The Role of the Lungs in the Adjustment of Acid-Base Balance

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ABSTRACT

Pulmonary regulation of acid-base balance operates by retention or elimination of CO₂ through adjustment of ventilation. Ventilation is controlled by a chemoreflex system with receptors in (1) the carotid bodies, which sense the arterial pH and (2) a locus on the ventrolateral surface of the medulla which senses the pH of the CSF. The carotid bodies also sense arterial PO₂, and this interacts significantly with the ventilatory control of pH.

The Pco₂ of CSF responds rapidly and in parallel to shifts in the arterial Pco₂. In contrast, CSF bicarbonate concentrations are controlled by an active pump which operates slowly to bring CSF pH to its normal value of 7.30 to 7.36. As a result, in acute respiratory acidosis or alkalosis the initial shift in CSF pH is in the same direction as the arterial pH. Outputs from the carotid bodies and from the medullary chemoreceptor exert a mutually reinforcing influence on the ventilatory rate. In acute metabolic acid-base disorders, the initial CSF pH shift is “paradoxical,” i.e., opposes the change in arterial pH. Thus, the effect of the carotid body neural impulses, which is to provide respiratory compensation for the arterial acid-base disturbance, is dampened by the output from the medullary center.

Introduction

Simply described, the function of the lungs is to enable the exchange of two gases between ambient air and the blood: O₂ in, CO₂ out. Carbon dioxide, in conjunction with its combination and dissociation products (carbonic acid, bicarbonate, and carbamino compounds), is the most important compound in the body for elimination of the acid waste of metabolism and for regulation of extracellular pH. The pH adjustment is both rapid and remarkably precise. Normally, the lungs excrete about 13,000 mEq per day of carbonic acid as CO₂, while the kidneys excrete 40 to 80 mEq per day of fixed acids. The carbonic acid-bicarbonate buffer system contributes 53 percent of the total buffering power of whole blood.

Oxygen exchange also has an impact on blood pH because oxyhemoglobin is a stronger acid than is reduced hemoglobin (Haldane effect). Oxidation of hemoglobin in the lungs causes hemoglobin to become a stronger acid, more or less offsetting the loss of acidity through exhaled CO₂. In the tissues, unloading of O₂ makes hemoglobin less acidic while the CO₂ influx is adding
to the acidity of the plasma. The Haldane effect is not a true regulatory mechanism in the sense that it does not make variable and appropriate corrections for pH abnormalities; however, it does function in a fixed manner to reduce the difference in pH between arterial and venous blood.

Blood pH is directly related to the PCO₂ of the blood. An increase in blood PCO₂ causes the pH to drop. The additional dissolved CO₂ passes rapidly into erythrocytes, where hydration proceeds quickly in the presence of carbonic anhydrase. The product is carbonic acid, which is added to the complex of blood buffers. The PCO₂ of blood is equal to the PCO₂ of alveolar gas in the absence of pulmonary disease. Alveolar gas partial pressures, in turn, are controlled by the rate of ventilation. Therefore, the mechanisms for regulation of pH are to be sought in the systems which control ventilation.

**Regulation of Ventilation**

Ventilation is controlled by chemoreflexes. A chemoreflex consists of (1) chemoreceptors, (2) afferent nerves, (3) central nervous connections, (4) efferent nerves and (5) skeletal muscles. The ventilatory system chemoregulators which have been identified respond to arterial pH and PO₂, and to CSF pH. The "drives" from all of these stimuli may act in concert to increase or to decrease ventilation or, under experimental or natural conditions, they may act in opposing directions. In the latter case, the respiratory response will be a compromise between the conflicting inputs. For example, respiratory compensation for metabolic alkalosis is frequently incomplete for the following reason. The appropriate respiratory response to elevated pH is to decrease ventilation and to retain CO₂. However, full compensation might dictate a ventilatory rate so low that it would not cause adequate oxygenation of the blood. The ventilatory rate will then represent a compromise between the need to reduce the pH by reducing ventilation and the need to maintain oxygenation through a higher rate of ventilation.

It has long been debated whether or not ventilation responds to pH or to PCO₂. It is possible to dissociate pH from PCO₂ by manipulation of buffer systems used as artificial stimuli for the individual chemoreceptors or by altering the electrolyte status of the body as a whole. Current evidence points to pH as the determining factor.

