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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
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- Cellular use of oxygen

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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_AO_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 diffusion = $K \times S/d \times \Delta P$

Diffusion from alveoli to pulmonary capillaries

- P_AO_2 is main determinant of PaO_2
- (A-a) gradient describes the overall efficiency of oxygen uptake
- Capillary blood is fully oxygenated before traversing ⅓ distance of alveolar capillary interface

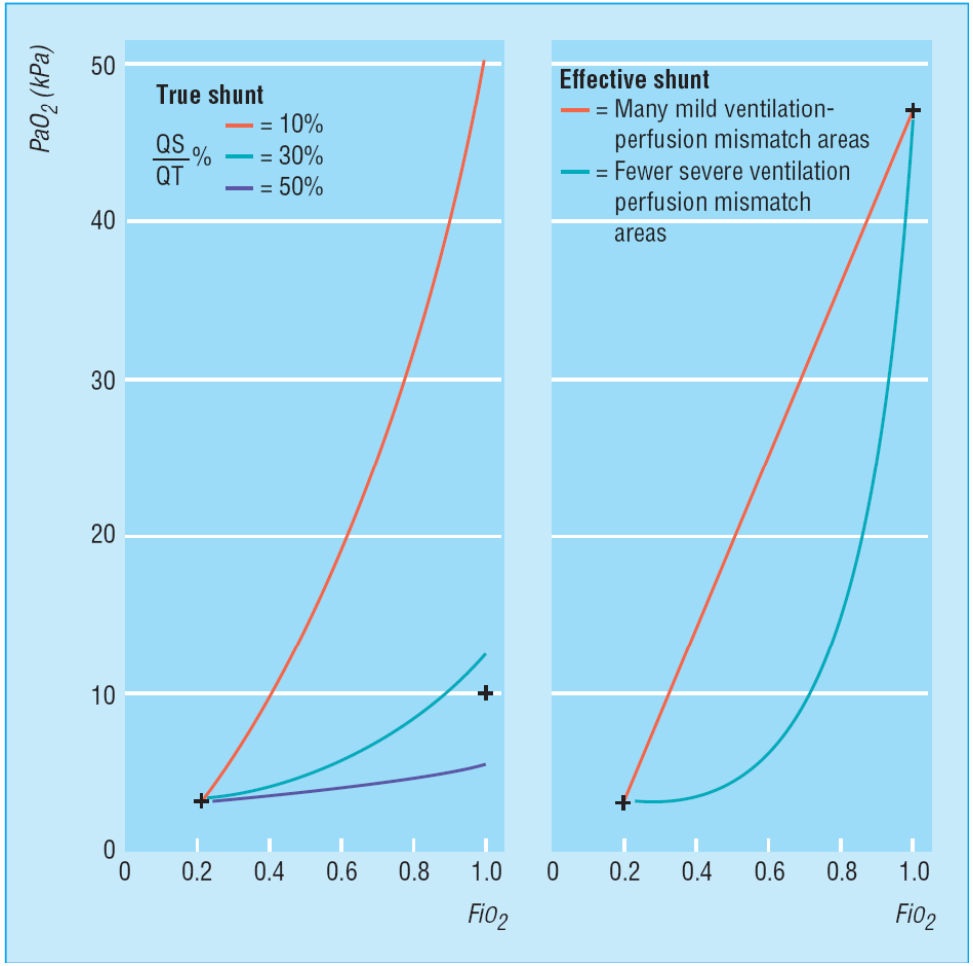
V/Q matching

-‘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

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Carriage of O_2 in blood

2% in plasma
98% in hemoglobin

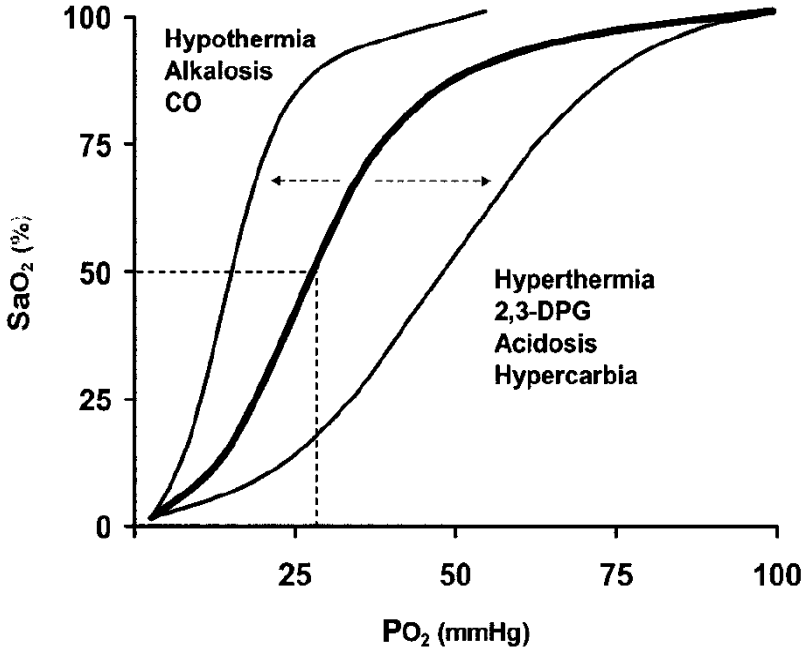
Hemoglobin saturation

- Extent to which the Hb is combined with O_2
- Depends on PO_2 of the blood
- Phenomenon of "cooperativity"
- P_{50} ~ 28 mm Hg
