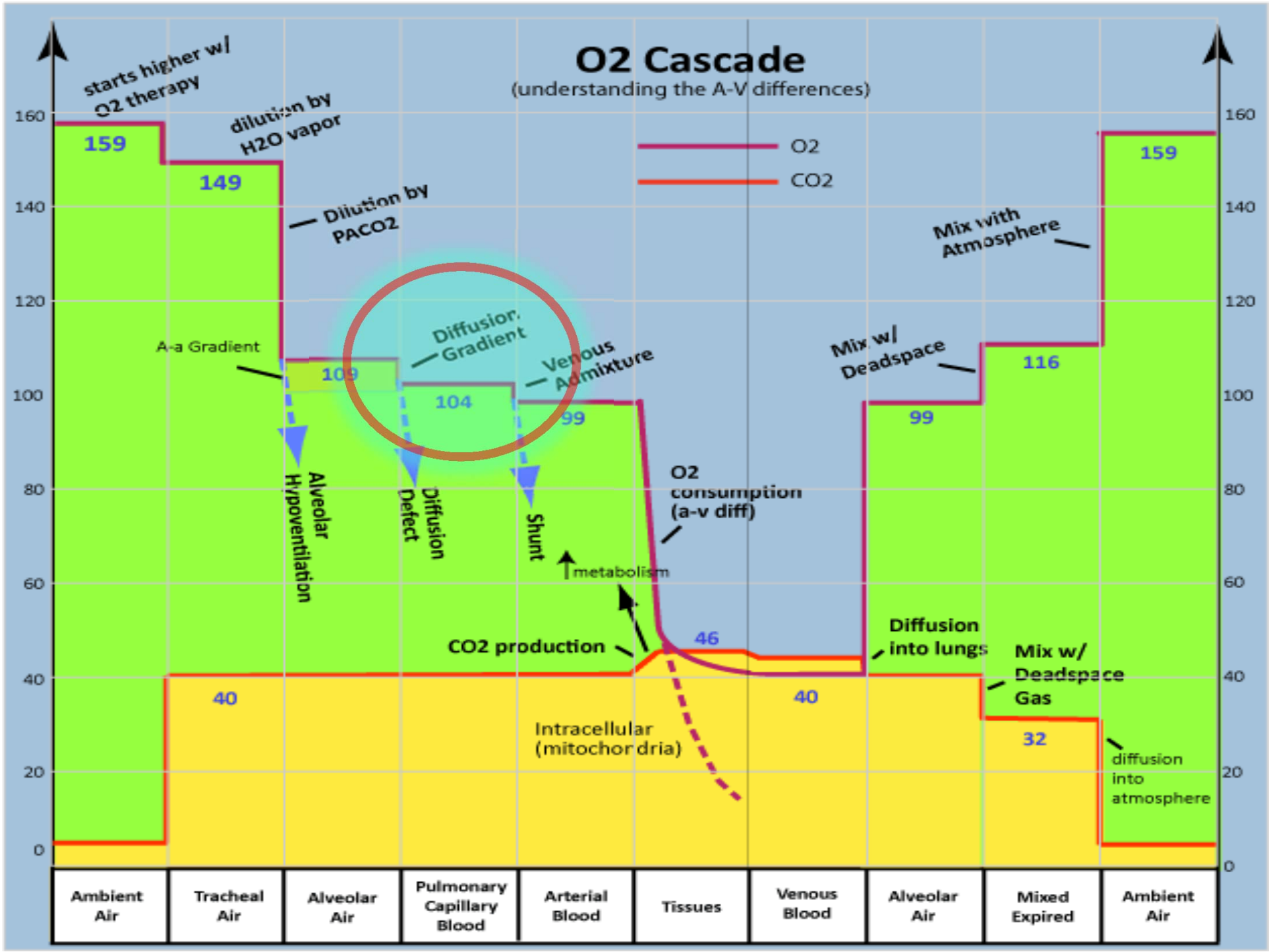
# Tracheal Air to Alveolar Air

- $CO_2$ added
- Hypoventilation
- A-a Gradient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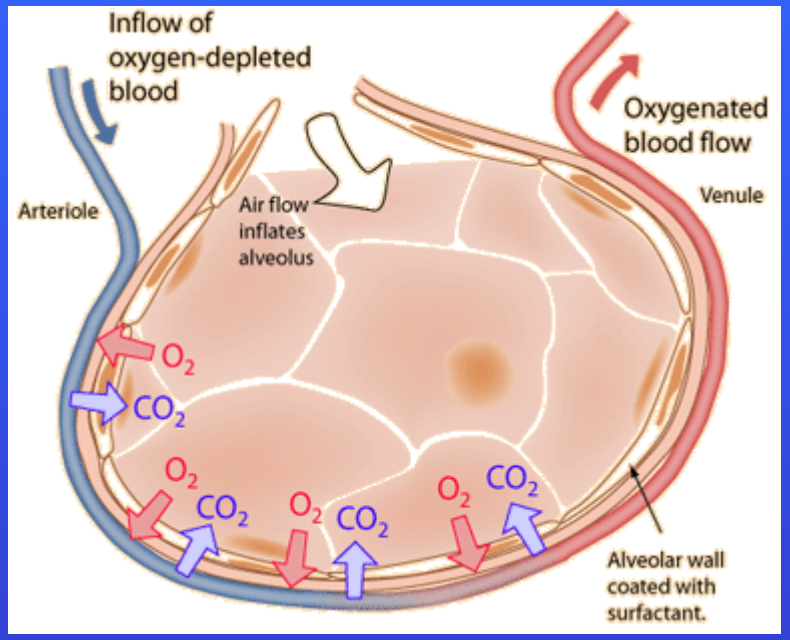
# Alveolar Air to Pulmonary Capillary

- Diffusion
- Solubility in plasma
- Uptake by Haemoglobin

# Graham's Law

- The **relative rate** at which gases dissolve in liquids is proportional to it's solubility and inversely proportional to the square root of it's atomic mass.
- For Oxygen and Carbon-dioxide in plasma:
  - $CO_2$ has 22 times the solubility
  - $CO_2$ is more massive (44 amu compared to 32 for oxygen).
- According to Graham's law, the relative rate of diffusion is given by:

$$\frac{diffusion\ rate\ of\ CO_2}{diffusion\ rate\ of\ O_2} = 22\sqrt{\frac{32}{44}} = 19$$




Source: http://hyperphysics.phy-astr.gsu.edu/hbase/kinetic/Henry.html

# Fick's Law

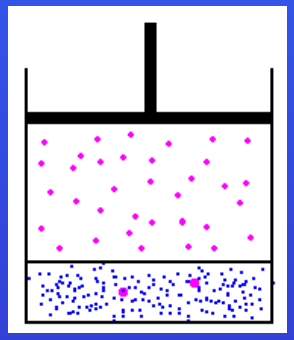
- The net diffusion rate of a gas across a fluid membrane is
  - Proportional to
    - the difference in partial pressure,
    - the area of the membrane
  - Inversely proportional to
    - the thickness of the membrane.

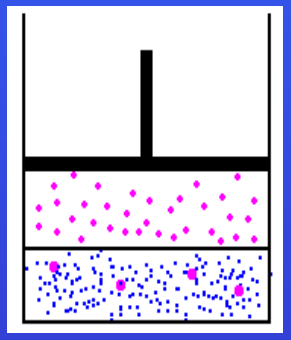
- Combined with the diffusion rate determined from **Graham's law**, Fick's law provides the means for calculating exchange rates of gases across membranes.
- Alveolar surface area is in the order of 100 square meters and has a thickness of $<10^{-6}$m - a very effective gas exchange interface.

# Henry's Law

William Henry

- At a constant temperature, the concentration of dissolved gas in a liquid is proportional to the partial pressure of the gas above the liquid.



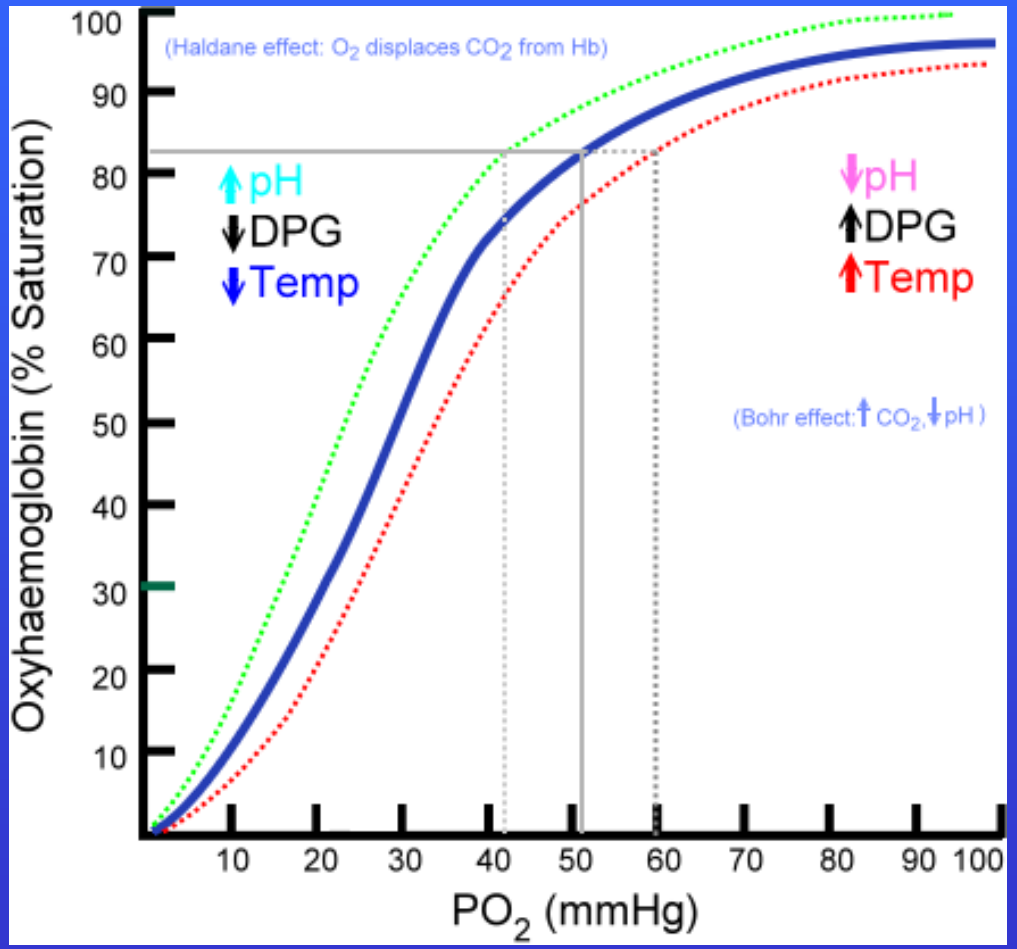


- Double the pressure and you double the solubility and concentration of dissolved gas.

Source:http://chemwiki.ucdavis.edu/Physical_Chemistry/Physical_Properties_of_Matter/Solutions/Ideal_Solutions/Dissolving_Gases_In_Liquids,_Henry's_Law

# Haemoglobin Dissociation Curve

| | **left shift** higher affinity for $O_2$ | **right shift** lower affinity for $O_2$ |
|---|---|---|
| Temperature | decrease | increase |
| 2.3-DPG | decrease | increase |
| $pCO_2$ | decrease | increase |
| pCO | increase | decrease |
| pH (Bohr effect) | increase (alkalosis) | decrease (acidosis) |
| type of haemoglobin | fetal Hb | adult Hb |



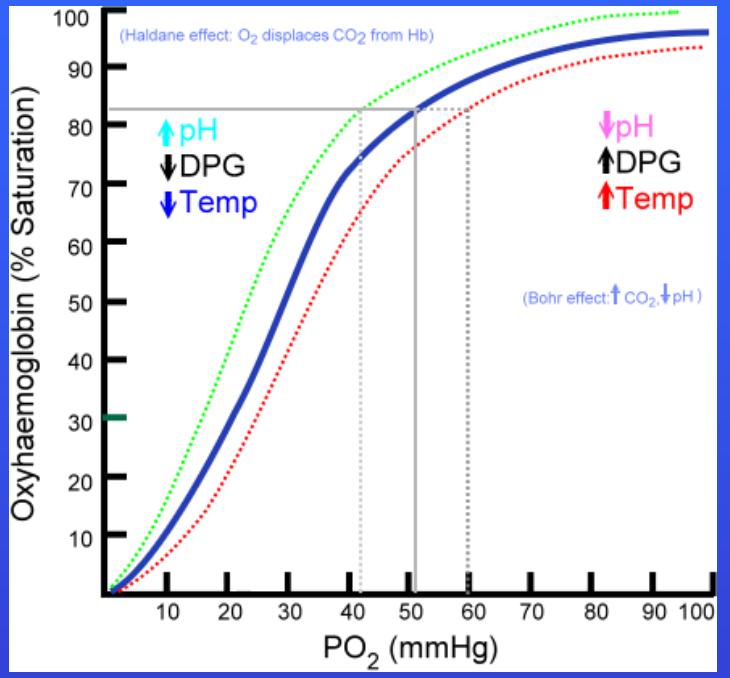

P50 = The $pO_2$ at which the Hb is 50% saturated, typically about 26.6 mmHg.