In contrasting pH to PO₂ as factors influencing the rate of ventilation, it is well known that the body is much more sensitive to changes in pH. A prompt increase in ventilation occurs when the PCO₂ of inspired air is increased by as little as 2 mm Hg. This corresponds to a pH drop of about 0.02. Hypoxia, however, does not cause measurable increases in ventilation until the PO₂ has been lowered to approximately 70 mm Hg, a gross maladjustment. However, the pH mechanism, while it is more sensitive, is subject to depression by a variety of agents. These include PCO₂ elevations to 70 to 80 mm Hg and above, anesthesia, drugs, severe anoxemia and cerebral injury. The most important of these is elevated PCO₂. High PCO₂ is known to cause acidosis of the CSF and of the brain interstitial fluid. This may be the mechanism for the respiratory depression.

The hypoxic drive, in contrast to the pH-sensitive mechanism, is not easily depressed. This explains the well-known clinical fact that a patient with severe respiratory failure may be "breathing on his hypoxic drive" because his "acidosis drive" has been depressed by elevated PCO₂. Treating the patient with nasal O₂ under these circumstances will remove the hypoxic drive and will reduce ventilation, perhaps to the point of apnea.

**Peripheral Chemoreceptors**

The carotid bodies have been known, for many decades, to function as ventilatory
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chemoreceptors. The aortic bodies, which contain similar argentaffin tissue, are anatomically inconstant and are thought not to contribute significantly to ventilatory regulation in humans. The carotid bodies are extremely sensitive to changes in pH. This can be demonstrated by perfusing them with relatively acidic solutions and observing (1) the increased number of neural impulses transmitted through the glosso-pharyngeal nerve and (2) the increase in ventilation. The carotid body exerts a constant tonic nervous output at a normal PCO$_2$ of 40 mm Hg. The output increases linearly as the PCO$_2$ is increased. This response is increased in the presence of hypoxia, (figure 1, left side). When the PCO$_2$ is lowered, the afferent output from the carotid body ceases when the PCO$_2$ drops to about 28 mm Hg.

The carotid bodies are also sensitive to PO$_2$. They exert a small tonic hypoxia-stimulated output even when the subject is breathing room air at rest. If the subject suddenly takes a few breathes of pure O$_2$, his ventilation will decrease transiently, presumably because of cessation of the normal tonic hypoxic neural output. This output is estimated to account for about 10 percent of the normal resting stimulus for ventilation. If the O$_2$ content of the inspired gas is decreased, the increase in ventilation is very slight at first, but then increases much more rapidly at lower PO$_2$'s, (figure 1, right side). The curve (ventilation rate vs PO$_2$) is hyperbolic, rising asymptotically toward the vertical axis. This curve agrees with the clinical observation that the hypoxic drive does not act as a strong ventilatory stimulus until PO$_2$ has dropped to at least 70 mm Hg, but does act strongly to correct more profound hypoxia.

The ventilatory response to hypoxia is increased in the presence of acidosis; thus, the potentiating relationship between hypoxia and acidosis is reciprocal.

A small number of surgical bilateral carotid body ablations have been performed in recent years on humans as a treatment for bronchial asthma. The operation has since been disapproved, but these patients provide an excellent opportunity to study the regulation of ventilation in the absence of the carotid bodies. It was found that these patients showed normal ventilatory function at rest and during steady-state exercise. However, they failed to show any hyperventilation when breathing gas mixtures with reduced oxygen, (12 percent O$_2$ in nitrogen). Thus, the hypoxic drive was completely eliminated, leading to the conclusion that the chemoreceptor system for PO$_2$ is entirely localized within the carotid bodies. The response to breathing increased concentrations of CO$_2$ was decreased 30 percent in these patients. An editorial which accompanies this article concludes that "Present evidence indicates that the carotid body probably does not play an important part in ventilatory control in normal persons at sea level, either at rest or during exercise." However, "... it is crucial to ventilatory compensation when disease impairs pulmonary gas exchange." The first conclusion seems questionable in light of the known activity of the carotid bodies. It is possible that the
Carotid bodies do exert a significant stimulus for respiration in the intact normal subject but that the absence of this stimulus can be compensated for when the carotid bodies are removed.

**Central Chemoreceptor**

Great strides have been made in our knowledge of the central chemoreceptor mechanism during the last 15 years. These discoveries have important clinical implications. In 1963, Mitchell et al. used mock CSF solutions with varying pH, PCO₂ and bicarbonate and applied them locally to the medulla with small pledgets. Localized perfusions were also performed. Mitchell and coworkers found that the most rapid and pronounced ventilatory responses were elicited from a region “... in the subarachnoid space on the ventrolateral surface of the medulla.” Their work “…suggests that part of the medullary ventilatory response to inhaled CO₂ originates in an (H⁺)-sensitive surface exposed to CSF on the ventrolateral medulla.” When ionized solutions were used as the localized stimulus, there was a slight time lag before the response. This was interpreted to mean that the chemoreceptor site lies within superficial brain tissue, and not directly on a surface exposed to CSF.

