Respiratory Adjustments in Health & Disease

INTRODUCTION

We will discuss the respiratory adjustments to exercise, hypoxia, including that produced by high altitude, hypercapnia, and respiratory disease. These respiratory adjustments highlight the operation of the different respiratory regulatory mechanisms.

EFFECTS OF EXERCISE

Many cardiovascular and respiratory mechanisms must operate in an integrated fashion if the O2 needs of the active tissue are to be met and the extra CO2 and heat removed from the body during exercise. Circulatory changes increase muscle blood flow while maintaining adequate circulation in the rest of the body. There is in addition an increase in the extraction of O2 from the blood in exercising muscles and an increase in ventilation that provides extra O2, eliminates some of the heat, and excretes extra CO2.

Changes in Ventilation

During exercise, the amount of O2 entering the blood in the lungs is increased because the amount of O2 added to each unit of blood and the pulmonary blood flow per minute are increased. The PO2 of blood flowing into the pulmonary capillaries falls from 40 to 25 mm Hg or less, so that the alveolar-capillary PO2 gradient is increased and more O2 enters the blood. Blood flow per minute is increased from 5.5 L/min to as much as 20-35 L/min. The amount of CO2 removed from each unit of blood is increased. The increase in O2 uptake is proportionate to work load up to a maximum. Above this maximum, O2 consumption levels off and the blood lactate level continues to rise (Figure 1). The lactate comes from muscles in which aerobic resynthesis of energy stores cannot keep pace with their utilization and an oxygen debt is being built.

Figure -1. Relation between workload, blood lactate level, and O2 uptake. I-VI, increasing work loads produced by increasing the speed and grade of a treadmill on which the subjects worked

There is an abrupt increase in ventilation with the onset of exercise, followed after a brief pause by a further, more gradual increase. With moderate exercise, the increase is due mostly to an increase in the depth of respiration; this is accompanied by an increase in the respiratory rate when the exercise is more strenuous.
There is an abrupt decrease in ventilation when exercise ceases, followed after a brief pause by a more gradual decline to preexercise values. The abrupt increase at the start of exercise is presumably due to psychic stimuli and afferent impulses from proprioceptors in muscles, tendons, and joints. The more gradual increase is presumably humoral even though arterial pH, PCO2, and PO2 remain constant during moderate exercise. The increase in ventilation is proportionate to the increase in O2 consumption.

When exercise becomes more vigorous, buffering of the increased amounts of lactic acid that are produced liberates more CO2, and this further increases ventilation. With increased production of acid, the increases in ventilation and CO2 production remain proportionate, so alveolar and arterial CO2 change relatively little (isocapnic buffering). Because of the hyperventilation, alveolar PO2 increases. With further accumulation of lactic acid, the increase in ventilation outstrips CO2 production and alveolar PCO2 falls, as does arterial PCO2. The increase in arterial PCO2 provides respiratory compensation for the metabolic acidosis produced by the additional lactic acid. The additional increase in ventilation produced by the acidosis is dependent on the carotid bodies and does not occur if they are removed.

The respiratory rate after exercise does not reach basal levels until the O2 debt is repaid. This may take as long as 90 minutes. The stimulus to ventilation after exercise is not the arterial PCO2, which is normal or low, or the arterial PO2, which is normal or high, but the elevated arterial H+ concentration due to the lactic acidemia.

Changes in the Tissues

Maximum O2 uptake during exercise is limited by the maximum rate at which O2 is transported to the mitochondria in the exercising muscle. However, this limitation is not normally due to deficient O2 uptake in the lungs, and hemoglobin in arterial blood is saturated even during the most severe exercise.

During exercise, the contracting muscles use more O2, and the tissue PO2 and the PO2 in venous blood from exercising muscle fall nearly to zero. The net effect is a threefold increase in O2 extraction from each unit of blood. Since this increase is accompanied by a 30-fold or greater increase in blood flow, it permits the metabolic rate of muscle to rise as much as 100-fold during exercise.