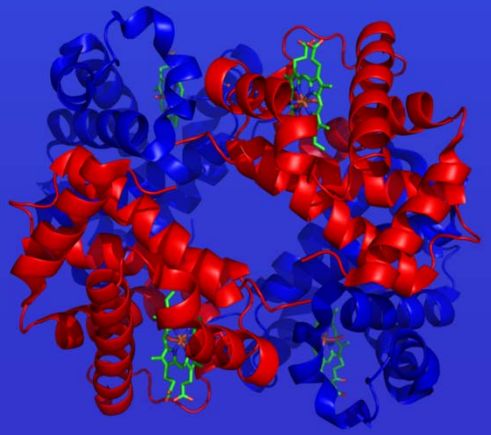
# 2,3 DPG

- It interacts with deoxygenated haemoglobin beta subunits by decreasing their affinity for oxygen, so it allosterically promotes the release of the remaining oxygen molecules bound to the haemoglobin, thus enhancing the ability of RBCs to release oxygen near tissues that need it most.

# Haemoglobin Dissociation Curve

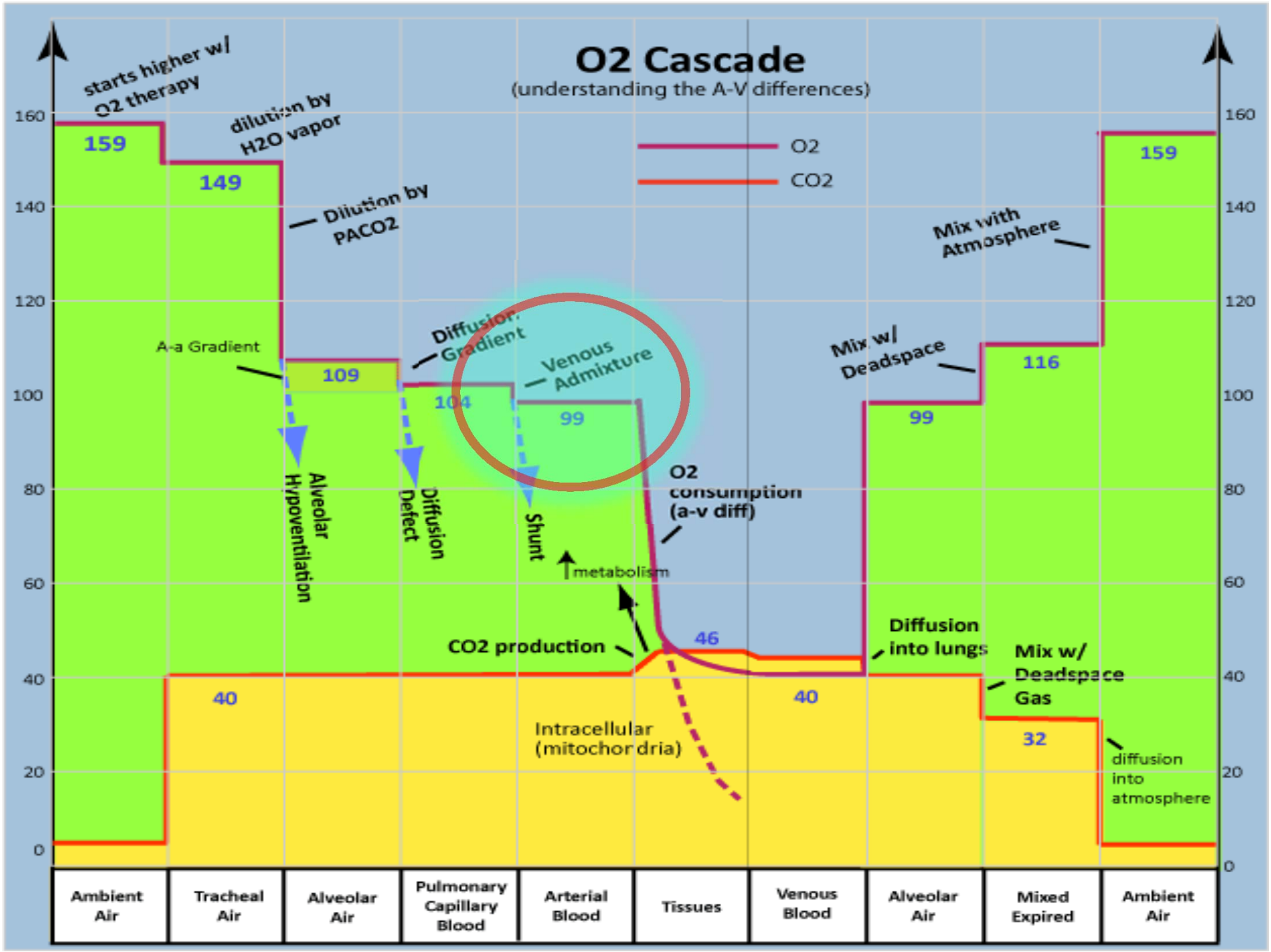
- P50 =The $pO_2$ at which the Hb is 50% saturated, typically about 26.6 mmHg.
- The 'plateau' portion in pulmonary capillaries (minimal reduction of oxygen transported until the $pO_2$ falls 50 mmHg).
- The 'steep' portion in systemic capillaries (a small drop in systemic capillary $pO_2$ can result in the release of large amounts of oxygen for the metabolically active cells).



# Haemoglobin

- Cooperative Binding
  - First  Oxygen is difficult
  - Each additional oxygen increases the oxygen affinity
  - Until all sites are filled
- Hemoglobin's oxygen-binding capacity is decreased in the presence of carbon monoxide because both gases compete for the same binding sites on hemoglobin, carbon monoxide binding preferentially in place of oxygen.
- The binding of oxygen is affected by molecules such as carbon monoxide (CO) (for example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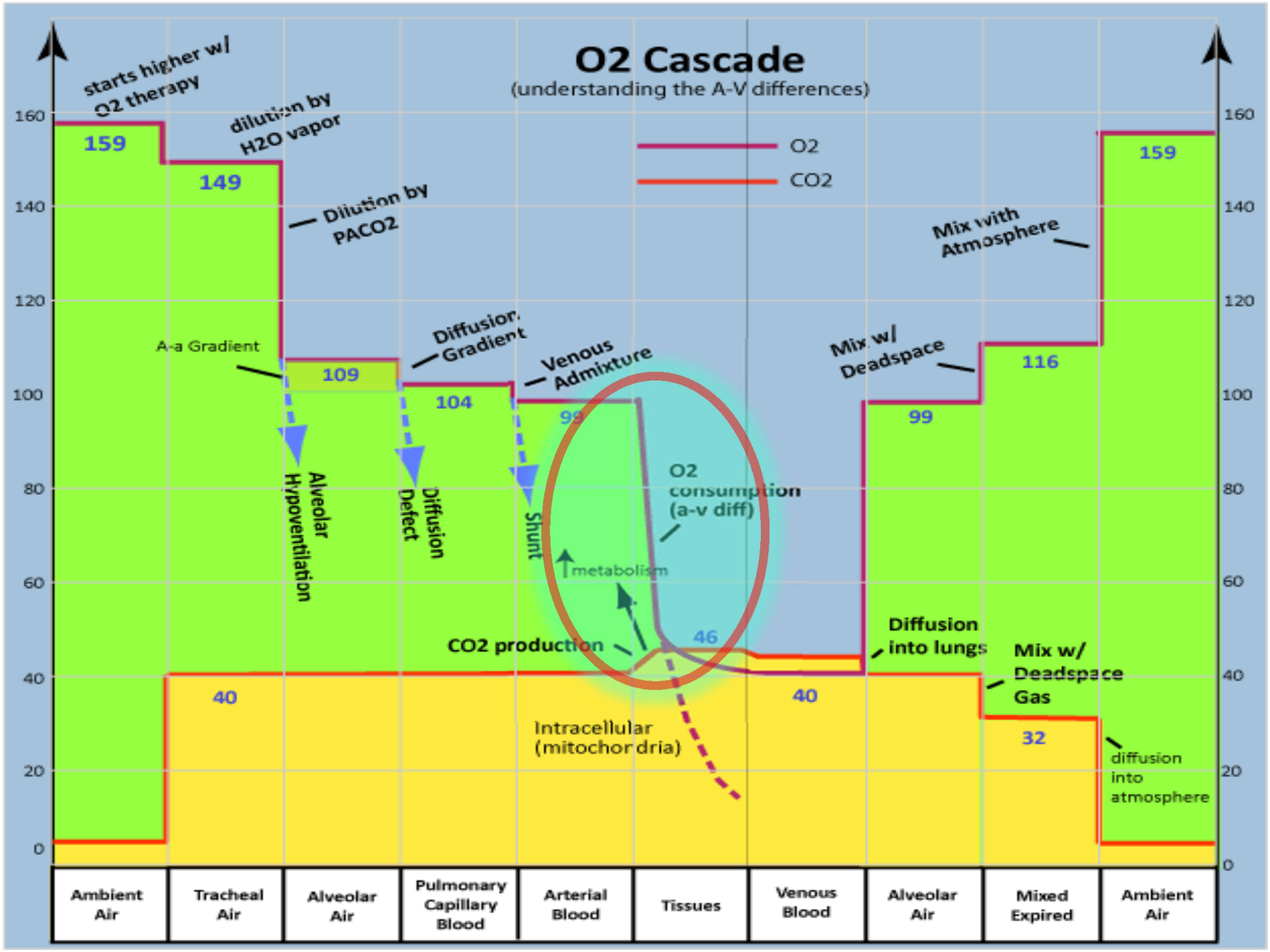
# Pulmonary Capillary Blood to Arterial Blood

- Venous Admixture
- Venous blood which bypasses oxygenation in the lungs
- Shunt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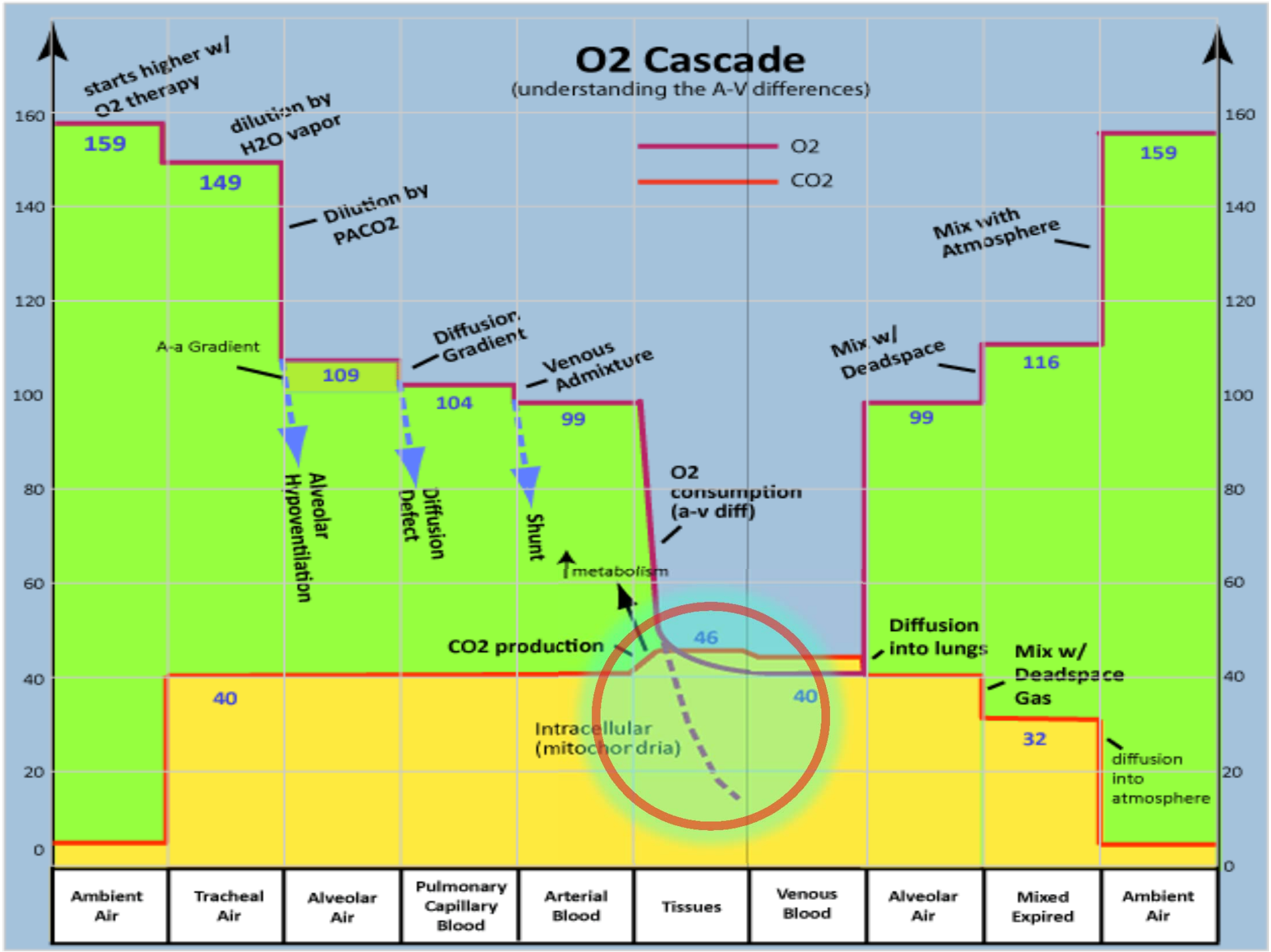
# Arterial Blood to Tissues

