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OXYGEN - CARBON DIOXIDE TRANSPORT

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HEADINGS

- INTRODUCTION
- OXYGEN TRANSPORT FROM LUNGS TO CELLS
- OXYGEN DELIVERY DURING EXERCISE
- OXYGEN DELIVERY DURING CRITICAL ILLNESS
- CARBON DIOXIDE TRANSPORT

INTRODUCTION TO PHYSIOLOGY OF OXYGEN TRANSPORT

- Substrate used by cells in max qty
- Key factor for aerobic metabolism and cell integrity
- No storage system in tissues - req for continuous supply
- Tissue hypoxia → anaerobic metabolism
- Cascade for transport from environmental air to mitochondria

OXYGEN TRANSPORT - CONVECTIVE AND DIFFUSIVE

- Convective - bulk movement
- Active energy dependant process
- Tracheobronchial tree and circulation

- Diffusive - passive movement down concentration gradient
- Alveolo-capillary membrane and capillary-tissue transport

REQUIREMENTS FOR OXYGEN TRANSPORT SYSTEM

- Energy efficient (avoid unnecessary cardiorespiratory work)
- Match O2 supply with demand
- Efficient transportation of oxygen (‘minimal wastage/ transmission losses’)

ROLE OF HEMOGLOBIN

- Increases oxygen transport capacity by 30-100 fold
- Increases CO2 transport capacity 15-20 fold

KEY STEPS IN OXYGEN CASCADE

- Uptake in the lungs
- Carrying capacity of blood
- Delivery from lungs to tissue capillaries
- Delivery from capillary blood to interstitium
- Delivery from interstitium to individual cells
- Cellular use of oxygen

OXYGEN UPTAKE IN LUNGS

DETERMINANTS OF PaO2

- Inspired O2 concentration & barometric pressure
- Alveolar ventilation
- V/Q distribution & matching
- O2 diffusion from alveoli to pul capillaries

DIFFUSION FROM ALVEOLI TO PULMONARY CAPILLARIES

- PAO2 – Driving Pressure for O2 Diffusion Into Pul Capillary Bed and Main Determinant of PaO2 normally
- PAO2-PaO2 reflects overall efficiency of O2 uptake from alveoli to arterial blood
- Capillary blood fully oxygenated before traversing 1/3 distance of alveolo-capillary interface
- Inadequate oxygenation due to reduced pul capillary time occurs only with very high C.O. or severe desaturation of mixed pul arterial blood

OXYGEN CARRYING CAPACITY OF BLOOD

- 97-98% Carried in Combination With Hb (2-3% Dissolved in Plasma)

  O_2 CONTENT = 1.31 x Hb x Sat + 0.0031 x PO_2

- 1gm Hb Binds 1.31 Though Expected 1.39 Due to Presence of Iron in non-heme form
- O_2 content in 100 ml blood (in normal adult with Hb 15 gm/dl) ~ 20 ml

  (19.4 ml as OxyHb + 0.3 ml in plasma)

- Shift of Curve to Right ↑ Release of O_2 to Tissues & Improves O_2 availability provided PaO_2 > 60 mm Hg

FACTORS AFFECTING O2-Hb DISSOCIATION CURVE

- PCO_2
- TEMPERATURE
- 2,3 – DIPHOSPHOGLYCERATE
- PRESENCE/PERCENTAGE OF FETAL Hb
- pH

EFFECT OF pH & TEMP

- ↓ In pH from 7.4 to 7.2 causes shift of curve to right by 15%
- ↑ In pH by similar value causes shift of curve to left by similar magnitude
- ↑ Temp ↓ affinity of O2 to Hb and hence shift of curve to right and more release of O2 at a given PO2. Opposite changes occur with ↓ temp

EFFECT OF PCO2

- Shift of O2-Hb dissociation curve to right by ↑ PCO2 **(BOHR EFFECT) -** Important to enhance oxygenation of blood in lungs and to enhance release of O2 in the tissues
- In the lungs, CO2 diffuses out of the blood (H+ conc also ↓ due to ↓ in H2CO3 conc) → Shift of O2-Hb curve to left & more avid binding of O2 to Hb → ↑ in quantity of O2 bound to Hb → ↑ O2 transport to tissues.