Exercise Tolerance & Fatigue

What determines the maximum amount of exercise that can be performed by an individual? Obviously, exercise tolerance has a time as well as an intensity dimension. For example, a fit young man can produce a power output on a bicycle of about 700 watts for 1 minute, 300 watts for 5 minutes, and 200 watts for 40 minutes. It used to be argued that the limiting factors in exercise performance were the rate at which O2 could be delivered to the tissues or the rate at which O2 could enter the body in the lungs. These factors play a role, but it is clear that other factors also contribute and that exercise stops when the sensation of fatigue progresses to the sensation of exhaustion. Fatigue is produced in part by bombardment of the brain by neural impulses from muscles, and the decline in blood pH produced by lactic acidosis also makes one feel tired. So do the rise in body temperature, dyspnea, and, perhaps, the uncomfortable sensations produced by activation of the J receptors in the lungs.

HYPOXIA

Hypoxia is O2 deficiency at the tissue level. Traditionally, hypoxia has been divided into four types. The four categories are
(1) hypoxic hypoxia (anoxic anoxia), in which the PO2 of the arterial blood is reduced;
(2) anemic hypoxia, in which the arterial PO2 is normal but the amount of hemoglobin available to carry O2 is reduced.

(3) stagnant or ischemic hypoxia, in which the blood flow to a tissue is so low that adequate O2 is not delivered to it despite a normal PO2 and hemoglobin concentration.

(4) histotoxic hypoxia, in which the amount of O2 delivered to a tissue is adequate but, because of the action of a toxic agent, the tissue cells cannot make use of the O2 supplied to them.

HYPOXIC HYPOXIA

Hypoxic hypoxia is a problem in normal individuals at high altitudes and is a complication of pneumonia and a variety of other diseases of the respiratory system.

A-Effects of Decreased Barometric Pressure

The composition of air stays the same, but the total barometric pressure falls with increasing altitude. Therefore, the PO2 also falls. At 3000 m (approximately 10,000 ft) above sea level, the alveolar PO2 is about 60 mm Hg and there is enough hypoxic stimulation of the chemoreceptors to definitely increase ventilation. As one ascends higher, the alveolar PO2 falls less rapidly and the alveolar PCO2 declines somewhat because of the hyperventilation. The resulting fall in arterial PCO2 produces respiratory alkalosis.

There are a number of compensatory mechanisms that operate over a period of time to increase altitude tolerance (acclimatization), but in unacclimatized subjects, mental symptoms such as irritability appear at about 3700 m. At 5500 m, the hypoxic symptoms are severe; and at altitudes above 6100 m (20,000 ft), consciousness is usually lost.

The total atmospheric pressure becomes the limiting factor in altitude tolerance when breathing 100% O2. At about 14,000 m, consciousness is lost in spite of the administration of 100% O2. At 19,200 m, the barometric pressure is 47 mm Hg, and at or below this pressure the body fluids boil at body temperature. The point is largely academic, however, because any individual exposed to such a low pressure would be dead of hypoxia before the bubbles of steam could cause death.

Of course, an artificial atmosphere can be created around an individual; in a pressurized suit or cabin supplied with O2 and a system to remove CO2, it is possible to ascend to any altitude and to live in the vacuum of interplanetary space.

Delayed Effects of High Altitude

When they first arrive at a high altitude, many individuals develop transient "mountain sickness." This syndrome develops 8-24 hours after arrival at altitude and lasts 4-8 days. It is characterized by headache, irritability, insomnia, breathlessness, and nausea and vomiting. Its cause is unsettled, but it appears to be associated with cerebral edema. The low PO2 at high altitude causes arteriolar dilation, and if cerebral autoregulation does not compensate, there is an increase in capillary pressure that favors increased transudation of fluid into brain tissue. Individuals who do not develop mountain sickness have a diuresis at high altitude, and urine volume is decreased in individuals who develop the condition.
All forms of high-altitude illness are benefited by descent to lower altitude and by treatment with the diuretic acetazolamide.

Acclimatization to Altitude

Acclimatization to altitude is due to the operation of a variety of compensatory mechanisms.

1. The respiratory alkalosis produced by the hyperventilation shifts the oxygen-hemoglobin dissociation curve to the left, but there is a concomitant increase in red blood cell 2,3-DPG, which tends to decrease the O2 affinity of hemoglobin. The net effect is a small increase in P50 (see Chapter 35). The decrease in O2 affinity makes more O2 available to the tissues. However, the value of the increase in P50 is limited because when the arterial PO2 is markedly reduced, the decreased O2 affinity also interferes with O2 uptake by hemoglobin in the lungs.