- Oxygen Consumption
- Metabolism
- Increased Temperature
- More Acidic (pH ↓)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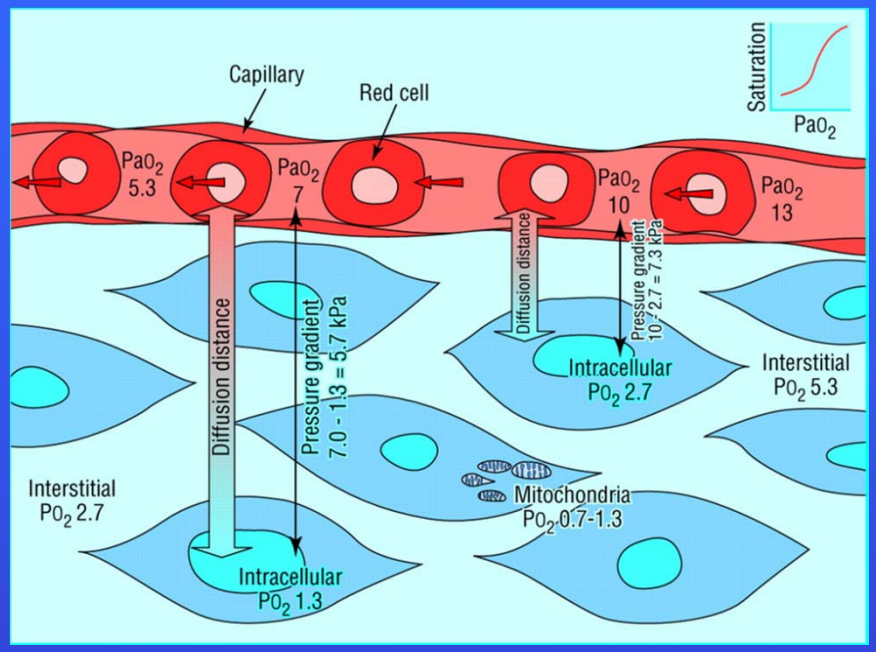
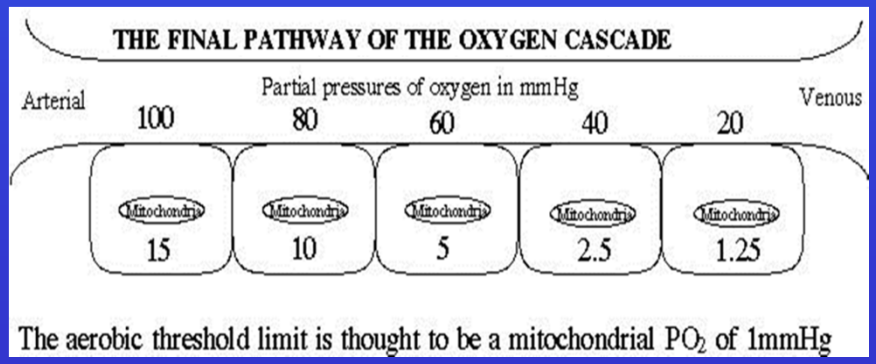
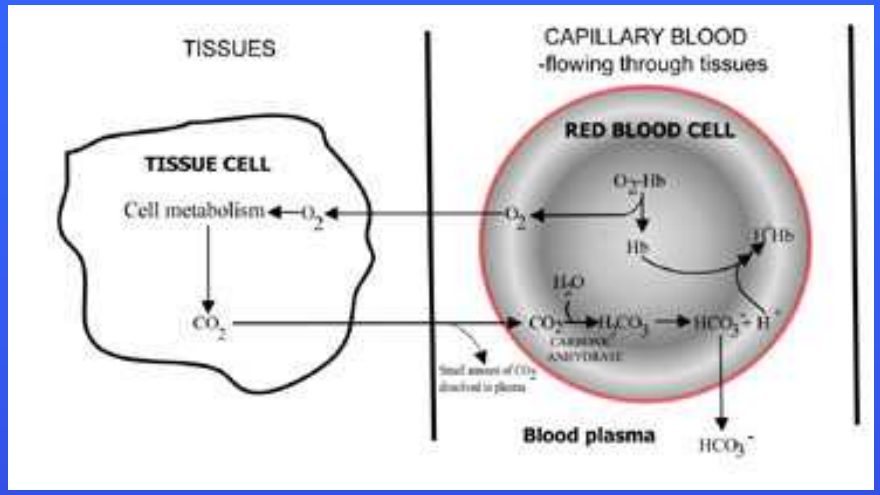
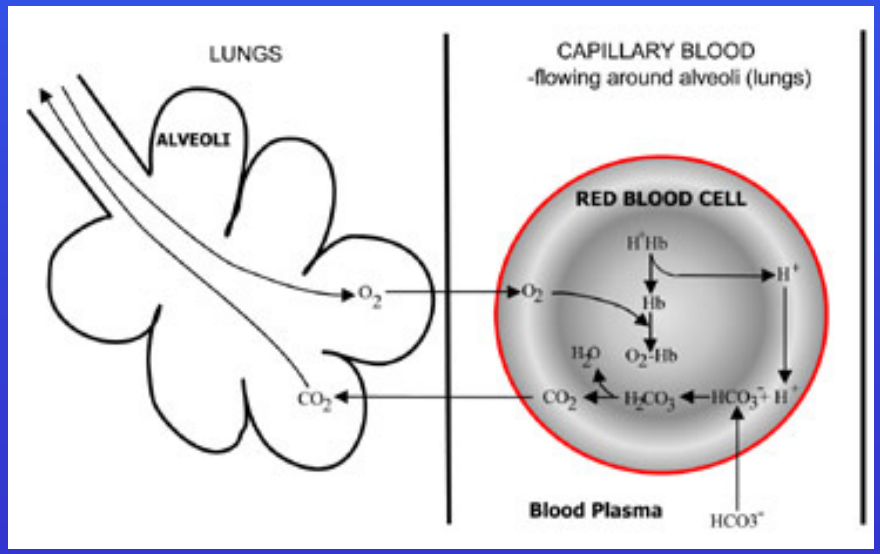
# Tissues to Mitochondria

- Haemoglobin to plasma
- Capillary walls
- Interstitial fluid
- Cell membrane
- Intercelular
- Mitochondria
- Aerobic threshold
- $PO_2$ ~ 1 mmHg



