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OXYGEN AND CARBONDIOXIDE CASCADE
Introduction

- Oxygen – indispensable for life
  - Substrate used in the greatest quantity
  - No storage system
  - Continuous supply required
- Carbondioxide - major by-product of energy metabolism
Mechanisms of oxygen transport

- Convection (bulk flow)
- Diffusion
- Chemical combination with hemoglobin
  - 30-100 fold increase in $O_2$ transport
  - 15-20 fold increase in $CO_2$ transport
Oxygen Cascade

- Uptake in the lungs
- Carrying capacity of blood
- Global delivery from lungs to tissue
- Regional distribution of oxygen delivery
- Diffusion from capillary to cell
- Cellular use of oxygen
Oxygen Cascade

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Oxygen uptake in the lungs

- Inspired O$_2$ concentration
- Barometric pressure
- Alveolar ventilation
- Diffusion of O$_2$ from alveoli to pulm capillaries
- Distribution and matching of ventilation and perfusion
Alveolar ventilation

- Depends on rate of breathing and tidal volume ($V_T$)
- Hyperbolic relationship between alveolar vent$^n$ and $P_{A\,O_2}$
- Affected by disorders of respiratory centre and respiratory muscles
- High-frequency ventilation allows lower tidal volumes while maintaining MV
Third gas effect

Administration of nitrous oxide

↓

Large quantities of more soluble gas replace smaller quantities of less soluble nitrogen

↓

Net transfer of ‘inert’ gas from alveoli into body

↓

Temporary increase in $O_2$ concentration

FINK EFFECT
Diffusion from alveoli to pulmonary capillaries

\[ O_2 \text{ diffusion} = K \times S/d \times \Delta P \]
Diffusion from alveoli to pulmonary capillaries

- $P_{A\text{O}_2}$ is main determinant of $PaO_2$

- (A-a) gradient describes the overall efficiency of oxygen uptake

- Capillary blood is fully oxygenated before traversing $\frac{1}{3}$ distance of alveolar capillary interface
V/Q matching

- ‘True shunt’ v/s ‘effective’ shunt

-Clinical correlates
  High PEEP strategy
  Prone ventilation

BMJ 1998;317:1302-6
Hypoxemia

Causes of arterial hypoxaemia

**Alveolar hypoventilation**
- Respiratory depression from sedation or analgesia
- Respiratory muscle weakness:
  - Prolonged mechanical ventilation
  - Catabolic effects of critical illness
  - Muscle relaxants or steroids
  - Phrenic nerve damage (cardiac surgery or trauma)
  - Neuromuscular disorders (Guillain-Barré, etc)
- Obstructive airways disease

**Diffusion**
- Pulmonary oedema
- Acute respiratory distress syndrome (particularly with fibrosis in later stages)

**Ventilation-perfusion mismatch**
- Alveolar collapse
- Acute respiratory distress syndrome
- Pneumothorax
- Obstructive airways disease
- Drugs—pulmonary vasodilators

BMJ 1998;317:1302-6
Oxygen Cascade

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Carriage of $O_2$ in blood

2% in plasma
98% in hemoglobin
Hemoglobin saturation

- Extent to which the Hb is combined with O₂
- Depends on PO₂ of the blood
- Phenomenon of “cooperativity”
- P₅₀ ~ 28 mm Hg
- Rapid and reversible reaction
Factors affecting OEC

- pH
- $\text{PCO}_2$
- Temperature
- 2,3 DPG
- Percentage of fetal Hb

Oxygen hemoglobin dissociation curve
(Oxyhemoglobin equilibrium curve)

Chest 2005; 128:554S–560S
Bohr Effect

- Christian Bohr (1855-1911)
- Effect of $P_{CO_2}$ on OEC
- Concept of permissive hypercapnia
2,3- Diphosphoglycerate

- Formed in the Rapoport-Luebering shunt of the glycolytic pathway
- DPG mutase activity increased at high pH
- Decreased DPG – in stored blood
- Increased in – anemia
  - high altitude
Oxygen content (CaO₂)

- Total amount of O₂ present in 100 ml of blood
  \[(1.34 \times \text{Hb} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)\]

- \(\text{CaO}_2 = 20 \text{ vol } \%\) \(\text{CvO}_2 = 15 \text{ vol } \%\)