2. The initial ventilatory response to increased altitude is relatively small, because the alkalosis tends to counteract the stimulating effect of hypoxia. However, there is a steady increase in ventilation over the next 4 days (Figure 37-6) because the active transport of H+ into CSF, or possibly a developing lactic acidosis in the brain, causes a fall in CSF pH that increases the response to hypoxia. After 4 days, the ventilatory response begins to decline slowly, but it takes years of residence at higher altitudes for it to decline to the initial level. Associated with this decline is a gradual desensitization to the stimulatory effects of hypoxia.

3. Erythropoietin secretion increases promptly on ascent to high altitude and then falls somewhat over the following 4 days as the ventilatory response increases and the arterial PO2 rises. The increase in circulating red blood cells triggered by the erythropoietin begins in 2-3 days and is sustained as long as the individual remains at high altitude.

4. There are also compensatory changes in the tissues.
   a. The mitochondria, which are the site of oxidative reactions, increase in number,
   b. there is an increase in myoglobin that facilitates the movement of O2 in the tissues.
   c. There is also an increase in the tissue content of cytochrome oxidase.

The effectiveness of the acclimatization process is indicated by the fact that in the Andes and Himalayas there are permanent human habitations at elevations above 5500 m (18,000 ft). The natives who live in these villages are barrel-chested and markedly polycythemic. They have low alveolar PO2 values, but in most other ways they are remarkably normal.

B-Diseases Causing Hypoxic Hypoxia

Hypoxic hypoxia is the most common form of hypoxia seen clinically. The diseases that cause it can be summarized.

Disorders causing hypoxic hypoxia.

1. Lung failure (gas exchange failure)
   a. Pulmonary fibrosis
   b. Ventilation-perfusion imbalance

2. Shunt

3. Pump failure (ventilatory failure)
   a. Fatigue
   b. Mechanical defects
   c. Depression of respiratory controller in the brain
Ventilation-Perfusion Imbalance

Patchy ventilation-perfusion imbalance is by far the most common cause of hypoxic hypoxia in clinical situations. In disease processes that prevent ventilation of some of the alveoli, the ventilation-blood flow ratios in different parts of the lung determine the extent to which systemic arterial PO2 declines. If nonventilated alveoli are perfused, the nonventilated but perfused portion of the lung is in effect a right-to-left shunt, dumping unoxgenated blood into the left side of the heart. On the other hand, the CO2 content of the arterial blood is generally normal in such situations, since extra loss of CO2 in overventilated regions can balance diminished loss in underventilated areas.

Venous-to-Arterial Shunts

When a cardiovascular abnormality such as an inter-atrial septal defect permits large amounts of unoxgenated venous blood to bypass the pulmonary capillaries and dilute the oxygenated blood in the systemic arteries ("right-to-left shunt"), chronic hypoxic hypoxia and cyanosis (cyanotic congenital heart disease) result. In patients with venous-to-arterial shunts and normal lungs, any beneficial effect of 100% O2 is slight and is due solely to an increase in the amount of dissolved O2 in the blood.

Asthma

Asthma is characterized by episodic or chronic wheezing, cough, and a feeling of tightness in the chest as a result of bronchoconstriction. Three abnormalities are present: airway obstruction that is at least partially reversible, airway inflammation, and airway hyperresponsiveness to a variety of stimuli. Asthma attacks are more severe in the late-night and early-morning hours because, as noted above, this is the period of maximal constriction in the circadian rhythm of bronchial tone. Cool air and exercise, both of which normally cause bronchoconstriction, also trigger asthma attacks, and in about 5% of asthmatics attacks are triggered by aspirin. However, innumerable other substances have been found to trigger asthma attacks.

Beta2-adrenergic agonists have long been the mainstay of treatment for mild to moderate asthma attacks because β2-adrenergic receptors mediate bronchodilation. Inhaled and systemic steroids and antileukotrienes are also used.

Emphysema

In the degenerative and potentially fatal pulmonary disease called emphysema, the lungs lose their elasticity as a result of disruption of elastic tissue and the walls between the alveoli break down so that the alveoli are replaced by large air sacs. The physiologic dead space is greatly increased, and because of inadequate and uneven alveolar ventilation and perfusion of underventilated alveoli, severe hypoxia develops. Late in the disease, hypercapnia also develops. Inspiration and expiration are labored, and the work of breathing is greatly increased. The chest becomes enlarged and barrel-shaped because the chest wall expands as the opposing elastic recoil of the lungs declines. The hypoxia leads to polycythemia. Pulmonary hypertension develops, and the right side of the heart enlarges (cor pulmonale) and then fails.
OTHER FORMS OF HYPOXIA

Anemic Hypoxia

Hypoxia due to anemia is not severe at rest unless the hemoglobin deficiency is marked, because red blood cell 2,3-DPG increases. However, anemic patients may have considerable difficulty during exercise because of limited ability to increase O2 delivery to the active tissues.