- Rapid and reversible reaction

Factors affecting OEC

- pH
- P_{CO_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- Diphosphogleycerate

- 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 (CaO_2)

- Total amount of O_2 present in 100 ml of blood

  $(1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)$

- CaO_2 = 20 vol % CvO_2 = 15 vol %

- O_2 content decreased in
  - Hypoxemia (low PO_2)
  - Anemia (low Hb)
  - Hypercarbia, acidemia, hyperthermia (low SaO_2)

Effect of anemia and CO

- Anemia $\rightarrow \downarrow$Hb $\rightarrow \downarrow O_2$ carrying capacity of blood & $\downarrow O_2$ 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

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Oxygen delivery (DO_2)

- Quantity of O_2 made available to body in one minute – O_2 delivery or flux
- Equal to cardiac output X arterial oxygen content
- DO_2 is approximately 1000 mL/min

Oxygen consumption (VO_2)

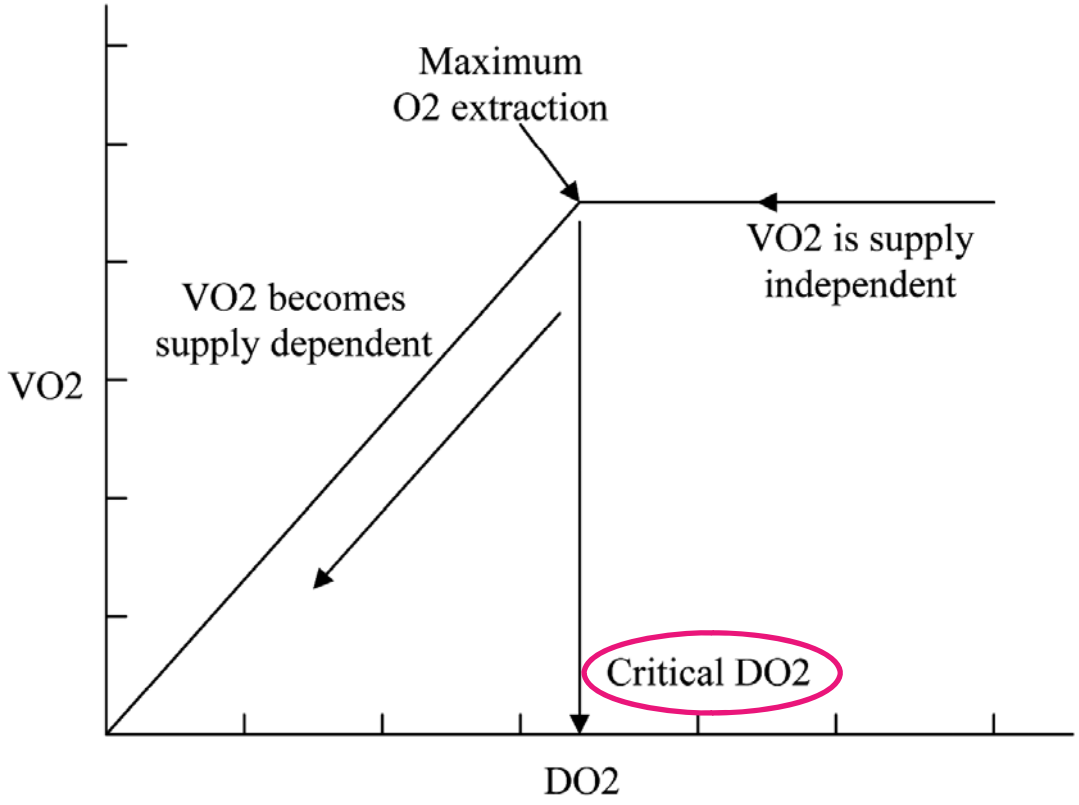
- Total amount of O_2 consumed by the tissues per unit of time