- O₂ content decreased in
  - Hypoxemia (low PO₂)
  - Anemia (low Hb)
  - Hypercarbia, acidemia, hyperthermia (low SaO₂)
Effect of anemia and CO

- **Anemia** → ↓Hb → ↓O$_2$
  - carrying capacity of blood & ↓ O$_2$ content

- **Carbon Monoxide**
  - affinity for Hb 250 fold relative to O$_2$
  - Competes with O$_2$ binding
  - L shift - interfere with O$_2$ unloading at tissues
  - Severe tissue hypoxia
Oxygen Cascade

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Oxygen delivery (DO₂)

- Quantity of O₂ made available to body in one minute – O₂ delivery or flux
- Equal to cardiac output X arterial oxygen content
- DO₂ is approximately 1000 mL/min
Oxygen consumption (VO₂)

- Total amount of O₂ consumed by the tissues per unit of time
  
  \[ \text{VO}_2 = 10 \times \text{CO} \times (\text{CaO}_2 - \text{CvO}_2) \]

- Normal resting O₂ consumption ~250 mL/min in adult humans

\[ \text{OER} = \frac{\text{VO}_2}{\text{DO}_2} \]
DO₂ – VO₂ relationship

Jindal SK, Agarwal R. Oxygen Therapy. 2nd Ed. pp78
**DO₂ – VO₂ relationship in critically ill**

Slope of maximum OER is less steep

↓

Reduced extraction of oxygen by tissues

↓

Does not plateau (consumption remains supply dependent even at “supranormal” levels of DO₂)

Critical level of DO₂ range from 2.1 to 6.2 mL/min/kg

BMJ 1998;317:1302-6
Mechanisms causing failure of global oxygen delivery

- Reduction in cardiac output
- Fall in hemoglobin concentration
- Failure of oxygen uptake by blood
Failure of oxygen delivery

Relative effects of changes in PaO₂, Hb and CO on DO₂ in a critically ill

Thorax 2002; 57:170–177
**DO₂ during exercise**

- **During exercise**
  - O₂ requirement may be 20 times
  - Blood remains in capillary blood < ½ N time

- **But saturation not affected**
  - Full saturation in first ⅓ of N time
  - Increased diffusion capacity
    - Additional capillaries open up
    - V/Q ratio improves
    - Dilatation of both alveoli and capillaries
  - OEC shifts to right- ↑ CO2, ↓ pH, ↑ temp, ↑ 2,3 DPG
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Regional distribution and Oxygen consumption

<table>
<thead>
<tr>
<th>Organs</th>
<th>Blood Flow, mL/100 g</th>
<th>Arterial-Venous Difference, Volume %</th>
<th>VO2, mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>70</td>
<td>11.4</td>
<td>23.9</td>
</tr>
<tr>
<td>Brain</td>
<td>50</td>
<td>6.3</td>
<td>47.9</td>
</tr>
<tr>
<td>Kidney</td>
<td>400</td>
<td>1.3</td>
<td>15.9</td>
</tr>
<tr>
<td>Liver</td>
<td>29</td>
<td>4.1</td>
<td>20.9</td>
</tr>
<tr>
<td>GI tract</td>
<td>35</td>
<td>4.1</td>
<td>29.3</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>2.5</td>
<td>6.4</td>
<td>60.8</td>
</tr>
</tbody>
</table>

Perfusion pressure is an important determinant

Chest 2005; 128:554S–560S
Oxygen Cascade

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Cellular use of oxygen

- Important for aerobic metabolism
  - EMP pathway
  - Krebs’ cycle
- Can be inhibited by cellular metabolic poisons
  - Exogenous (e.g. cyanide) or
  - Endogenous (e.g. endotoxins in septic shock)
Clinical features of tissue hypoxia

- Dyspnea
- Altered mental state
- Tachypnea or hypoventilation
- Arrhythmias
- Peripheral vasodilatation
- Systemic hypotension
- Coma
- Cyanosis (unreliable)
- Nausea, vomiting, and gastrointestinal disturbance
Issues in critically patient

- Disordered regional distribution of blood flow
  - Both between and within organs
  - Loss of autoregulation
  - Use of vasopressors
- Capillary microthrombosis after endothelial damage
- Cytokines induced disordered cellular O$_2$ use
Issues in critically patient

