Control of Respiration

Neural Generation of Rhythmical Breathing

The diaphragm and intercostal muscles are skeletal muscles and therefore do not contract unless stimulated to do so by nerves. Thus, breathing depends entirely upon cyclical respiratory muscle excitation of the diaphragm and the intercostal muscles by their motor nerves. Destruction of these nerves (as in the viral disease poliomyelitis, for example) results in paralysis of the respiratory muscles and death, unless some form of artificial respiration can be instituted.

Inspiration is initiated by a burst of action potentials in the nerves to the inspiratory muscles. Then the action potentials cease, the inspiratory muscles relax, and expiration occurs as the elastic lungs recoil. In situations when expiration is facilitated by contraction of expiratory muscles, the nerves to these muscles, which were quiescent during inspiration, begin firing during expiration.

By what mechanism are nerve impulses to the respiratory muscles alternately increased and decreased? Control of this neural activity resides primarily in neurons in the medulla oblongata, the same area of brain that contains the major cardiovascular control centers. (For the rest of this chapter we shall refer to the medulla oblongata simply as the medulla.) In several nuclei of the medulla, neurons called medullary inspiratory neurons discharge in synchrony with inspiration and cease discharging during expiration. They provide, through either direct or interneuronal connections, the rhythmic input to the motor neurons innervating the inspiratory muscles. The alternating cycles of firing and quiescence in the medullary inspiratory neurons are generated by a cooperative

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**TABLE 15-8 Effects of Various Factors on Hemoglobin**

- The affinity of hemoglobin for oxygen is decreased by:
  1. Increased hydrogen-ion concentration
  2. Increased $P_{CO_2}$
  3. Increased temperature
  4. Increased DPG concentration

- The affinity of hemoglobin for both hydrogen ions and carbon dioxide is decreased by increased $P_{O_2}$; that is, deoxyhemoglobin has a greater affinity for hydrogen ions and carbon dioxide than does oxyhemoglobin.
interaction between synaptic input from other medullary neurons and intrinsic pacemaker potentials in the inspiratory neurons themselves.

**Control of Ventilation by \( \text{PO}_2 \), \( \text{PCO}_2 \), and \( \text{H}^+ \) Concentration**

Respiratory rate and tidal volume are not fixed but can be increased or decreased over a wide range. For simplicity, we shall describe the control of ventilation without discussing whether rate or depth makes the greater contribution to the change.

There are many inputs to the medullary inspiratory neurons, but the most important for the automatic control of ventilation at rest are from peripheral chemoreceptor and central chemoreceptor.

The *peripheral chemoreceptor*, located high in the neck at the bifurcation of the common carotid arteries and in the thorax on the arch of the aorta are called the *carotid bodies* and *aortic bodies*. In both locations they are quite close to, but distinct from, the arterial baroreceptors and are in intimate contact with the arterial blood. The peripheral chemoreceptors are composed of specialized receptor cells that are stimulated mainly by a decrease in the arterial \( \text{PO}_2 \) and an increase in the arterial \( \text{H}^+ \) concentration. These cells communicate synaptically with neuron terminals from which afferent nerve fibers pass to the brainstem. There they provide excitatory synaptic input to the medullary inspiratory neurons. The *central chemoreceptors* are located in the medulla and, like the peripheral chemoreceptors, provide excitatory synaptic input to the medullary inspiratory neurons. They are stimulated by an increase in the \( \text{H}^+ \) concentration of the brain’s extra cellular fluid. As we shall see, such changes result mainly from changes in blood \( \text{PCO}_2 \).

The medullary inspiratory neurons receive a rich synaptic input from neurons in various areas of the pons, the part of the brainstem just above the medulla. This input modulates the output of the medullary inspiratory neurons and may help terminate inspiration by inhibiting them. It is likely that an area of the lower pons called the apneustic center is the major source of this output, whereas an area of the upper pons called the pneumotaxic center modulates the activity of the apneustic center. Another cutoff signal for inspiration comes from *pulmonary stretch receptors*, which lie in the airway smooth-muscle layer and are activated by large lung inflation. Action potentials in the afferent nerve fibers from the stretch receptors travel to the brain and inhibit the medullary inspiratory neurons. (This is known as the Hering-Breuer inflation reflex.) Thus, feedback from the lungs helps to terminate inspiration. However, this pulmonary stretch receptor reflex plays a role in setting respiratory rhythm only under conditions of very large tidal volumes, as in rigorous exercise. One last point about the medullary inspiratory neurons should be made: They are quite sensitive to depression by drugs such
as barbiturates and morphine, and death from an overdose of these drugs is often due directly to a cessation of ventilation.