$$VO_2 = 10 \times CO \times (CaO_2 - CvO_2)$$

- Normal resting O_2 consumption ~250 mL/min in adult humans

$$OER = VO_2/DO_2$$

$DO_2 - VO_2$ relationship



Jindal SK, Agarwal R. Oxygen Therapy. 2nd Ed. pp78

$DO_2 – VO_2$ relationship in critically ill

Slope of maximum OER is less steep

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Reduced extraction of oxygen by tissues

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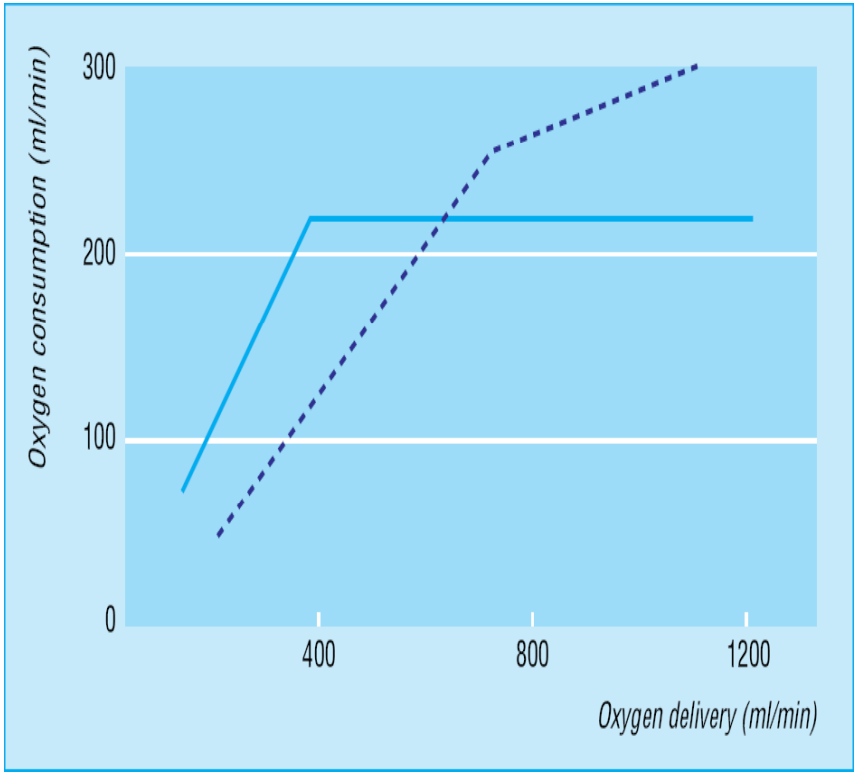
Does not plateau (consumption remains supply dependent even at “supranormal” levels of DO_2)