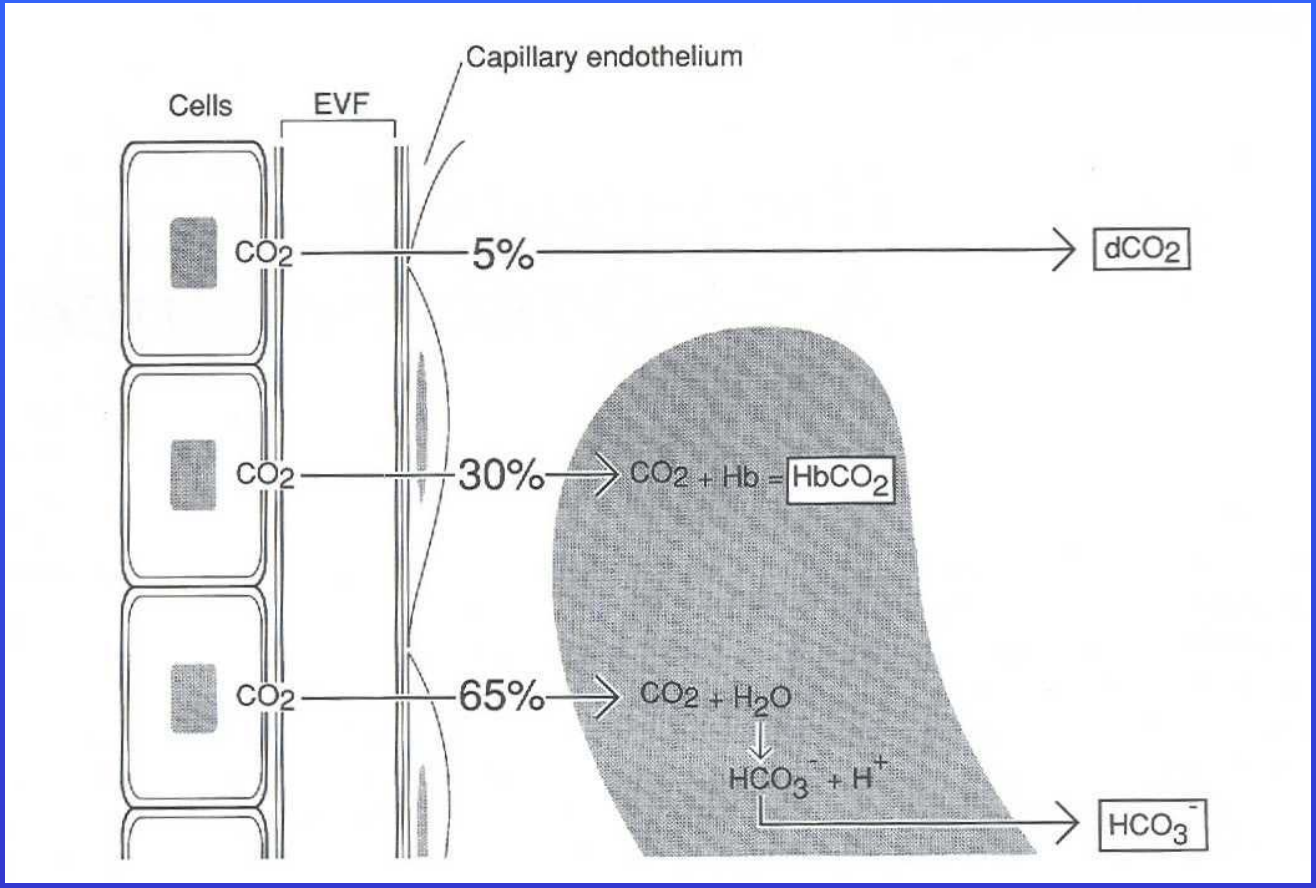


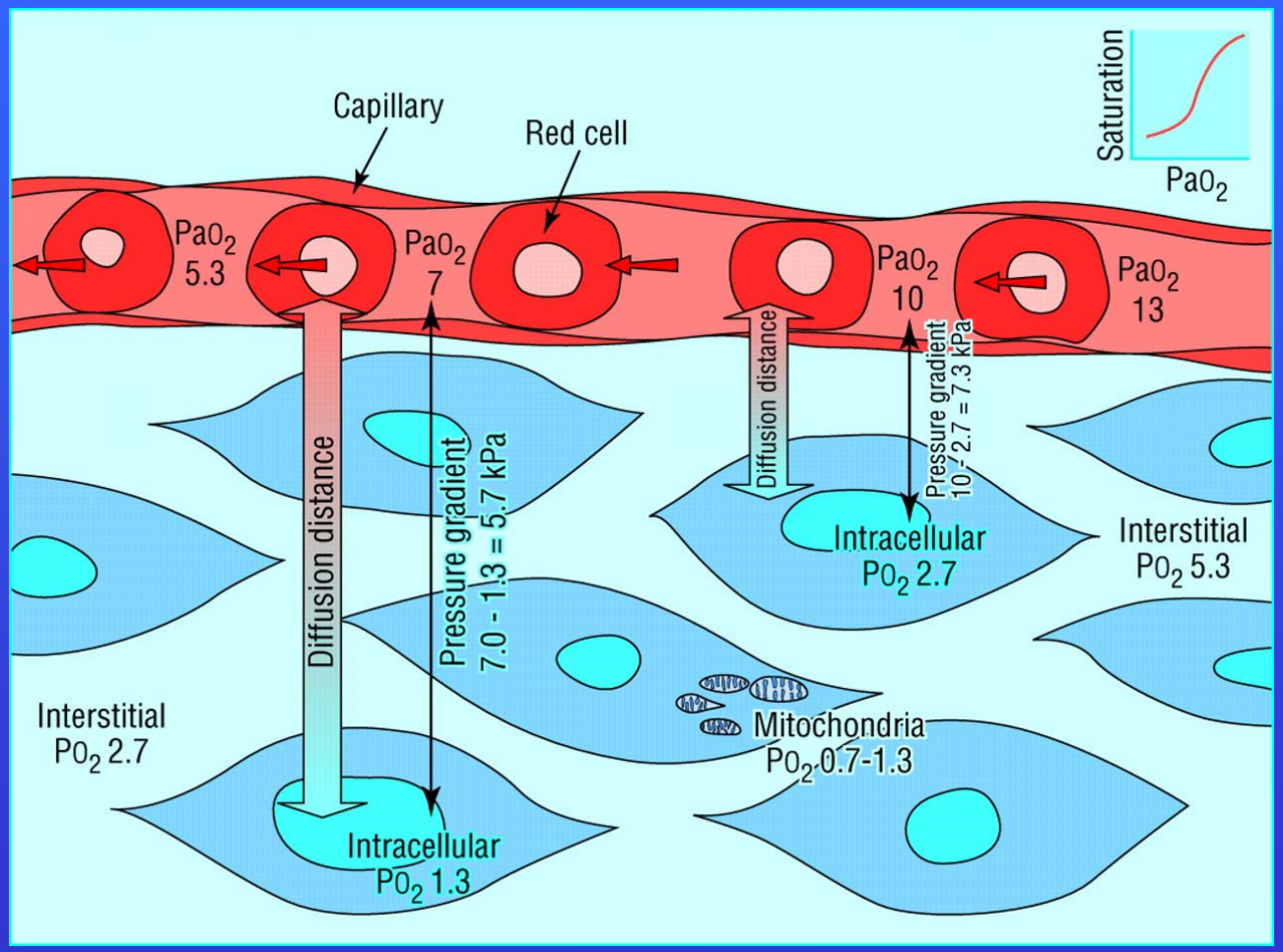



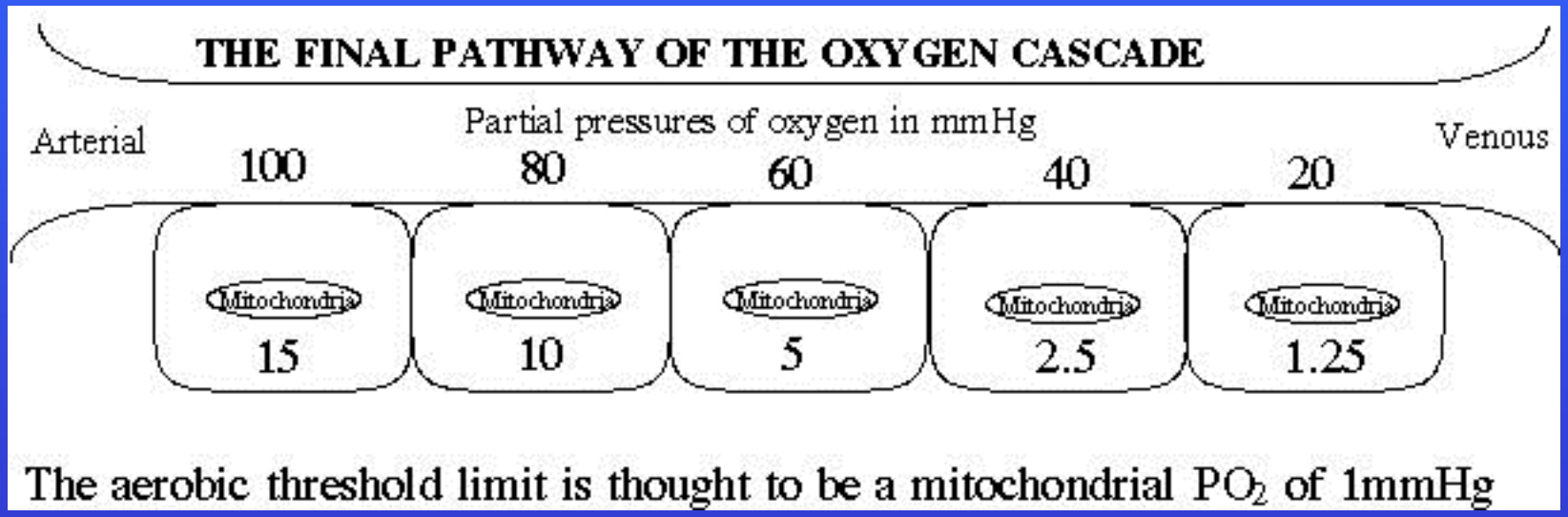

**$CO_2$ produced in tissues converted to bicarbonate for transport to lungs.**

**At the lungs bicarbonate converted back to CO2 and eliminated by the lungs.**

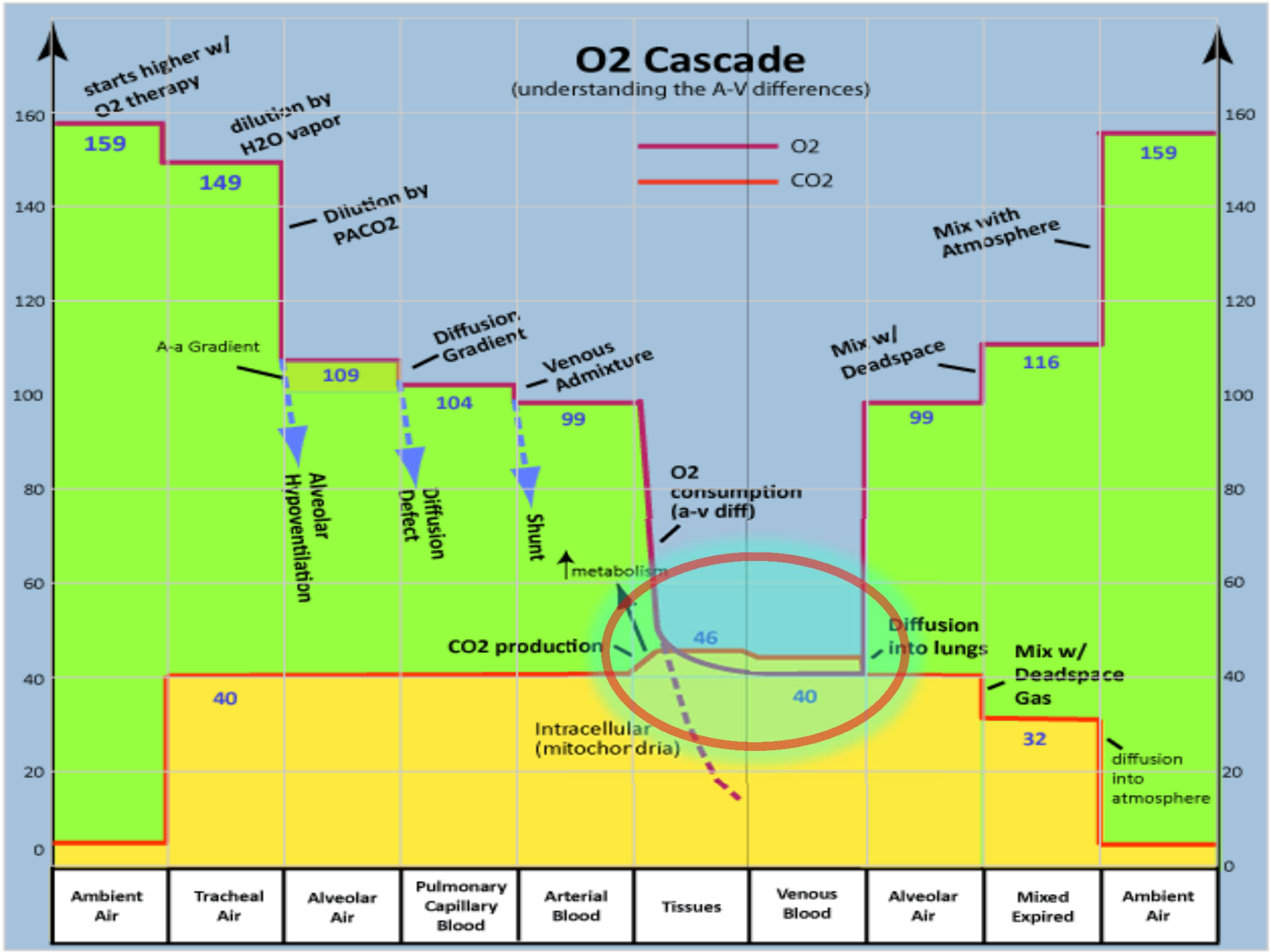
# Carbon Dioxide Transport In Blood (cont)







# Tissues
# Metabolism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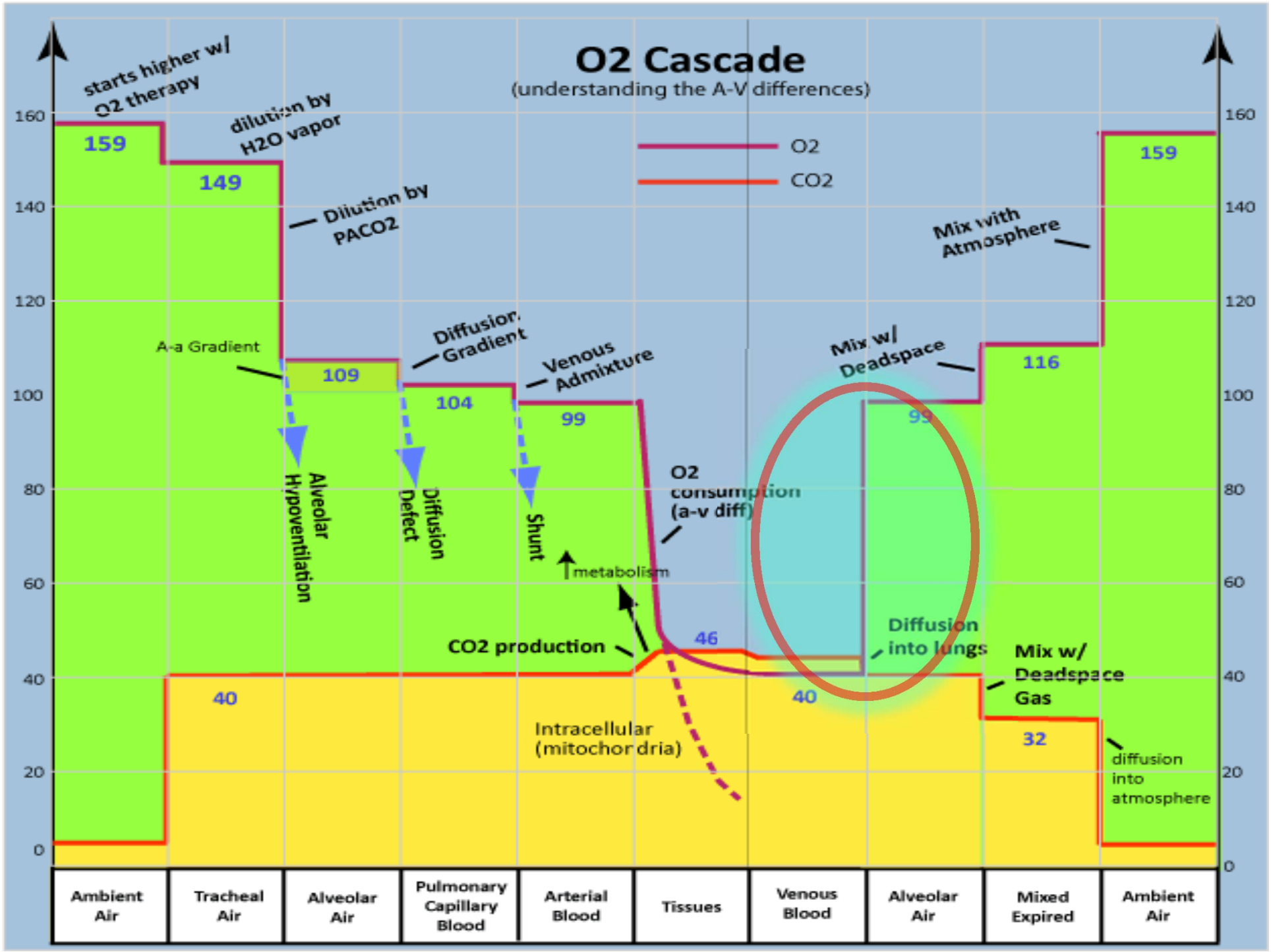
# Arterial Blood to Venous Blood

