

PHYO6200 Concepts in Human Physiology - Hypoxia Physiology

Introduction:

- Oxygen pressure profile: P_{O_2} falls from ambient to lung and blood to mitochondria
- Oxygen dissociation curve: oxygen transport by blood
- Tissue gas exchange: cardiovascular functions and diffusion
- Energy metabolism: aerobic versus anaerobic conditions

Hypoxia:

- Tissue hypoxia: an inadequate supply of oxygen to tissues (<3 mmHg).
 - hypoxic: shortage of pulmonary supply
 - anemic: decreased blood carriage
 - ischemic: reduced blood flow
 - histotoxic: disrupted utilization
- Systemic hypoxia (e.g. high altitude-with lower atmospheric pressure) elicits the chemoreflex mediated by peripheral chemoreceptors for the cardiopulmonary responses. (*Marshall JM 1994 Physiol Rev 74(3): 544-584*)
 - Carotid bodies and aortic bodies:
 - Primary effects:
 - hyperventilation, increase coronary flow
 - bradycardia, decreased contractility
 - vasoconstriction in peripheral circulation
 - Secondary effects:
 - inspiration increases HR, sympathetic flow and decreases cardiac vagal tone
- Tissue/local (ischemia-with metabolite accumulation):

Cardiac output:

It depends on coronary blood supply, ATP production & neurohumoral control

Heart rate & contractility:

Acute (severe) hypoxia:

- Blood flow: Reduced coronary resistance with local mediators (metabolites, adenosine, prostaglandin, PGI_2).
- Hormonal and neurogenic regulation: increased circulating catecholamines, sympathetic stimulation for an increase in coronary flow
- Isolated heart:
 - decreased contractility, arrhythmias, inexcitable, cardiac injury

Chronic (moderate) hypoxia:

- Hyperventilation with renal compensation
- O₂ dissociation curve right shift
- Polycythemia: increased hematocrit
- increased number of capillaries in tissues
- pulmonary vasoconstriction & remodelling
- Right ventricular hypertrophy

Blood flow:

- Hormonal and neurogenic regulation: increased circulating catecholamines, e.g. sympathetic stimulation for an increase in coronary flow

Oxygen delivery:

- Angiogenesis with vascular endothelial growth factor (VEGF) (Hashimoto E et al. 1994 *Am J Physiol.* 267(5 Pt 2):H1948-1954.)

Energy utilization:

- Anaerobic metabolism: Enhanced glucose utilization and lactate production (Silverman HS et al. 1997 *Circ Res* 80: 699-707).
- Enhanced capacity for glucose phosphorylation and amino acid metabolism (Rumsey WL et al. 1999 *Am J Physiol* 276: H71-80)

Cardiac hypertrophy:

- Right ventricular hypertrophy due to increased pulmonary arterial pressure

Cellular response to hypoxia via hypoxia-inducible factor (HIF) pathway for the transcriptional control of HIF-target gene products (e.g. erythropoietin, VEGF, glycolytic enzymes, vasoactive factors):

(Wenger, R.H. 2002 *FASEB J.* 16, 1157.)

(Yu AY et al. 1999 *J Clin Invest.* 103(5):691-696)