In 1965, Pappenheimer et al. performed experiments with unanaesthetized goats in which the cisterno-ventricular system was perfused with mock CSF. They concluded that the ventilatory response was controlled by the (H⁺) of the medullary respiratory center. After making certain assumptions about the distribution of bicarbonate, (acting as buffer) in the medullary interstitial tissue, Pappenheimer and coworkers calculated that the entire range of ventilatory response is mediated by a pH range of only 0.1 within the medulla.

The relative influence of pH on ventilation, acting on the carotid bodies as compared to the central medullary chemoreceptor, has been estimated as follows: carotid bodies 45 percent, and medulla 55 percent. These percentages have been used in computer models to predict the effect on ventilation of pH changes at both sites.

**CSF pH Mechanics**

The pH of CSF is not directly controlled by arterial pH. Carbonic acid and other small uncharged molecules diffuse freely through the blood-brain barrier. Therefore, changes in arterial PCO₂ are rapidly transmitted to the CSF. The CSF PCO₂ is normally about 10 mm Hg higher than arterial PCO₂. This has been attributed to the influx of CO₂ from the tissue metabolism of the brain and meninges.

Ions, including bicarbonate, diffuse very slowly across the blood-brain barrier, and their concentrations may be regulated by active pump systems. Following a disturbance in arterial PCO₂, the CSF-bicarbonate pump acts to normalize the CSF pH, adapting to the new level of PCO₂ (figure 2). The bicarbonate adjustment takes approximately two days. In chronic stable acid-base disturbances, the CSF pH is reestablished at the normal pH of 7.30 to 7.36, regardless of the arterial pH.
Activity of the bicarbonate pump is required even when the body is in normal and stable acid-base status. Bicarbonate is steadily pumped from the CSF into the blood to maintain the normal CSF pH.

**Clinical Implications**

It follows that a sudden increase in arterial Pco₂, as in acute respiratory acidosis, will sharply elevate the CSF Pco₂; adjustment of CSF bicarbonate will take place much more slowly. Thus, the CSF pH will initially be abruptly reduced and will gradually be restored to normal by the activity of the bicarbonate pump. The same processes operate in reverse in acute respiratory alkalosis to make the CSF temporarily alkalotic. These changes are summarized in figure 3.

CSF pH has been implicated as the probable cause of stupor and coma in acute respiratory failure. Bulger et al. found that "... mental confusion, delirium or coma invariably occurred when the value [of CSF pH] dropped below 7.25."

In contrast to respiratory disturbances, "Acute metabolic acidosis and alkalosis produce an initial shift in pH opposite to that in blood, which precedes the compensatory change in CSF bicarbonate" (figure 4). This shift can be readily demonstrated in experimental animals. It is expected that patients with acute diabetic ketoacidosis would show alkalosis of the CSF; however, when they present for treatment, the CSF pH is quite variable. Apparently the bicarbonate pump has already made significant correction of the CSF pH. It has been pointed out that a direct therapeutic attack on the systemic acidosis with parenteral bicarbonate causes a rapid rise in arterial Pco₂. This would make the CSF more acidic and might cause the patient's mental status to become worse. It has been shown that a dip in CSF pH does occur during therapy for diabetic acidosis, even when bicarbonate is not used. However, the authors argue that the presence and degree of encephalopathy correlates better with the CSF osmolality than with the CSF pH.

Obviously, these changes in CSF pH influence the medullary chemoreceptor and must be taken into account. For example, respiratory compensation of acute metabolic acidosis is initially limited by the alkalosis of the CSF, which results from its low Pco₂. Later, when the CSF pH has normalized, the force of the peripheral chemoreceptors can act unopposed, ventilation is further increased, and alveolar and arterial Pco₂ are decreased until the arterial pH becomes normal.

An early clue to the effect of CSF pH on the ventilatory mechanism was provided by Severinghaus et al. Normal sea-level volunteers were rapidly transported to an altitude of 3,800 meters. The CSF bicar-
bonate levels decreased during the eight days of the high-altitude study. The effect of this was to "readjust" the sensitivity of the medullary chemoreceptor. The adjustment is appropriate, i.e., results in greater sensitivity where the barometric pressure is lower and where absolute changes in alveolar 
Pco2 are smaller.

It is apparent that the time-span of an acid-base disturbance must be taken into account when interpreting the respiratory compensation.

References