- A – v Difference
- $PO_2$ Decreased
- $PCO_2$ Increased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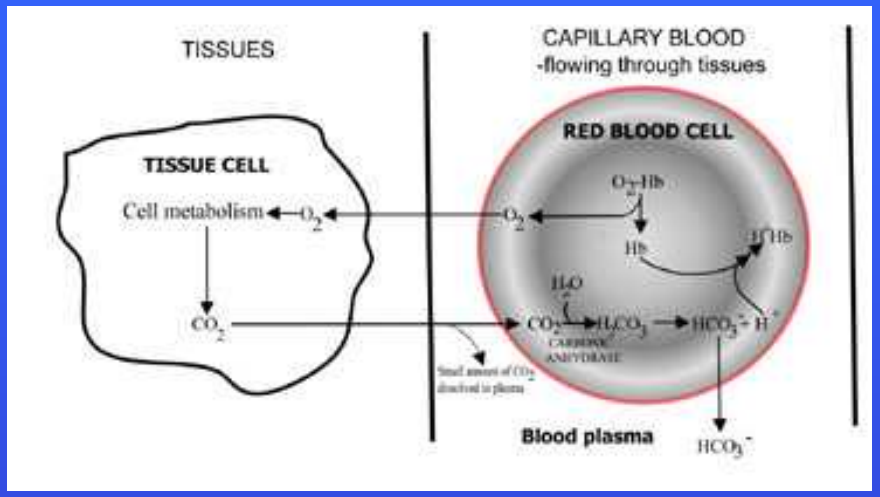
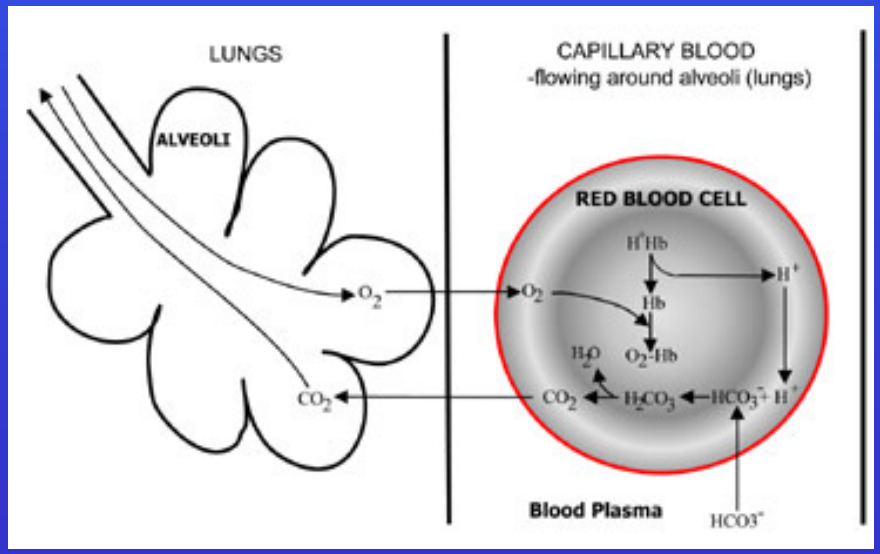
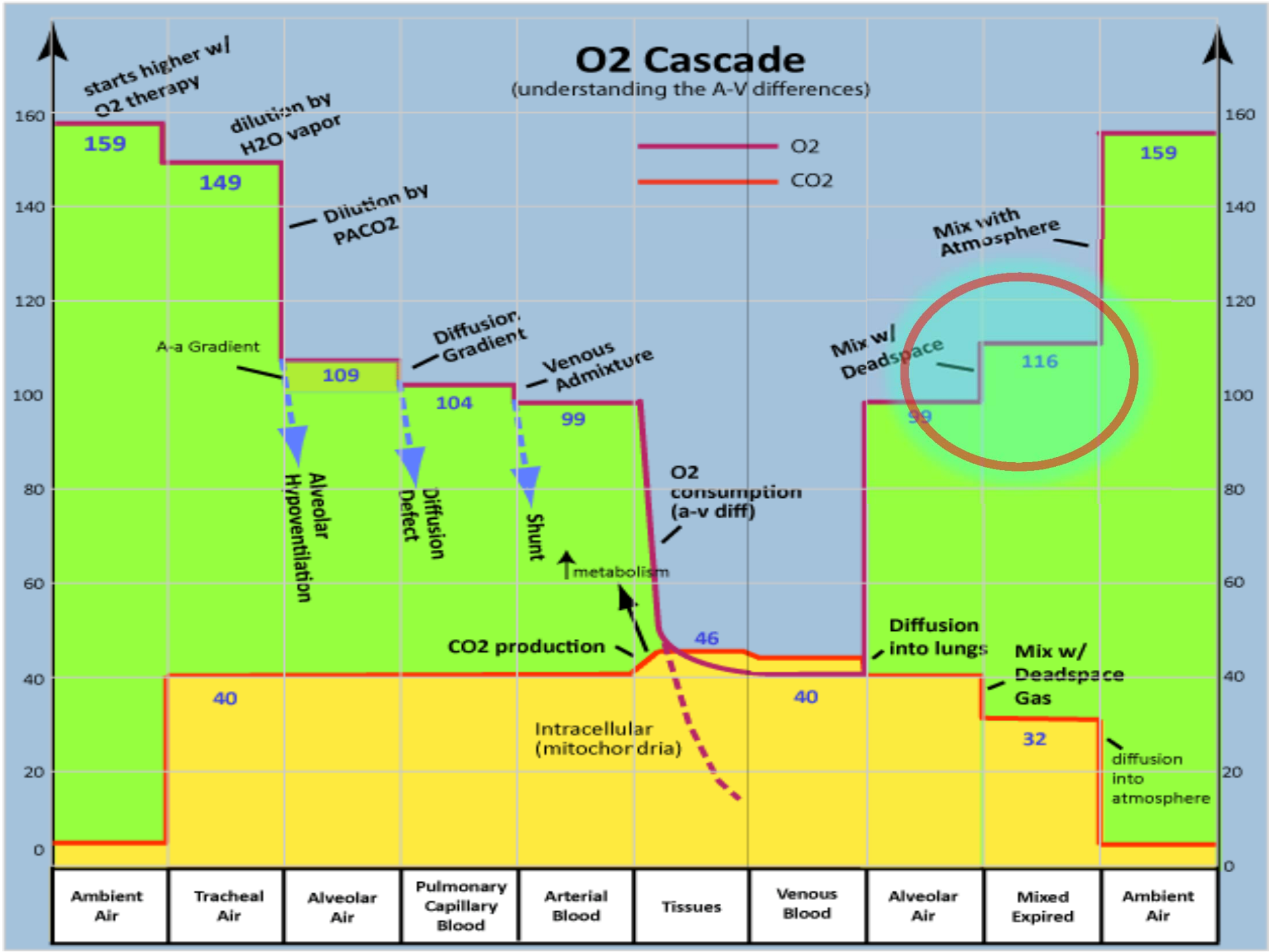
# Alveolar Air Diffusion into the Lungs




**$CO_2$ produced in tissues converted to bicarbonate for transport to lungs.**

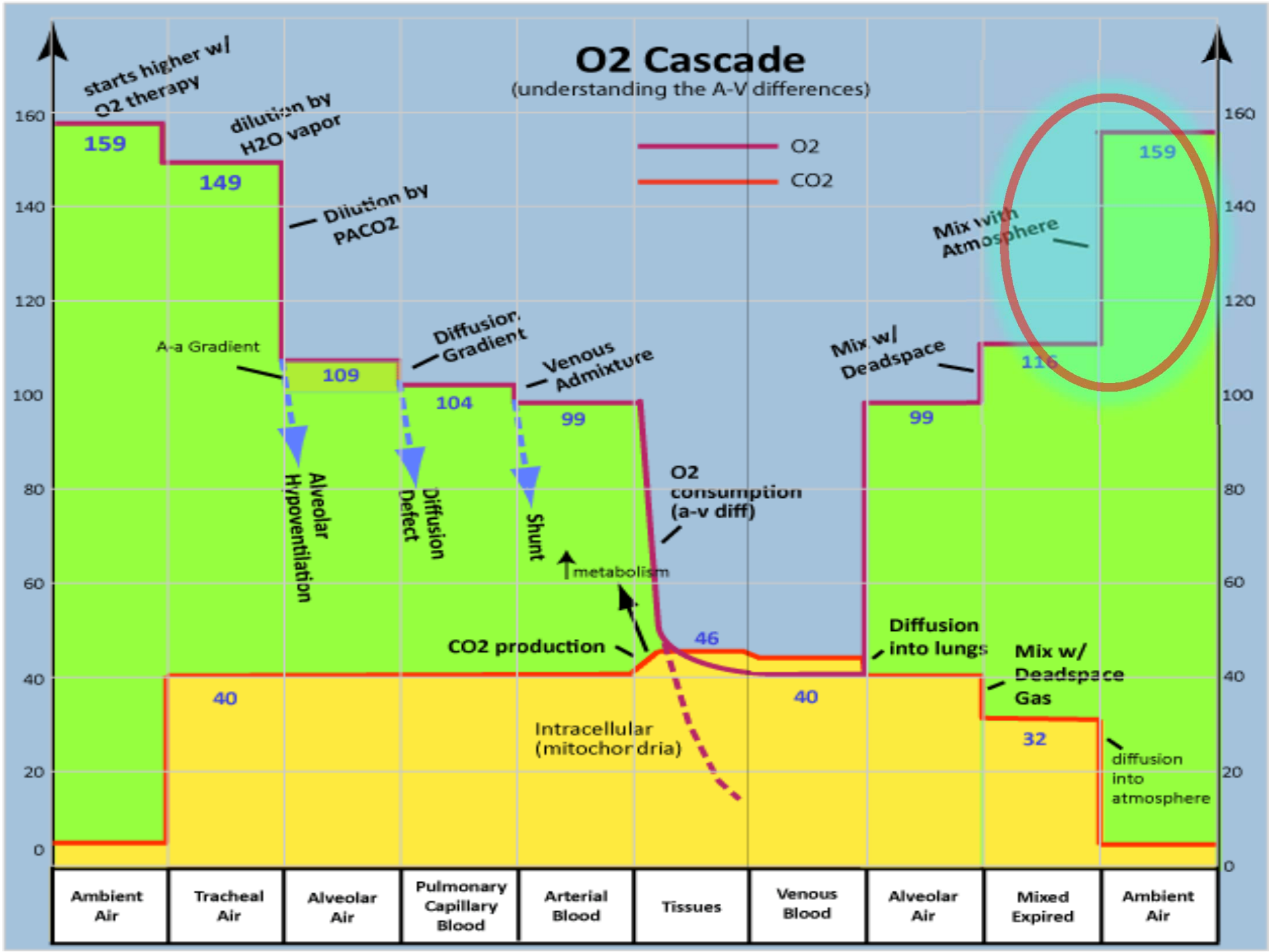



**At the lungs bicarbonate converted back to CO2 and eliminated by the lungs.**


O2 Cascade
(understanding the A-V differences)
O2
CO2
starts higher w/ O2 therapy
159
dilution by H2O vapor
149
Dilution by PACO2
A-a Gradient
109
Diffusion Gradient
104
Venous Admixture
99
Alveolar Hypoventilation
Diffusion Defect
Shunt
metabolism
O2 consumption (a-v diff)
CO2 production
46
40
Intracellular (mitochondria)
Mix with Atmosphere
159
Mix w/ Deadspace
116
99
Diffusion into lungs
40
Mix w/ Deadspace Gas
32
diffusion into atmosphere
160
140
120
100
80
60
40
20
0
Ambient Air
Tracheal Air
Alveolar Air
Pulmonary Capillary Blood
Arterial Blood
Tissues
Venous Blood
Alveolar Air
Mixed Expired
Ambient Air

# Mixed Expired Air
# Mixed with Deadspace

- Deadspace air was the last of the inhaled breath
- Resides in the airways and does not participate in gas exchange so $PO_2$= 149 mmHg
- Raises the $PO_2$ from alveolar levels to that seen in mixed expired air. $PO_2$ = 116 mmHg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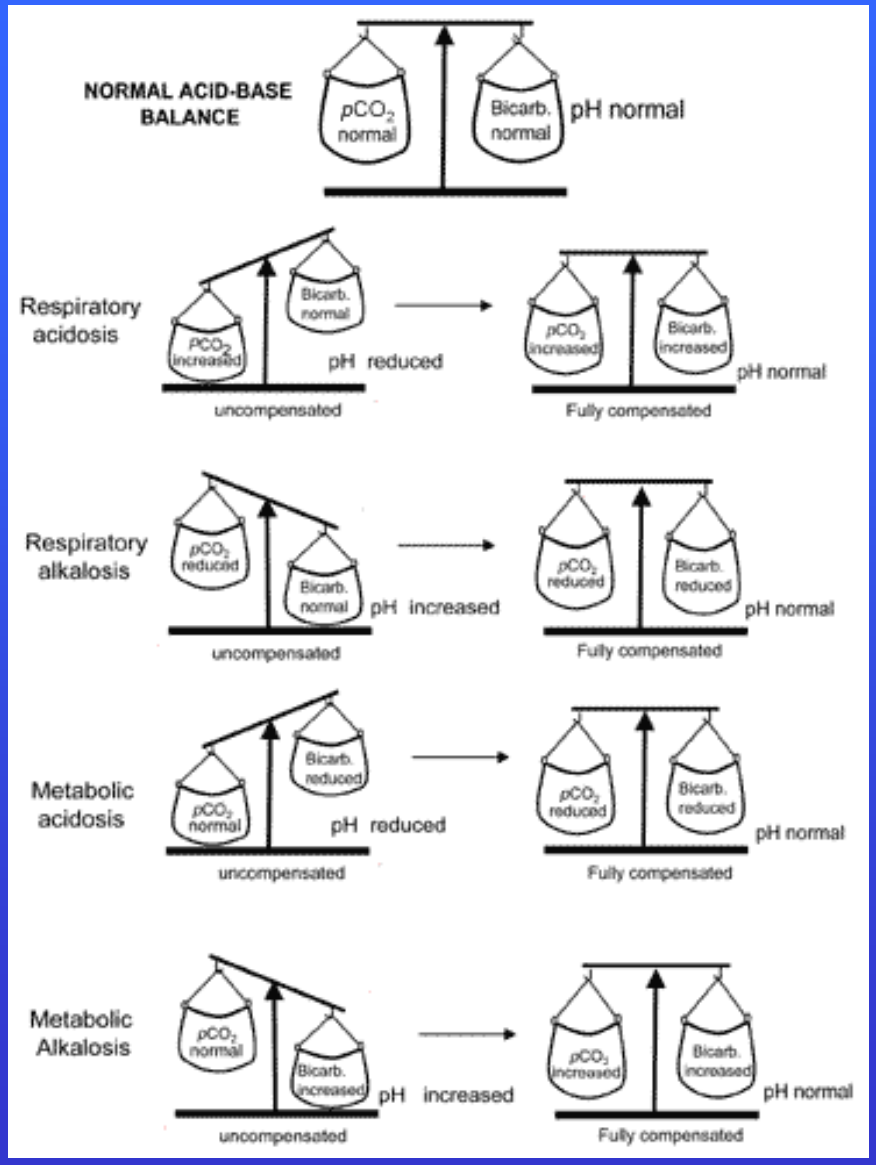
Venous Blood
Alveolar Air
Mixed Expired
Ambient Air

# Ambient Air

Artist Julian Voss-Andreae created a sculpture called "Heart of Steel (Hemoglobin)" in 2005, based on the protein's backbone. The sculpture was made from glass and weathering steel. The intentional rusting of the initially shiny work of art mirrors hemoglobin's fundamental chemical reaction of oxygen binding to iron.