Control of Ventilation during Exercise
During exercise, the alveolar ventilation may increase as much as twenty fold. On the basis of our three variables—$P_O$, $P_C$, and H+ concentration it might seem easy to explain the mechanism that induces this increased ventilation. Unhappily, such is not the case, and the major stimuli to ventilation during exercise, at least that of moderate degree, remain unclear.

Increased $P_C$ as the Stimulus?
It would seem logical that, as the exercising muscles produce more carbon dioxide, blood $P_C$ would increase. This is true, however, only for systemic venous blood but not for systemic arterial blood. Why doesn’t arterial $P_C$ increase during exercise? Recall two facts from the section on alveolar gas pressures: (1) alveolar $P_C$ sets arterial $P_C$, and (2) alveolar $P_C$ is determined by the ratio of carbon dioxide production to alveolar ventilation. During moderate exercise, the alveolar ventilation increases in exact proportion to the increased carbon dioxide production, and so alveolar and therefore arterial $P_C$ do not change. Indeed, for reasons described below, in very strenuous exercise the alveolar ventilation increases relatively more than carbon dioxide production. In other words, during severe exercise the person hyperventilates, and thus alveolar and systemic arterial $P_C$ actually decrease.

Decreased $P_O$ as the Stimulus?
The story is similar for oxygen. Although systemic venous $P_O$ decreases during exercise, alveolar $P_O$ and hence systemic arterial $P_O$ usually remain unchanged. This is because cellular oxygen consumption and alveolar ventilation increase in exact proportion to each other, at least during moderate exercise. That even though the hyperventilation of very strenuous exercise lowers arterial $P_C$, it does not produce the increase in arterial $P_O$ you would expect to occur during hyperventilation. In fact, not shown in the figure, alveolar $P_O$ does increase during severe exercise, as expected, but for a variety of reasons, the increase in alveolar $P_O$ is not accompanied by an increase in arterial $P_O$. (Indeed, in highly conditioned athletes the arterial $P_O$ may decrease somewhat during strenuous exercise and may also contribute to stimulation of ventilation at that time.) In normal individuals, ventilation are not the limiting factor in endurance exercise— cardiac output is. Ventilation can, as has just been seen, increase enough to maintain arterial $P_O$. 

Respiratory System Lecture No; 6
Dr.Abdul Majeed Al-Saffar
Increased H⁺ Concentration as the Stimulus?

Since the arterial $P_{CO_2}$ does not change during moderate exercise and decreases in severe exercise, there is no accumulation of excess H⁺ resulting from carbon dioxide accumulation. However, during strenuous exercise, there is an increase in arterial H⁺ concentration, but for quite a different reason, namely, generation and release of lactic acid into the blood. This change in H⁺ concentration is responsible, in part, for stimulating the hyperventilation of severe exercise.

Other Factors

A variety of other factors play some role in stimulating ventilation during exercise. These include (1) reflex input from mechanoreceptors in joints and muscles; (2) an increase in body temperature; (3) inputs to the respiratory neurons via branches from axons descending from the brain to motor neurons supplying the exercising muscles; (4) an increase in the plasma epinephrine concentration; (5) an increase in the plasma potassium concentration (because of movement out of the exercising muscles); and (6) a conditioned (learned) response mediated by neural input to the respiratory centers. There is an abrupt increase—within seconds—in ventilation at the onset of exercise and an equally abrupt decrease at the end; these changes occur too rapidly to be explained by alteration of chemical constituents of the blood or altered body temperature. The possibility that oscillatory changes in arterial $P_{O_2}$, $P_{CO_2}$, or H⁺ concentration occur, despite unchanged average levels of these variables, and play a role has been proposed but remains unproven.

Other Ventilatory Responses Protective Reflexes

Protective Reflexes

A group of responses protect the respiratory system from irritant materials. Most familiar are the cough and the sneeze reflexes, which originate in receptors located between airway epithelial cells. The receptors for the sneeze reflex are in the nose or pharynx, and those for cough are in the larynx, trachea, and bronchi. When the receptors initiating a cough are stimulated, the medullary respiratory neurons reflexes cause a deep inspiration and a violent expiration. In this manner, particles and secretions are moved from smaller to larger airways, and aspiration of materials into the lungs is also prevented. The cough reflex is inhibited by alcohol, which may contribute to the susceptibility of alcoholics to choking and pneumonia. Another example of a protective reflex is the immediate
cessation of respiration that is frequently triggered when noxious agents are inhaled. Chronic smoking causes a loss of this reflex.

References
2. Human Physiology the Basis of Medicine 2nd, Edition. By Gillian Pocock and Christopher D.R.