- Decreased O2 carrying capacity of blood
  - Phlebotomy
  - Hemorrhage secondary to trauma / surgery
  - Inflammation
  - Nutritional deficiencies
  - Decreased erythropoietin production

- Altered dissociation profile of OEC
  - Acidosis, fever
  - Decreased 2,3 DPG
Issues in critically patient

- Cardiac dysfunction in ICU patients
  - Underlying organic heart disease
  - Insufficient DO$_2$ to the coronary circulation, precipitated by anemia
  - Subendocardial ischemia from LVH
  - Compromised myocardial contractility from the effects of inflammatory cytokines
  - Inappropriate intravascular fluid status
CARBON DIOXIDE CASCADE
Blood transports more CO$_2$ than O$_2$

- CO$_2$ is twenty fold more soluble than O$_2$ in plasma
- CO$_2$ content reflects the sum of CO$_2$ in the blood in all three forms
- CaCO$_2$ = 48 vol%  \( \text{CvCO}_2 = 52 \text{ vol%} \)
- Each time blood circulates through the body, 4 vol% of CO$_2$ is removed from the tissues and delivered to the lungs to be exhaled
Dissolved $\text{CO}_2$

- Only $\sim$5% of total arterial content is present in the form of dissolved $\text{CO}_2$
- 0.3 ml of $\text{CO}_2$/100 ml in absolute terms
- During heavy exercise may increase up to sevenfold
Carbonic anhydrase (CA)

- Key enzyme in CO₂ transport
- Catalyzes reaction in both direction (~5000 fold)
- Not present in plasma
- 7 isozymes
- CA II in RBCs and CA IV membrane bound isozyme present in pulmonary capillaries
- Inhibited by thiazides and acetazolamide
Chloride shift

- Hamburger in 1918
- $\text{HCO}_3^-$ exchange with $\text{Cl}^-$ ions across RBC membrane
- Passive process
- Mediated by membrane bound protein ‘band 3’
- Band 3 anchoring site for ankyrin and spectrin
CO₂ bound as carbamate

- CO₂ reacts directly with Hb
- Reversible reaction with a loose bond
- Depends on
  - O₂ satⁿ of Hb and 2,3 DPG (binding to Hb)
  - H⁺ concⁿ (both Hb & plasma proteins)
- However, ↑ Hb desat and ↑ in H⁺ concⁿ work in opposite direction
Haldane Effect

![Graph showing CO₂ content vs. PCO₂ with normal range and Haldane effect highlighted.]

JBS Haldane [1892-1964]

Christiansen J, Douglas CG, Haldane JS. J Physiol 1914;48:244-71
Molecular basis for Haldane Effect

Reduced Hb is better than oxygenated Hb in combining with--

1. H⁺ ions
2. CO₂ to form carbamino compounds

in turn assisting blood to load more CO₂ from the tissues
Haldane Effect

- Binding of O₂ with hemoglobin tends to displace CO₂ from the blood

- Leads to ↑ uptake of CO₂ in the tissues and ↑ release of CO₂ in the lungs

- Approximately doubles the amount of CO₂ released from the blood in the lungs and that picked up in the tissues
Coupled transport within the red cell in peripheral tissues
Influence of CO₂ on blood pH

- Carbonic acid–bicarbonate buffer system resists blood pH changes
  - If H⁺ concentrations in blood begin to rise, excess H⁺ removed by combining with HCO₃⁻
  - If H⁺ concentrations begin to drop, carbonic acid dissociates, releasing H⁺
Hypercapnia

Signs of ventilatory failure:

- Tachypnea
- Acidemia
- Increased pulsus paradoxus
- Hyperinflation
- Somnolence / Decreased mental status
**Hypercapnia - Etiologies**

\[ P_a \text{CO}_2 \propto \frac{V_{CO_2}}{\text{RR} \ (V_T - V_D)} \]

**↑VCO₂ (Hypermetabolism)**
- Fever
- Seizures
- Sepsis
- Hyperalimentation

**↓VT**
- Skeletal muscle weakness
- Impaired neuromuscular transmission
- ↓ Lung / chest wall compliance
- Airway obstruction
- COPD
- Asthma
- Obstructive sleep apnea

**↓RR (Central hypoventilation)**
- Drugs
- Brainstem lesions
- Obesity-hypoventilation syndrome

**↑VD**
- Excessive PEEP