**The "acid-base balance" : compensation restores normal pH**

# CRFS SELF ASSESSMENT QUESTIONS - BLOOD GASES (8 questions)

**Q5 The mechanism responsible for transporting the greatest amount of $CO_2$ in the blood is -**

carbamino compounds
dissolved $CO_2$
bicarbonate ion
carboxyhaemoglobin

⇨ $CO_2$ transport in the blood

**Q6 With normal metabolic rate and respiratory function, an increase in cardiac output will result in -**

increased arterial $PO_2$
decreased arterial-venous content difference for oxygen
decreased mixed venous content difference
no change in mixed venous oxygen content

⇨ Fick equation describing $O_2$ transport

**Q10 Hypoventilation always results in -**

hypoxia
hypercapnia
respiratory alkalosis
hypoxia and hypercapnia

⇨ Alveolar ventilation - arterial blood gas relationship

**Q23 Which of the following causes hypoxaemia ?**

Shunt
Diffusion limitation
Ventilation - perfusion mismatch
All of the above

⇨ Causes of hypoxaemia

**Q40** **Alveolar ventilation will increase in response to stimulation of -**

- the medullary chemoreceptors by increased H+ ion concentration in the cerebrospinal fluid
- the medullary chemoreceptors by increased O2 concentration in the cerebrospinal fluid
- the carotid chemoreceptors by decreased CO2 concentration in the blood
- the carotid chemoreceptors by increased pH of arterial blood

⇨ Regulation of blood gases

**Q53** **A patient breathing 100% O2 (ie FIO2=1.0) is cyanotic and has a PaO2 of 50 mmHg. The best explanation for these findings is -**

- increased COHb
- diffusion limitation
- Ventilation - perfusion mismatch
- A shunt

⇨ Causes of hypoxaemia

**Q55** **Which blood gas parameter will ALWAYS be low in a patient with a Hb = 8.0 gm/dl ?**

- O2 content
- CO2 partial pressure
- O2 partial pressure
- O2 saturation

⇨ O2 transport in the blood

**Q63** **A shift in the oxyhaemoglobin curve to the right -**

- occurs in the pulmonary capillaries
- is prevented by a rise in the blood $H^+$ ion concentration
- favours the passage of O2 to the tissues
- increases the affinity of tissue cells for O2

⇨ O2 transport in the blood

# BLOOD GAS PHYSIOLOGY - TOPIC LIST

- **Physics of gases**
  - Ideal gas equation
  - Gas laws (Boyles etc)
  - Partial pressure vs concentration
  - Henry's law (gas solubility)
  - Fick's law of diffusion

- **Respiration**
  - Pulmonary ventilation
  - Pulmonary gas exchange
  - Blood transport
    - $CO_2$ Transport in the blood
    - $O_2$ Transport in the blood
      - Haemoglobin
      - O2Hb dissociation curve
      - Fick equation
  - Tissue gas exchange
  - Cellular metabolism

- **Acid-Base Regulation**
  - Henderson-Hasselbach equation
  - Regulation of pH by lungs and kidneys
  - Buffer systems

Regulation of blood gases
  - Respiratory control centre
  - Chemoreceptors (central, peripheral)
  - Alveolar ventilation/arterial blood gas relationship

- **Disorders of blood gas and acid-base regulation**
  - Acidosis (respiratory vs metabolic, compensated vs uncompensated)
  - Alkalosis (respiratory vs metabolic, compensated vs uncompensated)
  - Hypoxaemia
  - Hypo and hypercapnoea

PART 1: Normal control of blood gases and pH

- Respiration
- Acid base balance

PART 2: Disorders of blood gas and pH regulation

- Acidosis (respiratory and metabolic)
- Alkalosis (respiratory and metabolic)
- Hypercapnoea
- Hypocapnoea
- Hypoxaemia

# Metabolism - “Fire of Life” (Lavoisier, 18th century)

Otherwise known as Respiration

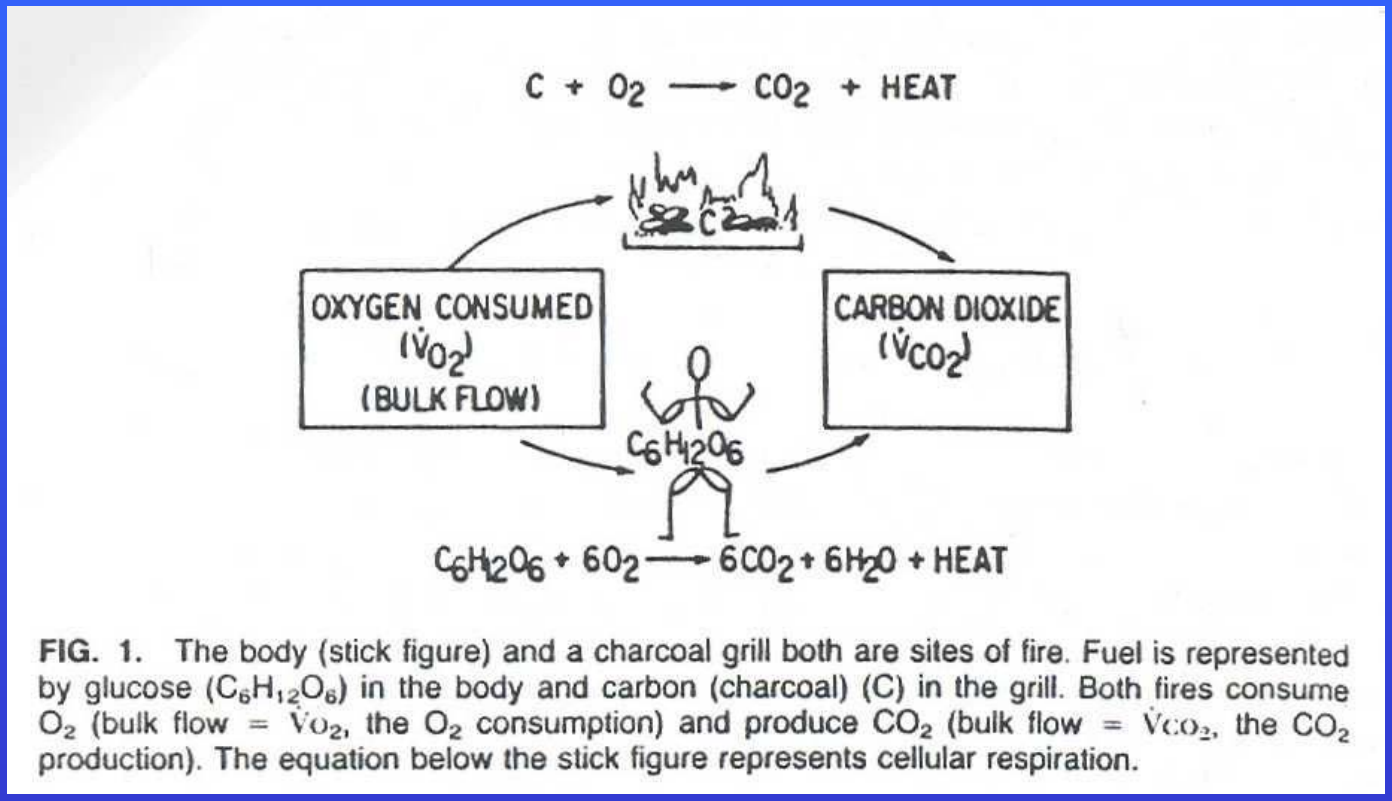


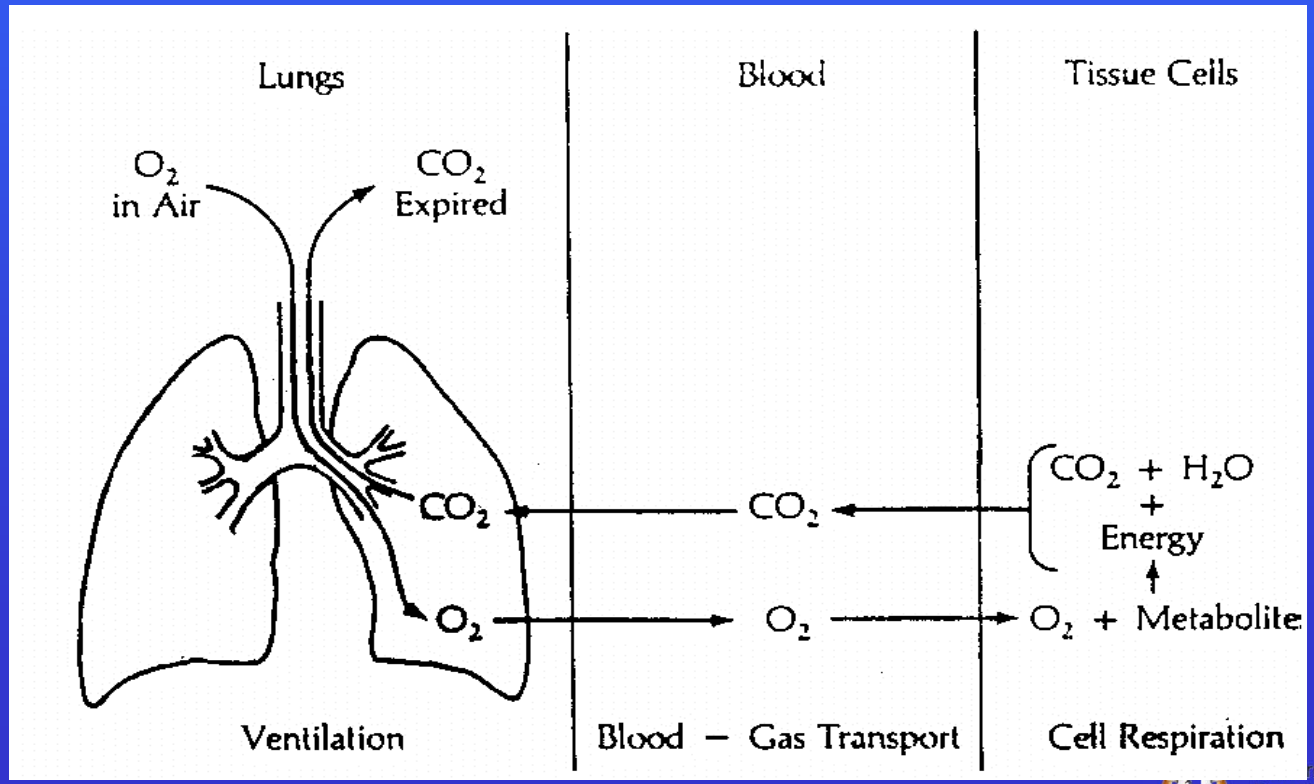

**FIG. 1.** The body (stick figure) and a charcoal grill both are sites of fire. Fuel is represented by glucose ($C_6H_{12}O_6$) in the body and carbon (charcoal) (C) in the grill. Both fires consume $O_2$ (bulk flow = $\dot{V}O_2$, the $O_2$ consumption) and produce $CO_2$ (bulk flow = $\dot{V}CO_2$, the $CO_2$ production). The equation below the stick figure represents cellular respiration.

- **Oxygenation**
- **Acid-base homeostasis**

# Respiration - 5 main components

1. Pulmonary ventilation
2. Pulmonary gas exchange
3. Blood transportation
4. Tissue gas exchange
5. Cellular metabolism

All of these processes contribute to PO2, PCO2 and acid-base status of blood



# $O_2$ and $CO_2$ partial pressures (Sea level, at rest)

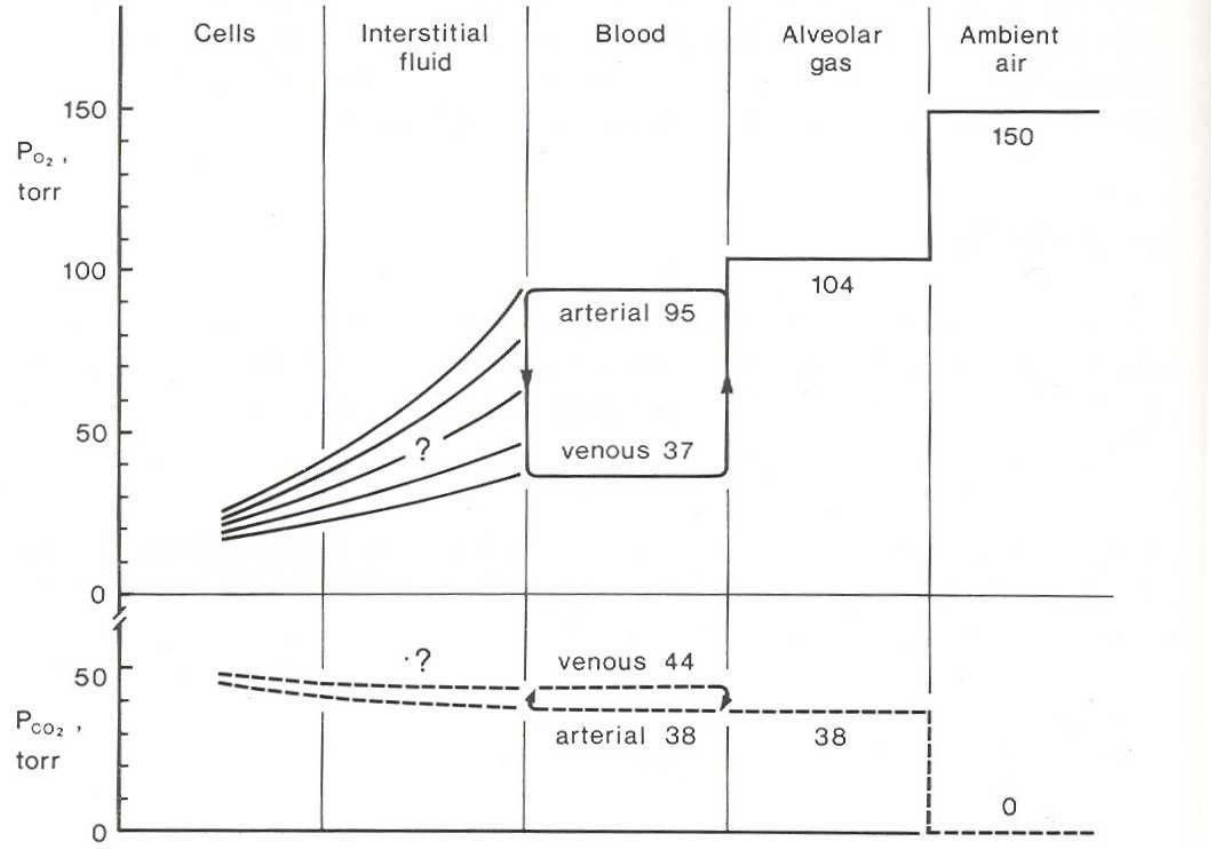



Fig. 7.2. Partial pressures of $O_2$ and $CO_2$, $P_{O_2}$ and $P_{CO_2}$, in ambient air and in the various compartments of the gas exchange system of a man at rest and at sea level. The partial pressures of $O_2$ and $CO_2$ in the interstitial fluid and inside the cells are not well known.