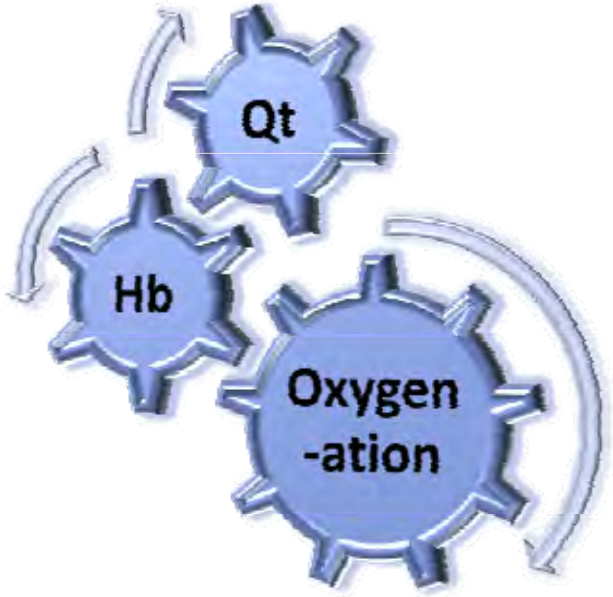


Critical level of DO_2 range from 2.1 to 6.2 mL/min/kg

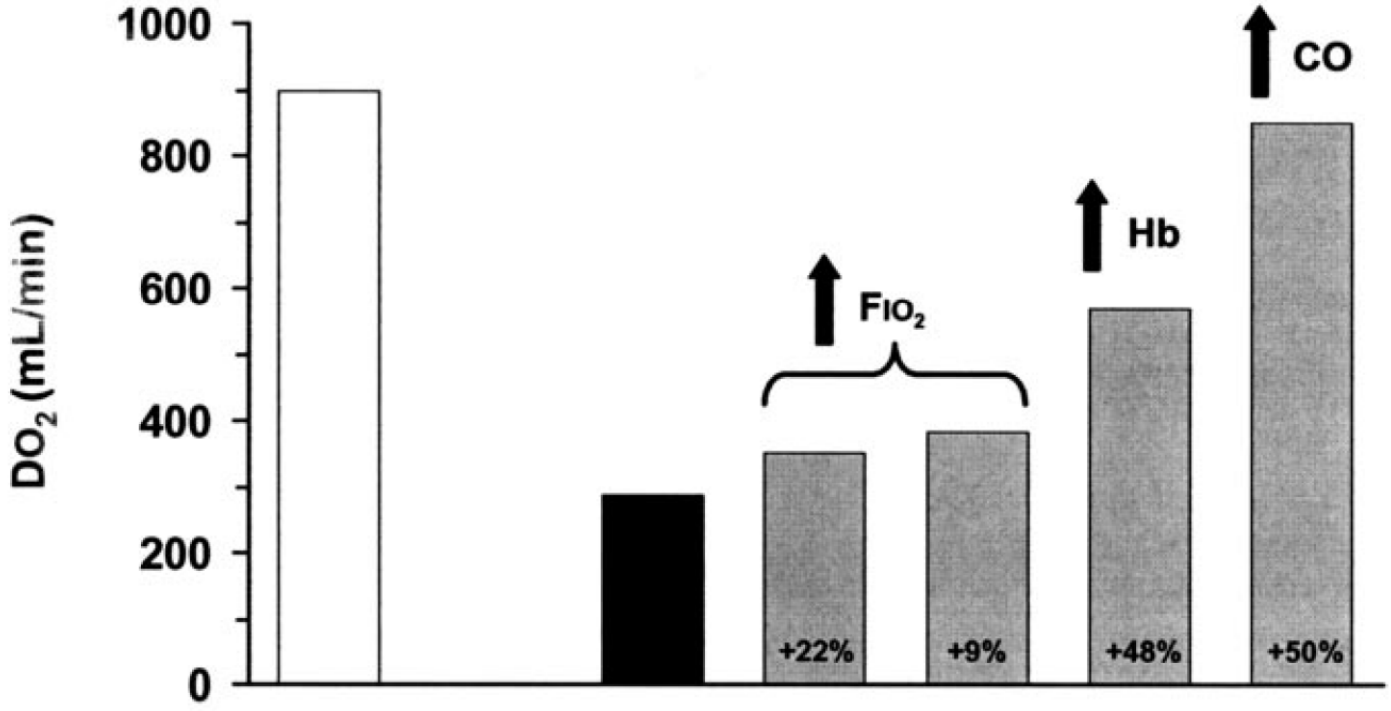
BMJ 1998;317:1302-6

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 PaO_2, Hb and CO on DO_2 in a critically ill