When the blood reaches the tissue capillaries, the opposite occurs (↑ CO_2 and ↑ H^+) and hence greater release of O_2 due to less avid binding of O_2 to Hb.

EFFECT OF 2,3 - DPG

↑ levels shift curve to right & vice-versa with ↓ levels.

Concentration 2,3 - DPG in RBCs affects the structure of the Hb molecule and its affinity for O_2.

Reduced concentrations (as found in old blood from blood banks) reduce the P50 → ↓ delivery to tissues

O2 DELIVERY FROM LUNGS TO TISSUES

- Major function of circulation to transport O2 from lungs to peripheral tissues at a rate that satisfies overall oxygen consumption.
- Failure to supply sufficient O2 to meet metabolic req of tissues defines circulatory shock.
- Under normal resting conditions total or “global” oxygen delivery (DO2) is more than adequate to meet the total tissue oxygen requirements (VO2) for aerobic metabolism.

- DO_2 (ml/min) = Qt x CaO_2

  CaO_2 = Hb x SaO_2 x K

where K is coefficient for Hb-O_2 binding capacity

DO_2 = Qt x Hb x SaO_2 x K

- VO_2 = Qt x (CaO_2 - CvO_2)
- O_2 Extraction ratio (VO_2/DO_2)

Normally ~ 25% but ↑ to 70-80% during maximal exercise in well trained athletes

- SvO_2 in blood draining from diff organs varies widely
  - hepatic SvO_2 ~ 30-40%
  - renal SvO_2 ~ 80%

Reflects regional differences in DO_2 and VO_2

- O2 not extracted by tissues returns to lungs & mixed venous saturation (SvO2) measured in the pul A represents the pooled venous saturation from all organs.
- SvO2 influenced by changes in both DO2 and VO2
- > 65% if supply matches demand (provided regional perfusion and mechanisms for cellular O2 uptake are normal).

- As metabolic demand (VO2) ↑ or supply (DO2) ↓ O2 Extraction Ratio (VO2/DO2) ↑ to maintain aerobic metabolism.
- After max VO2/DO2 reached (60-70% for most tissues) further ↑ in demand or ↓ in supply lead to hypoxia
- Under normal circumstances 5 ml of O2 transported to tissues by each 100 ml of blood since the amount of O2 in blood reduces from 19.4 ml to 14.4 ml/100 ml of blood on passing though the capillaries
- This reflects a change in PO2 from 95 mm Hg to 40 mm Hg (O2 Sat of 97% and 75% respectively)

O2 DIFFUSION FROM INTERSTITIUM TO CELLS

Intracellular PO2 < Interstitial fluid PO2

- O2 constantly utilized by the cells
- Considerable distance between capillaries and cells in some tissues

N PcO2 ~ 5-40 mm Hg (average 23 mmHg)

N intracellular req for optimal maintenance of metabolic pathways ~ 3 mm Hg

CELLULAR USE OF OXYGEN

- Cellular metabolic rate determines overall O2 consumption
- Cellular use of O2 #$^{-}$ by metabolic poisons (CN^{-}, Cellular toxins (e.g. endotoxins)
- Relative effects of tissue hypoxia due to #$^{-}$ of cellular use or excessive O2 consumption not fully established

FACTORS AFFECTING VO2/DO2 FROM CAPILLARY BLOOD

- Rate of O2 delivery to capillary
- O2-Hb dissociation relation
- PiO2 - PcO2
- 1/diffusion distance
- Rate of use of oxygen by cells

O2 DELIVERY DURING EXERCISE

- During strenuous exercise VO2 may ↑ to 20 times N
- Blood also remains in the capillary for <1/2 N time due to ↑ C.O.