# Oxygen Transport In Blood

Oxygen is poorly soluble in water and very little O2 can be carried in dissolved form. Most O2 is carried in “loose” chemical combination with haemoglobin.

| At 50mmHg - | 100ml Water | 100 ml blood | |
|---|---|---|---|
| O2 | 0.15 ml | 16.8 ml | ↑ x110 |
| CO2 | 3.8 ml | 50 ml | ↑ x13 |

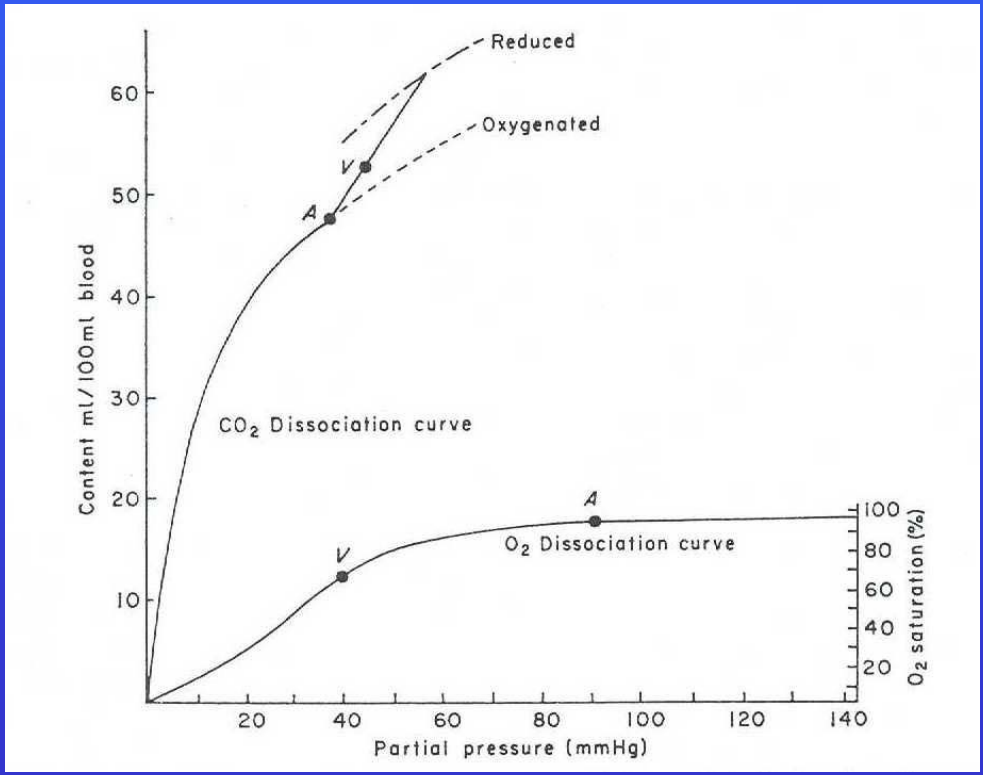
Therefore the O2 carrying capacity of blood depends on [Hb]. In normal arterial blood -

Dissolved O2 = 0.3 ml/100ml
HbO2 = 20.1 ml/100ml
Total O2 = 20.4 ml/100ml

O2 “loads” in the lungs and “unloads” in the tissues through the reversible reaction with Hb. Occurs passively in response to local PO2.

# Oxygen Transport In Blood (cont)

- O2-Hb dissociation curve sigmoidal (S-shaped)
- Consequences of flattened top end of curve → FiO2 insensitivity of O2 content, loading
- Consequences of steep bottom end of curve → enhanced unloading



# Oxygen Transport In Blood (cont)

P50 is a measure of the position of the O2-Hb curve.

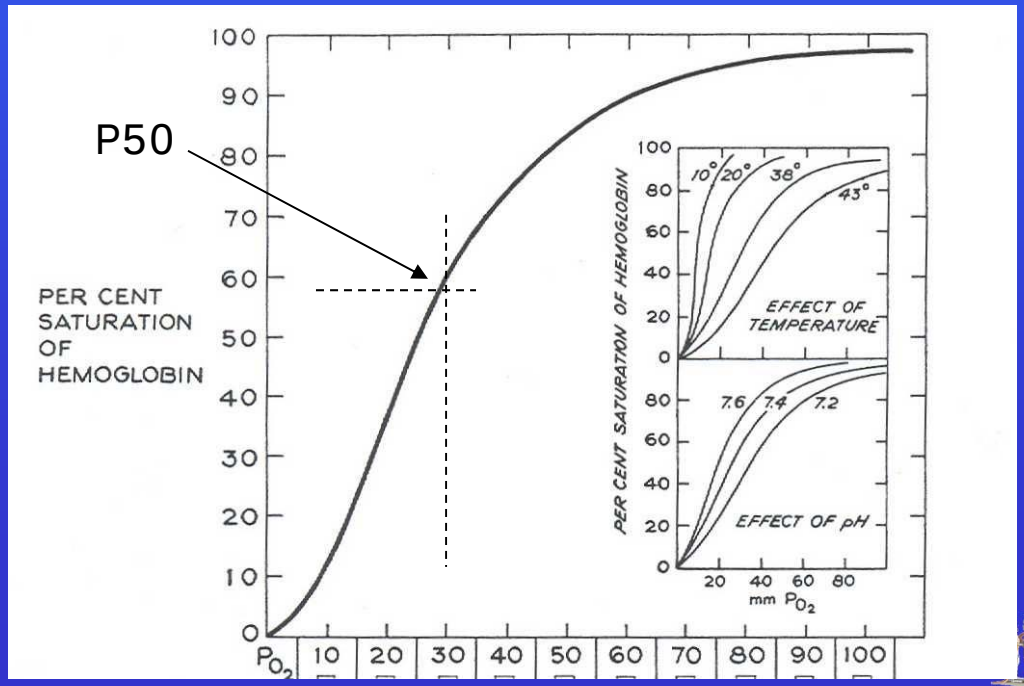
Position of the O2 dissociation curve altered by a number of factors including -

1. pH (PCO2) - increased acidity reduces affinity of Hb for O2 (Haldane Effect)
   - unloading of O2 is enhanced at tissue capillaries (↑ PCO2)
   - decreased acidity in lung capillaries increases Hb-O2 affinity

(Bohr Effect)

2. Temperature - ↑ temp causes right shift (similar effects to pH)

3. 2,3-DPG (diphosphoglycerate) - regulates Hb affinity for O2 (slowly, eg altitude, COPD)



# Carbon Dioxide Transport In Blood

Transported in various forms in blood -

| | | |
|---|---|---|
| 1. Dissolved $CO_2$ | 5% | |
| 2. Carbamino $CO_2$ ($Hb\text{-}CO_2$) | 30% | (very rapid) |
| 3. Bicarbonate ($HCO_3^-$) | 65% | (1/3 in RBCs, 2/3 in plasma) |

All bicarbonate is derived from $CO_2$ via -

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$

However very slow reaction, accelerated x1000 by carbonic anhydrase (in RBCs).
$H_2CO_3$ readily dissociates -

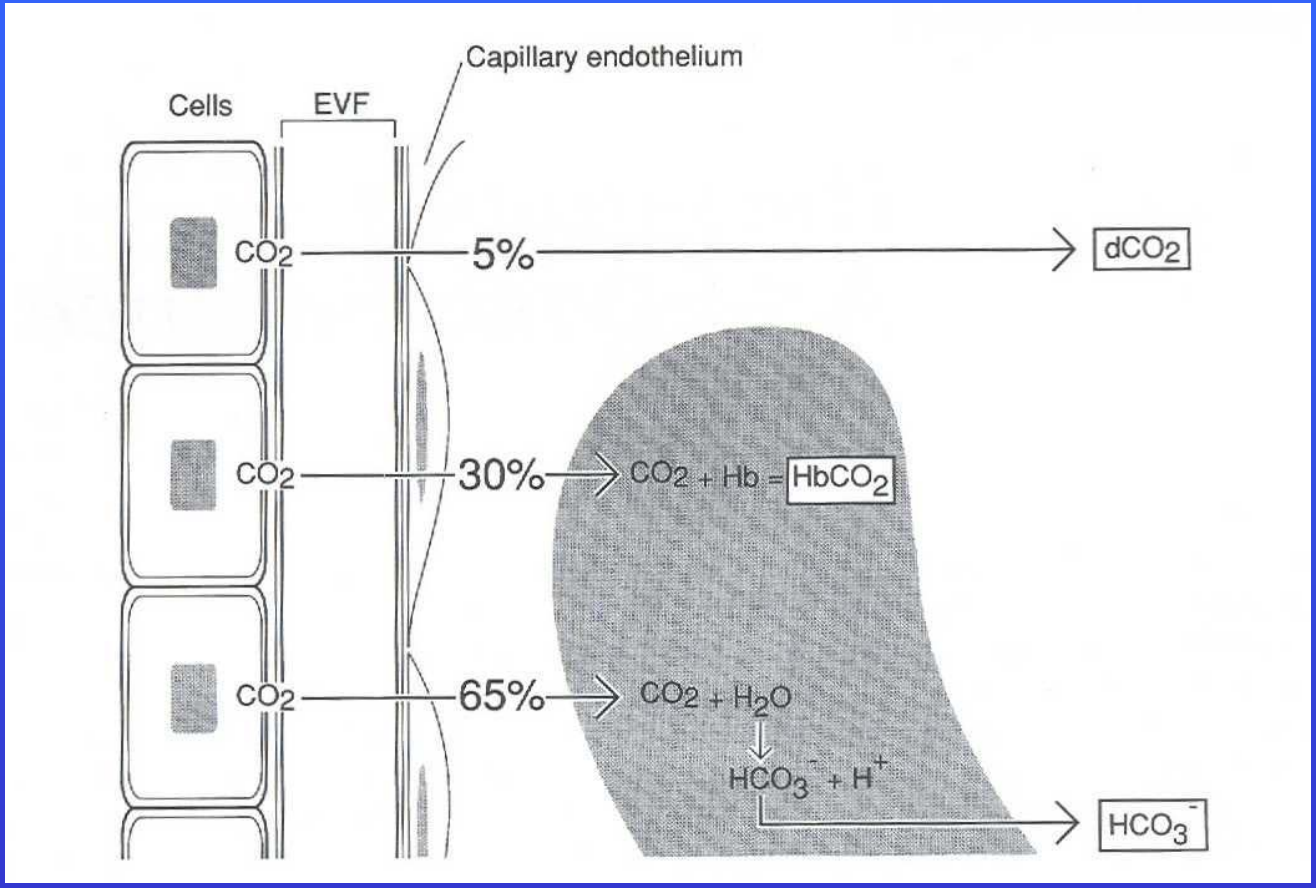
$$H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Haemoglobin buffers the released acid ($H^+$) via -

$$H^+ + HCO_3^- + K^+ + Hb^- \leftrightarrow HHb + K^+ + HCO_3^-$$

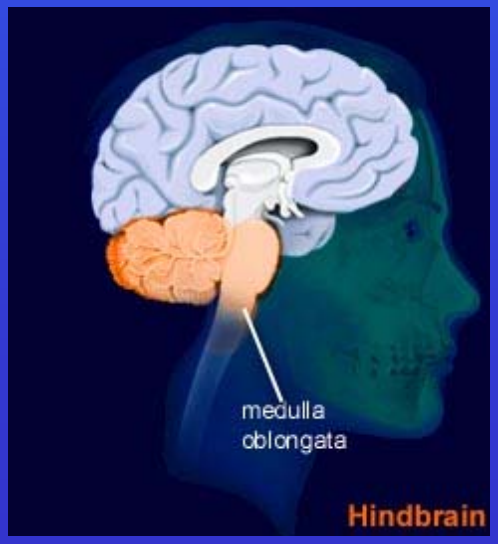
Newly formed bicarbonate exchanges with plasma chloride ($Cl^-$) (Chloride shift)

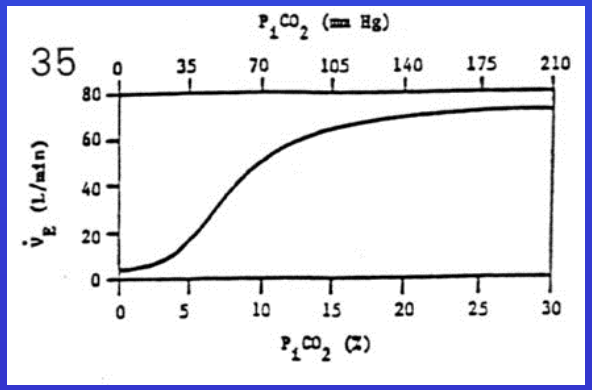
# Carbon Dioxide Transport In Blood (cont)