Thorax 2002; 57:170–177

DO_2 during exercise

- During exercise
  - O_2 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

Organs	Blood Flow, mL/100 g	Arterial-Venous Difference, Volume %	$\dot{V}O_2$, mL/mi
Heart	70	11.4	23.9
Brain	50	6.3	47.9
Kidney	400	1.3	15.9
Liver	29	4.1	20.9
GI tract	35	4.1	29.3
Skeletal muscle	2.5	6.4	60.8
Skin			

Perfusion pressure is an important determinant

Chest 2005; 128:554S–560S

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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

CARBONDIOXIDE 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 % $CvCO_2$=52 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 CO_2

- Only ~5% of total arterial content is present in the form of dissolved CO_2
- 0.3 ml of CO_2/100 ml in absolute terms
- During heavy exercise may increase up to sevenfold

Carbonic anhydrase (CA)

- Key enzyme in CO_2 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

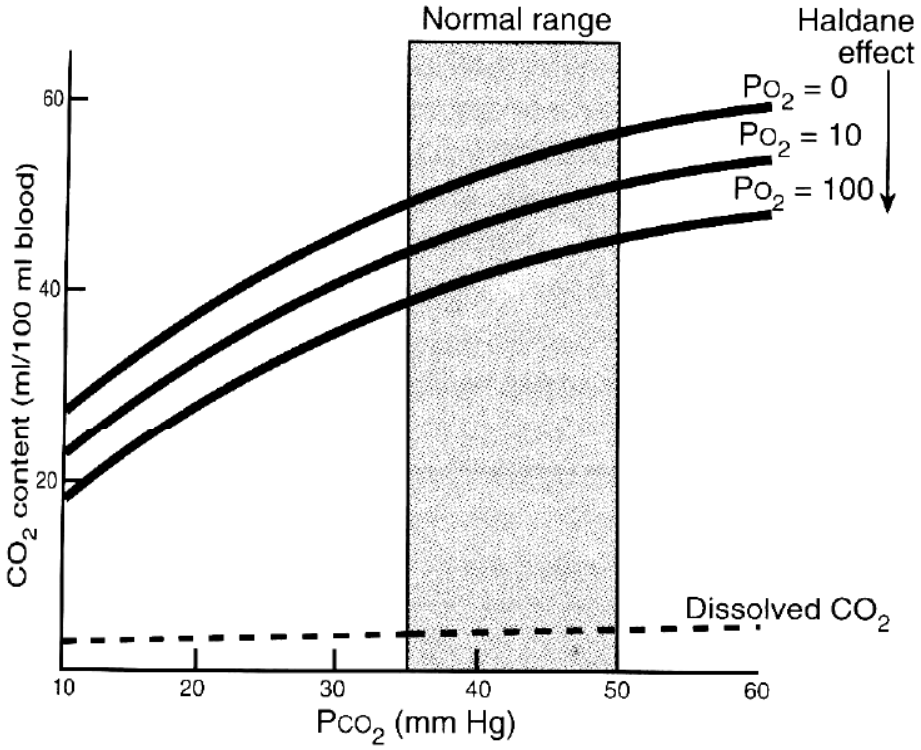
Chloride shift

- Hamburger in 1918
- HCO_3^- exchange with Cl^- ions across RBC membrane
- Passive process
- Mediated by membrane bound protein ‘band 3’
- Band 3 anchoring site for ankyrin and spectrin

CO_2 bound as carbamate

- CO_2 reacts directly with Hb
- Reversible reaction with a loose bond
- Depends on
  - O_2 sat^n of Hb and 2,3 DPG (binding to Hb)
  - H^+ $conc^n$ (both Hb & plasma proteins)
- However, ↑ Hb desat and ↑ in H^+ $conc^n$ work in opposite direction