O2 Sat not affected

- Blood fully sat in first 1/3 of N time available to pass through pul circulation

- Diffusion capacity ↑ upto 3 fold since:

1. Additional capillaries open up →↑ no of capillaries participating in diffusion process
2. Dilatation of both alveoli and capillaries → ↓ alveolo-capillary distance
3. Improved V/Q ratio in upper part of lungs due to ↑ blood flow to upper part of lungs

Shift of O2-Hb dissociation curve to right because of:

1. ↑ CO2 released from exercising muscles
2. ↑ H+ ions → ↓ pH
3. ↑ Temp
4. Release of phospates → ↑ 2,3 - DPG

OXYGEN DELIVERY IN CRITICAL ILLNESS

- Optimum Hb conc in critically ill patients is 10-11 gm/dL - represents balance between maximising O2 content & adverse microcirculatory effects associated with marked ↑ in viscosity at high PCV
- In many critically ill pts tissue hypoxia is due to disordered regional distribution of blood flow both between and within organs
- In critical illness, particularly sepsis, hypotension and loss of normal autoregulation cause shunting and tissue hypoxia in some organs despite high DO2 and SvO2

- Perfusion pressure is an imp determinant of regional perfusion and drugs often used in attempt to improve regional tissue perfusion

However :

- Inotropes given to maintain Sys BP may ↓ regional distribution, particularly to the renal and splanchnic capillary beds.
- Dopamine previously used to improve renal blood flow but ↑ overall C.O. rather than regional distribution.

- During critical illness tissue hypoxia is often caused by capillary microthrombosis after endothelial damage and neutrophil activation rather than by arterial hypoxaemia

- Ideally, individual tissue oxygenation needs to be measured directly to assess and manage organ hypoxia correctly

INTRODUCTION TO PHSYIOLOGY OF CO2 TRANSPORT

1. CO2 is the end-product of aerobic metabolism.
2. Produced almost entirely in the mitochondria where the PCO2 is the highest
3. Elimination of CO2 - one of major req of body. Large but highly variable amount of CO2 produced

- CO_2 in blood present in 3 forms:
  - Dissolved
  - Bound as bicarbonate
  - Bound as carbamate
- Relative contribution of diff forms to overall CO_2 transport changes markedly along the elimination pathway of CO_2
- For diffusion across membrane barriers, gaseous form more appropriate while for transport within intra- or extracellular compartments, other forms more imp
- Kinetics of interchange between diff forms very imp

- Products of hydration reaction of CO2 , HCO3 , and H+ reqd for variety of other cellular f_x such as secretion of acid or base and some reactions of intermediary metabolism.
- In exercising skeletal muscle, the other “end product” of metabolism, lactic acid, contributes huge amounts of H+ and affects predominance of the three forms of CO2 , because HCO3 as well as carbamate are critically dependent on concentration of H+.

CO_2 DIFFUSION

- At each point in gas transport chain, CO_2 diffuses in exactly the opp direction to O_2 diffusion.
- CO_2 diffuses 20 times as rapidly as O_2.
- Pressure differences reqd for CO_2 diffusion far less than those reqd to cause O_2 diffusion

CO_2 TRANSPORT IN BLOOD

- Under N resting conditions av 4 ml CO_2 transported from tissues to lungs/dL blood
- CO_2 diffuses out of tissue cells in gaseous form but does not leave cells to any significant extent in form of HCO_3 since cell memb almost impermeable to HCO_3
- Most of CO_2 entering and leaving blood also in gaseous form though amount carried in sol very small

- Within plasma little chemical combination of CO_2 because:
  - No carbonic anhydrase in plasma → H_2CO_3 formed very slowly
  - Little buffering power in plasma to promote dissociation of H_2CO_3

DISSOLVED CO_2

CO_2 belongs to group of gases with moderate solubility in water

- According to Henry's law of solubility:

$PCO_2 \times \alpha = CO_2$ conc in sol

α = Solubility Coefficient

Value dependant upon temp (inversely proportional) → more temp lesser amount of CO_2 dissolved

- Only ~5% of total arterial content of CO_2 present in dissolved form

- At rest, contribution of dissolved CO_2 to total A-V CO_2 conc diff only ~10%. In absolute terms only 0.3 ml of CO_2/dL transported in dissolved form
- During heavy exercise contribution of dissolved CO_2 can ↑ 7 fold → ~1/3 of total CO_2 exchange
- During heavy work load of muscle, ↑ levels of lactic acid present in addition to CO_2 → aggravating ↓ in pH → fraction of HCO_3 in total CO_2 diminished