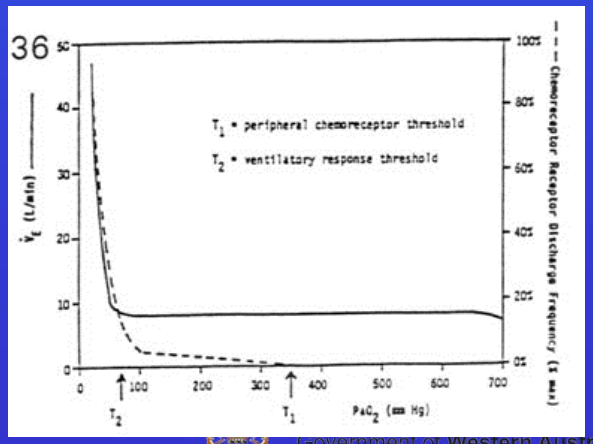


# Regulation of blood gases - control of ventilation

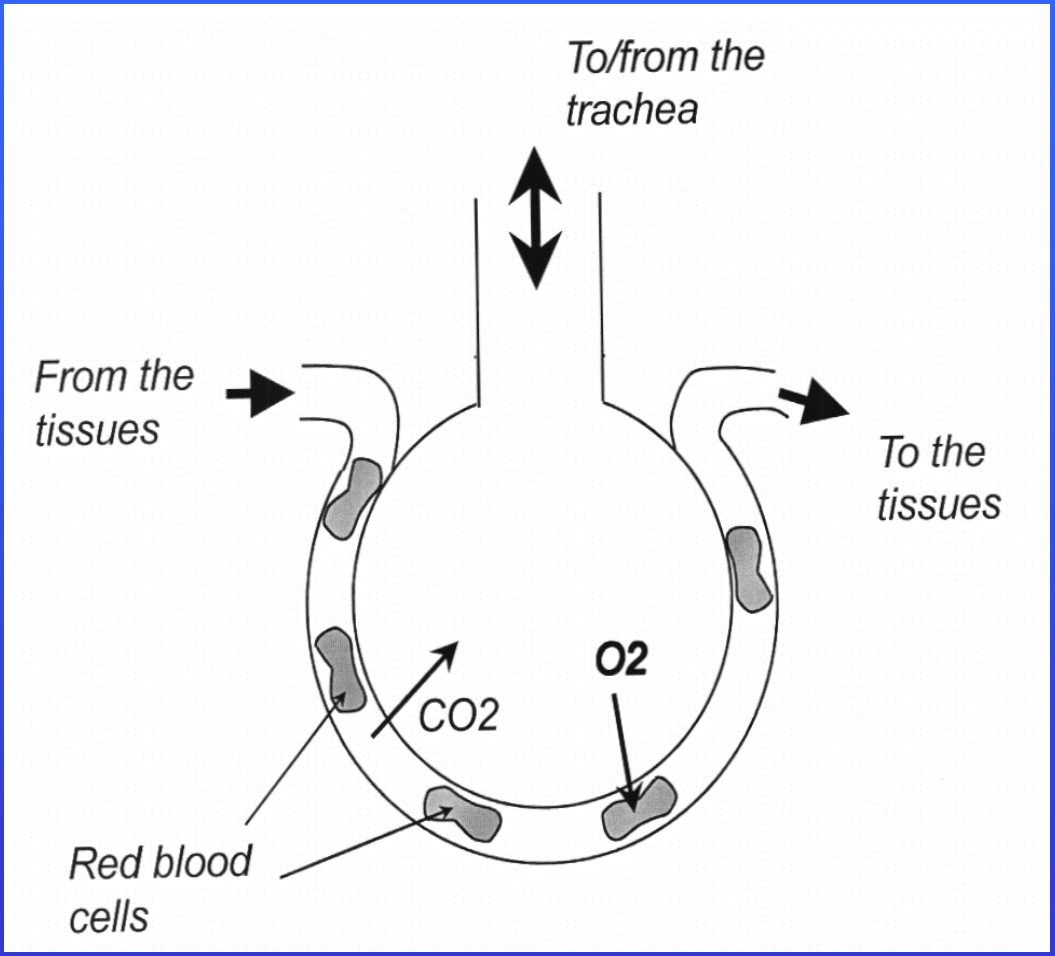
- Respiratory control centre located in the brainstem (medulla)
- Responsive to ↑ PCO2 or $H^+$ via central chemoreceptors (medulla).
- Also responsive to low PO2 (via peripheral chemoreceptors in the carotid bodies), but must be very low (<60mmHg)
- Under normal conditions, CO2 is the main driver of ventilation with PaCO2 being tightly controlled.



# Pulmonary ventilation and gas exchange




- **Gas exchange occurs by simple diffusion**
- **Within the transit time thru the lung (0.75sec), O2/CO2 in blood fully equilibrates with O2/CO2 in alveolar air**
- **Arterial O2/CO2 is determined by alveolar O2/CO2**
- **Alterations in ventilation directly affect alveolar O2/CO2 (and therefore arterial O2/CO2)**

# Pulmonary Ventilation

## EFFECT OF CHANGES IN ALVEOLAR VENTILATION

### HYPERVENTILATION

- Increased exchange of alveolar air with room air
- CO2 is “washed out” and $O_2$ is “washed-in” to the lungs
- Alveolar and arterial $CO_2$ falls
- Alveolar and arterial $O_2$ rises

### HYPOVENTILATION

- Opposite occurs

## SUMMARY

### Respiration - 5 stages

1. **Ventilation** - alveolar $O_2/CO_2$ regulated by altering ventilation which determines the rate of wash-in of $O_2$ and wash-out of $CO_2$ (respiratory centre control)
2. **Lung Gas Exchange** - equilibration (by diffusion) of $O_2/CO_2$ in alveolar air with $O_2/CO_2$ in pulmonary capillary blood
3. **Transport of O2/CO2 to and from the tissues** - $O_2$: haemoglobin, $CO_2$: bicarbonate, proteins, carbonic acid
4. **Tissue Gas Exchange**
5. **Cellular Respiration**

# Causes of hypoxaemia

1. Low inspired $O_2$ partial pressure
2. Hypoventilation
3. R to L Shunt
4. Diffusion limitation
5. V/Q mismatch

# Acid base regulation -

- pH scale $pH=\log(1/[H^+])$
  0 = extremely acid
  7 = neutral
  14 = extremely alkaline
- Acids (and less commonly bases) are continually entering the blood tending to change its pH
- Despite this, blood acidity is carefully maintained between narrow limits (pH 7.35-7.45)
- The <u>dominant acid</u> in blood is carbonic acid ($H_2CO_3$)

  $CO_2 + H_20 \leftrightarrow H_2CO_3$

  Carbonic acid concentration is proportional to $PCO_2$

  $[H_2CO_3] = 0.03 \times PCO2$
- The <u>dominant base</u> is bicarbonate ($HCO_3^-$)
- The pH of blood depends on the <u>balance</u> between $CO_2$ and $HCO_3^-$

# Acid base regulation (cont)

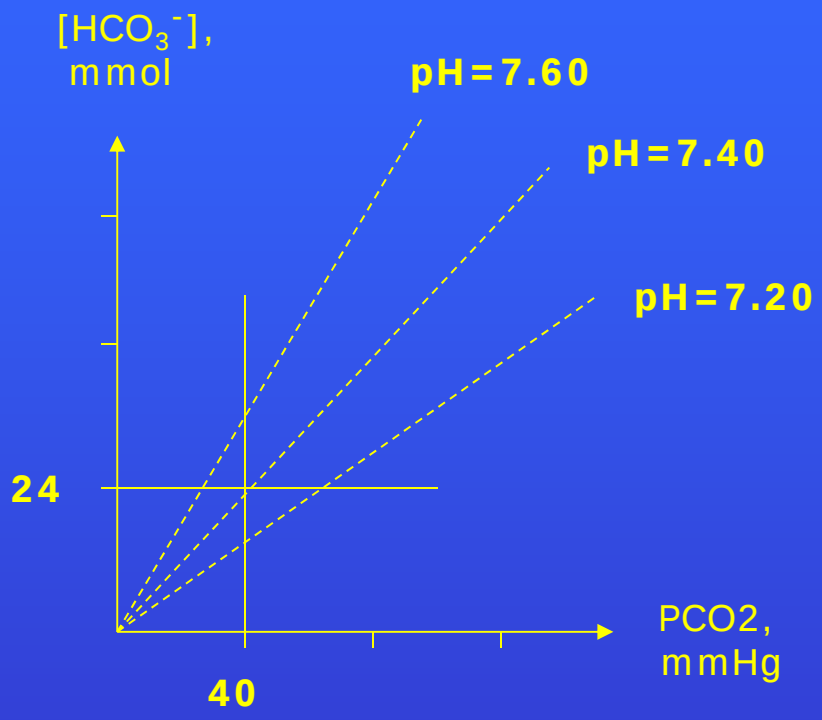
- Henderson-Hasselbalch equation links pH, bicarb and carbonic acid -

$$pH = pK + \log \frac{[HCO3]}{0.03 \times PCO2}$$

- pH of blood therefore depends on the ratio of bicarb to PCO2
- For normal values of bicarb and PCO2 in arterial blood we get -

$$pH = 6.1 + \log (24.0/0.03x40)$$
$$= 7.4$$

# Acid base regulation -




- Rate of respiration influences $PCO_2$ therefore the level of carbonic acid in blood is controlled by the lungs
- The level of bicarbonate in blood is controlled by the kidneys
- pH disturbances due to fluctuations in $CO_2$ are termed "respiratory" in origin
  eg respiratory acidosis/alkalosis
- pH disturbances due to fluctuations in other acids/bases are termed "metabolic" in origin
  eg metabolic acidosis/alkalosis

# Acid base regulation - renal control

- The kidneys can regulate bicarbonate levels in blood by converting carbonic acid into bicarb and hydrogen ions and excreting hydrogen in the urine.

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

$HCO_3^-$: Retained in bloodstream

$H^+$: Excreted in urine

- Slow to effect changes (hours to days)
- If a pH abnormality is chronic, renal compensation can occur
- Blood pH therefore depends on the interaction between the lungs and kidneys

$$pH = pK + \log \frac{[HCO_3]}{0.03 \times PCO_2}$$

$[HCO_3]$ ← *Kidneys*

$0.03 \times PCO_2$ ← *Lungs*

# Patterns of acid-base abnormality

| | pH | PaCO2 | |
|---|---|---|---|
| Normal | 7.40 | 35 | |
| Respiratory acidosis: | | | |
| Uncompensated | 7.30 | 50 | |
| Compensated | 7.40 | 50 | |
| Respiratory alkalosis: | | | |
| Uncompensated | 7.50 | 30 | |
| Compensated | 7.40 | 30 | |
| Metabolic acidosis: | | 7.20 | 25 |
| Metabolic alkalosis: | 7.50 | 55 | |

# Acid base regulation - Chemical buffers

- In addition to the lungs and the kidneys, the body has a third method for controlling the effect on pH of acids or alkalis entering the bloodstream

$\Rightarrow$ CHEMICAL BUFFERING

- Act by chemically reacting with acids/alkalis to neutralize effects on pH
- Blood contains 2 main buffer systems -

1. Carbonic acid/bicarbonate buffer pair

$$HCl + NaHCO_3 \Rightarrow NaCl + H_2CO_3 \quad \text{(Acid)}$$
$$NaOH + H_2CO_3 \Rightarrow NaHCO_3 + H_2O \quad \text{(Alkali)}$$

2. Haemoglobin

$$Hb + H_2CO_3 \Rightarrow HbH + HCO_3^-$$

- Buffers provide a rapid (seconds) but temporary method for dealing with excess acid or base. Must eventually be excreted.

## SUMMARY

# Acid base regulation -

The body has 3 systems for countering changes to blood pH -

| SYSTEM | SPEED OF ACTION | MODE OF ACTION |
|---|---|---|
| **1. BUFFERING** | instantaneous | neutralizes acids/alkalis |
| **2. LUNGS** | seconds to minutes | regulates carbonic acid ($CO_2$) |
| **3. KIDNEYS** | hours to days | regulates bicarbonate |

# Metabolic acid/base disturbances - mechanisms

Metabolic acidosis

1. Renal failure
2. Diabetic ketoacidosis
3. Lactic acidosis (sepsis)

Metabolic Alkalosis

1. Potassium depletion (poor IV therapy, diuretics, diarrhea)
2. Chloride loss
3. Excessive bicarbonate administration

# QUESTIONS

**Q In a resting subject, a voluntary increase in ventilation will result in -**

a) Increased alveolar $PO_2$ and decreased alveolar $PCO_2$
b) Increased alveolar $PO_2$ and increased alveolar $PCO_2$
c) Increased arterial $PCO_2$
d) None of the above

**Q Renal compensation of acid base disturbances occurs over –**

a) Seconds
b) Minutes to hours
c) Hours to days
d Never

# QUESTIONS

**Q A right shift in the $O_2$ – Hb dissociation curve may be caused by -**

a) Increased temperature
b) Increased $PCO_2$
c) Decreased pH
d) All of the above