Carbon Monoxide Poisoning

Small amounts of carbon monoxide (CO) are formed in the body, and this gas may function as a chemical messenger in the brain and elsewhere. In larger amounts, it is poisonous. Outside the body, it is formed by incomplete combustion of carbon.

CO is toxic because it reacts with hemoglobin to form carbonmonoxyhemoglobin (carboxyhemoglobin, COHb), and COHb cannot take up O2 (Figure 37-8). Carbon monoxide poisoning is often listed as a form of anemic hypoxia because there is a deficiency of hemoglobin that can carry O2, but the total hemoglobin content of the blood is unaffected by CO. The affinity of hemoglobin for CO is 210 times its affinity for O2, and COHb liberates CO very slowly. An additional difficulty is that when COHb is present the dissociation curve of the remaining HbO2 shifts to the left, decreasing the amount of O2 released. This is why an anemic individual who has 50% of the normal amount of HbO2 may be able to perform moderate work, whereas an individual whose HbO2 is reduced to the same level because of the formation of COHb is seriously incapacitated.

Stagnant Hypoxia

Hypoxia due to slow circulation is a problem in organs such as the kidneys and heart during shock. The liver and possibly the brain are damaged by stagnant hypoxia in congestive heart failure. The blood flow to the lung is normally very large, and it takes prolonged hypotension to produce significant damage. However, ARDS can develop when there is prolonged circulatory collapse.

Histotoxic Hypoxia

Hypoxia due to inhibition of tissue oxidative processes is most commonly the result of cyanide poisoning. Cyanide inhibits cytochrome oxidase and possibly other enzymes. Methylene blue or nitrites are used to treat cyanide poisoning. They act by forming methemoglobin, which then reacts with cyanide to form cyanmethemoglobin, a nontoxic compound. Hyperbaric oxygenation may also be useful.

HYPERCAPNIA & HYPOCAPNIA

Hypercapnia

Retention of CO2 in the body (hypercapnia) initially stimulates respiration. Retention of larger amounts produces symptoms due to depression of the central nervous system: confusion, diminished sensory acuity, and, eventually, coma with respiratory depression and death. In patients with these symptoms, the PCO2 is markedly elevated, there is severe respiratory acidosis, and the plasma HCO3- may exceed 40 meq/L. Large amounts of HCO3- are excreted, but more HCO3- is reabsorbed, raising the plasma HCO3- and partially compensating for the acidosis.
CO2 is so much more soluble than O2 that hypercapnia is rarely a problem in patients with pulmonary fibrosis. However, it does occur in ventilation-perfusion inequality and when for any reason alveolar ventilation is inadequate in the various forms of pump failure. It is exacerbated when CO2 production is increased. For example, in febrile patients there is a 13% increase in CO2 production for each 1 °C rise in temperature, and a high carbohydrate intake increases CO2 production. Normally, alveolar ventilation increases and the extra CO2 is expired, but it accumulates when ventilation is compromised.

Hypocapnia

Hypocapnia is the result of hyperventilation. During voluntary hyperventilation, the arterial PCO2 falls from 40 to as low as 15 mm Hg while the alveolar PO2 rises to 120-140 mm Hg.

The more chronic effects of hypocapnia are seen in neurotic patients who chronically hyperventilate. Cerebral blood flow may be reduced 30% or more because of the direct constrictor effect of hypocapnia on the cerebral vessels (see Chapter 32). The cerebral ischemia causes light-headedness, dizziness, and paresthesias. Hypocapnia also increases cardiac output. It has a direct constrictor effect on many peripheral vessels, but it depresses the vasomotor center, so that the blood pressure is usually unchanged or only slightly elevated.

Other consequences of hypocapnia are due to the associated respiratory alkalosis, the blood pH being increased to 7.5 or 7.6. The plasma HCO3- level is low, but HCO3- reabsorption is decreased because of the inhibition of renal acid secretion by the low PCO2. The plasma total calcium level does not change, but the plasma Ca2+ level falls and hypocapnic individuals develop carpopedal spasm, a positive Chvostek sign, and other signs of tetany.