CO_2 BOUND AS HCO_3

- Resp for ~ 70% of CO_2 transport from tissues to lungs.
- Dissolved CO_2 in blood reacts with water to form Carbonic Acid

$$CO_2 + H_2O \Leftrightarrow H_2CO_3$$

- Under physiological conditions, equilibrium of equation to extreme left i.e. very negligible amounts dissolved as H_2CO_3 (<1%)

- Carbonic Anhydrase (C.A.) present inside RBCs, pul capillary endo & other tissues but not plasma catalyzes this RX - acc it 5000 fold both ways & markedly ↓ time reqd for completion of RX
- Other roles for C.A.:

  Generation of H & HCO3 in secretory organs esp kidney

  Transfer of CO2 in skeletal & cardiac muscle

- Carbonic acid dissociates into H+ & HCO3

$$H_2CO_3 \Leftrightarrow H + HCO_3$$

- Most of H+ combine with Hb (powerful buffer) & HCO3 diffuse out of RBCs into plasma in exchange for Cl - Band 3 HCO3/Cl carrier protein in RBC memb
- Cl content of RBCs V>A -

HAMBURGER (CHLORIDE) SHIFT

- Ping-pong mech (1st ion moves out of cell before 2nd ion moves inwards - most other ion pumps simultaneous exchange 2 ions)

- Related to proteins ankyrin & spectrin - involved in maint of cell shape & memb stability.
- Genetically altered Band 3 protein asso with small fragile spherical RBCs in exp animals
- #- C.A. by acetazolamide → PiCO2 ↑ from 45 upto 80 mm Hg
- At pH 7.4 qty of CO2 as HCO3 20-fold that as dissolved CO2 → 13-fold at pH 7.2 (N inside RBCs), ratio ↓ further as plasma pH ↓ during max exercise. Absolute A-V diff is ↑ during exercise compared to that at rest, relative contribution of HCO3 to overall exchange less.

CO_2 BOUND AS CARBAMATE

- Resp for ~ 15-25% of total CO_2 transport
- CO_2 reacts directly with Hb to form the carbaminoHb (Hgb.CO)
- Reversible RX - very loose bond → CO_2 easily released into alveoli where $PACO_2 < PCO_2$ of pul cap
- Small qty of CO_2 reacts with plasma proteins - less significant (qty of proteins $1/4^{th}$ that of Hb)
- Amount of CO_2 bound as carbamate to Hb or plasma proteins depends on:
  1) O_2 Sat of Hb (RBCs)
  2) H^+ conc (RBCs & plasma)

- During passage of blood thru muscle & tissues, O2 Sat and H+ conc change considerably, in particular during exercise.
- ↓ in Hb Sat & ↑ in H+ conc in RBCs in capillary affect qty of CO2 bound to Hb in opp directions
- H+ conc - Acidification ↓ qty of carbamate formed by Hb (Avoided to some extent by buffering of H+ produced with imidazole groups on the histidine residues of Hb
- O2 Sat of Hb - Deoxygenation of Hb ↑ qty of CO2 bound to Hb (HALDANE EFFECT)

HALDANE EFFECT

- Binding of O2 with Hb tends to displace CO2 from blood
- Quantitatively more imp in promoting CO2 transport than is Bohr effect in promoting O2 transport
- Haldane effect ~ doubles qty of CO2 released from blood in lungs and that picked up in tissues.

Oxygenation of Hb

↓

↑ acidity of Hb

↓

↓ tendency to combine with CO_2 to form Hgb.CO

↓

Displacement of CO_2 from Hb

↓ H+ binding to Hb

↓

↑ Release of H+ from Hb

↓

↑ formation of H_2CO_3

↓

↑ release of CO_2

LUNGS

Reduction of Hb (↓ oxygenation of heme)

↓

TISSUES ↑ basicity of Hb

↓

↑ H+ binding to reduced Hb

↓

↑ dissociation of H_2CO_3

↓

↑ carriage of CO_2 as HCO_3


Thank You