Haldane Effect



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--

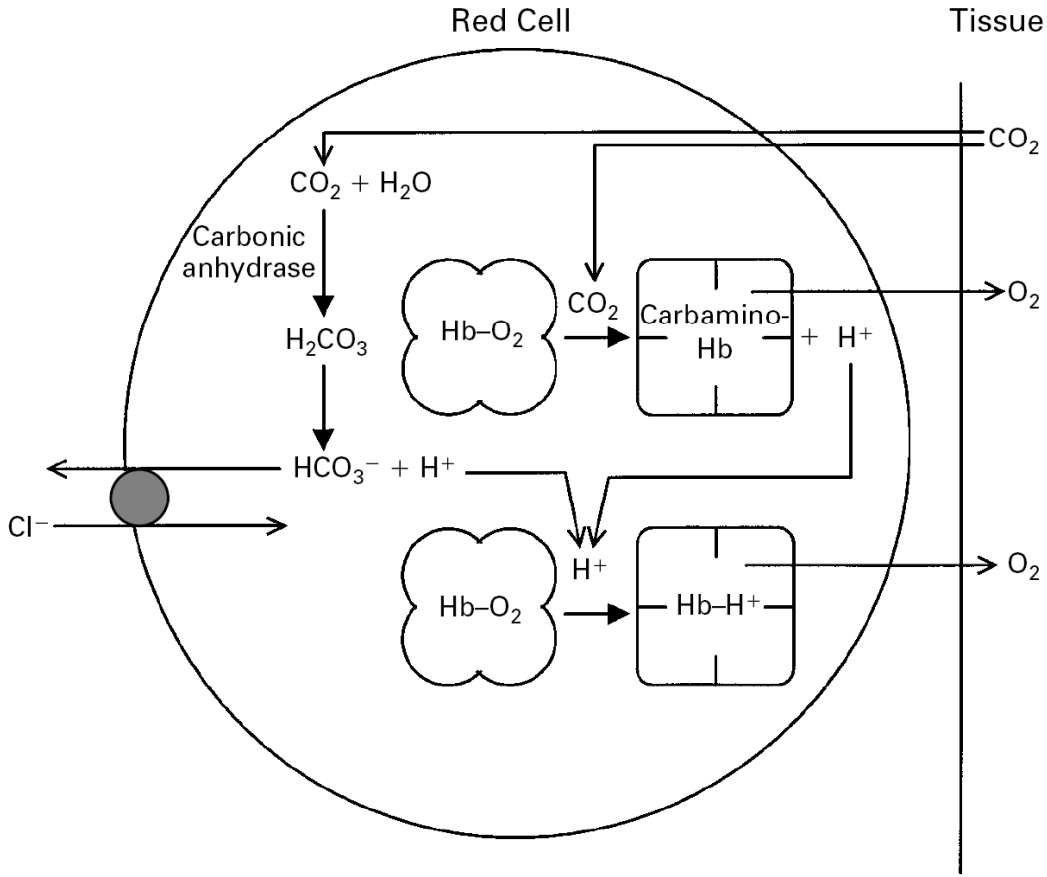
1. H^+ ions
2. CO_2 to form carbamino compounds

in turn assisting blood to load more CO_2 from the tissues

Haldane Effect

- Binding of O_2 with hemoglobin tends to displace CO_2 from the blood
- Leads to ↑ uptake of CO_2 in the tissues and ↑ release of CO_2 in the lungs
- Approximately doubles the amount of CO_2 released from the blood in the lungs and that picked up in the tissues

Coupled transport within the red cell in peripheral tissues



N Eng J Med 1998;338:239-47

Influence of CO_2 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 HCO_3^-
  - 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

$$P_aCO_2 \quad \alpha \quad \frac{VCO_2}{RR\ (V_T - V_D)}$$

↑VCO_2 (Hypermetabolism)

Fever

Seizures

Sepsis

Hyperalimentation

↓RR (Central hypoventilation)

Drugs

Brainstem lesions

Obesity-hypoventilation syndrome

↓V_T

Skeletal muscle weakness

Impaired neuromuscular transmission

↓ Lung / chest wall compliance

Airway obstruction

- COPD
- Asthma
- Obstructive sleep apnea

↑V_D

Excessive PEEP