Tissue Hypoxia

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I. Definition
   A. Tissue hypoxia occurs when oxygen transport is reduced below a critical level (i.e., below the metabolic demand), at which point either metabolism must be maintained anaerobically or tissue metabolic rate must be reduced.
   B. Under experimental conditions, if demands are kept constant, there is a biphasic response in oxygen consumption as oxygen transport is progressively reduced.
      1. Initially, oxygen consumption is independent of oxygen transport.
      2. Subsequently, oxygen consumption becomes dependent on oxygen transport and declines in proportion (physiologic supply dependency).

II. Evaluating Tissue Oxygenation
   A. Mixed venous saturation identifies global tissue hypoxia, but tissue hypoxia can exist with a normal mixed venous saturation.
   B. Blood lactate concentrations; elevation can be present in the absence of tissue hypoxia, particularly in patients with sepsis.
   C. Fractional oxygen extraction increases as oxygen transport is progressively compromised. Fractional oxygen extraction (FOE) can be measured by near-infrared spectroscopy (NIRS). Using spatially resolved spectroscopy, an NIRS method, it is possible to measure regional tissue oxygen saturation in different organs (e.g., brain, kidney, liver, muscle or body regions, preductal, postductal peripheral tissue).

III. Oxygen Transport
   A. Determinants
      1. Cardiac output
      2. Hemoglobin concentration
      3. Hemoglobin saturation (to a lesser extent)

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B. Oxygen–hemoglobin dissociation curve
   1. The quaternary structure of hemoglobin determines its affinity for oxygen. By shifting the relationship of its four component polypeptide chains, and hence a change in the position of the heme moieties, it can assume:
      (a) A relaxed (R) state—favors O_2 binding
      (b) A tense (T) state—decreases O_2 binding
   2. When hemoglobin takes up a small amount of the oxygen, the R state is favored and additional O_2 uptake is facilitated.
   3. The oxygen–hemoglobin dissociation curve (which relates percentage oxygen saturation of hemoglobin to PaO_2) has a sigmoidal shape.

C. Factors affecting the affinity of hemoglobin for oxygen:
   1. Temperature
   2. pH
   3. 2,3 Diphosphoglycerate (2,3-DPG)
      (a) A rise in temperature, a fall in pH (Bohr effect, elevated $PaCO_2$), or an increase in 2,3-DPG all shift the curve to the right, liberating more oxygen.
      (b) The P_{50} is the PaO_2 at which the hemoglobin is half saturated with O_2; the higher the P_{50}, the lower the affinity of hemoglobin for oxygen.
      (c) A right shift of the curve means a higher P_{50} (i.e., a higher PaO_2 is required for hemoglobin to bind a given amount of O_2).

D. 2,3-DPG
   1. Formed from 3-phosphoglyceride, a product of glycolysis
   2. It is a high charged anion, which binds to the β chains of deoxygenated hemoglobin, but not those of oxyhemoglobin.
   3. 2,3-DPG concentration
      (a) Increased by
         (1) Thyroid hormones
         (2) Growth hormones
         (3) Androgens
         (4) Exercise
         (5) Ascent to high altitude (secondary to alkalosis)
      (b) Decreased by
         (1) Acidosis (which inhibits red blood cell glycolysis)
         (2) Fetal hemoglobin (HbF) has a greater affinity for O_2 than adult hemoglobin (HbA); this is caused by the poor binding of 2,3-DPG to the δ chains of HbF. Increasing concentrations of 2,3-DPG have much less effect on altering the P_{50} if there is HbF rather than HbA.

IV. Response to Reduced Oxygen Transport
   A. From low cardiac output: if chronic, 2,3-DPG increases unless there is systemic acidemia
   B. From anemia
      1. Cardiac output and oxygen extraction increase.
      2. If chronic, the HbO_2 dissociation curve shifts to the right.
   C. From alveolar hypoxemia
      1. Increased cardiac output and oxygen extraction
      2. Increased hemoglobin

V. Oxygen Extraction Increases Progressively as Oxygen Transport Is Reduced if Oxygen Consumption Remains Constant.
   A. Alterations in vascular resistance with adjustments to the microcirculation—opening of previously closed capillaries. This has three positive effects:
      1. The increase in capillary density decreases the distance for diffusion between the blood and site of oxygen utilization.
      2. It increases the lateral surface area for diffusion.
      3. The increase in cross-sectional area of the capillaries reduces the blood linear velocity and increases the transit time for diffusion.
   B. Changes in hemoglobin–oxygen affinity
      1. Increase in hydrogen (H^+) concentration results in a right shift of the dissociation curve.
      2. Changes in the 2,3-DPG concentration
      3. The concentration of 2,3-DPG is regulated by red blood cell H^+ concentration (as the rate-limiting enzyme is pH sensitive)—a high pH stimulates 2,3-DPG synthesis.
      4. Deoxyhemoglobin provides better buffering than oxyhemoglobin and thereby raises red cell pH; thus, low venous oxygen promotes DPG synthesis.

         Note: This adaptive mechanism is less prominent in young infants with high levels of HgF, as HbF binds 2,3-DPG poorly and its synthesis is inhibited by unbound DPG.

VI. Consequences of Tissue Hypoxia
   A. Reduced oxidative phosphorylation.
   B. Electron transport chain slows.
   C. Reduced phosphorylation of adenosine-5′-diphosphate (ADP) to adenosine-5′-triphosphate (ATP).
   D. Increased adenosine-5′-monophosphate (AMP), which is rapidly catabolized to inosine and hypoxanthine during hypoxia.
   E. Creatinine phosphate acts as a "supplementary" energy reservoir if creatinine kinase is available but becomes rapidly depleted.
   F. ADP can be phosphorylated anaerobically, but this is much less efficient than aerobic metabolism. During aerobic glycolysis, production of ATP is 19 times greater than it is under anaerobic conditions (i.e., production of 38 versus 2 mmol of ATP). Lactic acid accumulates.
   G. Adverse effect on immune function and inflammation
      1. Increased neutrophil sequestration
      2. Increased vascular permeability
      3. Decreased cellular immune function

Suggested Reading

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