Acid–Base Disorders and Their Treatment

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Determinants of Carbon Dioxide Tension

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INTRODUCTION

The major function of the respiratory system is to maintain normal arterial blood partial pressures of the two vital respiratory gases, O_2 and CO_2, and a normal pH. This important regulatory function is automatically controlled, and is referred to as the homeostatic (chemostatic or metabolic) function. Homeostatic regulation is achieved by adjustment of ventilation to the metabolic (O_2 consumption/CO_2 production) and acid–base needs of the organism (1). The respiratory system is also utilized for behavioral (nonhomeostatic) functions such as phonation and swallowing. The act of breathing, therefore, is complex and needs to be governed precisely by a set of hierarchically arranged control systems. The focus of this chapter is chemical control of breathing and regulation of PCO_2.

In humans, arterial PCO_2 ($PaCO_2$) is tightly controlled in wakefulness and sleep. $PaCO_2$ remains constant throughout life, in contrast to the progressive decline in arterial PO_2 (PaO_2) that occurs with aging. Thus, any sustained deviation in $PaCO_2$ indicates a major disturbance in its homeostasis.

WHY IS $PaCO_2$ 40 mmHg IN MAN?

Values for $PaCO_2$ differ considerably among various species. In sea animals with gill ventilation, for example, water is the respiratory vehicle. Because of the low solubility of O_2 in water, a large amount of gill ventilation is

required to extract sufficient O_2 to meet metabolic demands. Because CO_2 is ~30 times more soluble in water than O_2, the large volume of ventilation results in CO_2 washout and a very low PCO_2, 1–4 mmHg (2). With an equal exchange of O_2 and CO_2 (respiratory quotient equal to one), PO_2 in water drops by about 30 mmHg as it flows over the gills, whereas PCO_2 rises by ~1 mmHg.

With land invasion and air breathing, high-level ventilation was no more necessary to provide adequate O_2 delivery. Land invasion, therefore, set the stage for ventilation to decrease. This change had the advantage of decreasing the metabolic cost of breathing and providing considerable ventilatory reserve. At the same time, PCO_2 had to rise with two consequent problems. First, PCO_2 is a key determinant of acid–base status and secondly, with air breathing, a reciprocal relation (almost 1 for 1) between PO_2 and PCO_2 was established. As a result, hypoxemia limited the reduction in ventilation that could occur.

Given these considerations, the PCO_2, PO_2, and pH values that evolved in humans are the result of a complex interaction between optimization and prioritization of respiratory functions to fulfill a number of important physiological demands (3). Issues such as efficiency of breathing at rest and exercise, acid–base status, and optimal PO_2 for interaction with hemoglobin in arterial blood contributed to the evolution of "normal" arterial PCO_2, PO_2, and pH values in terrestrial organisms. Maintaining proper acid–base balance is of utmost biological importance, because changes in pH alter the charged state of enzymes and impair their function. At a $PaCO_2$ of 40 mmHg, intracellular pH at 37°C is ~6.8. At this temperature, the pH of pure water is also 6.8, by definition at neutrality. This intracellular pH appears to serve biologically important functions well (see Chapters 1 and 2) (2–8). Thus, an arterial PCO_2 of 40 mmHg was an excellent evolutionary choice to set intracellular pH close to neutrality at 37°C. Given other biochemical determinants of $[H^+]$ in blood and $PaCO_2$ of 40 mmHg, arterial blood pH had to be 7.40 at 37°C.

THE IMIDAZOLE α-STAT HYPOTHESIS

The pH of water is inversely related to temperature. In pure water at all temperatures, of course, $[H^+]$ and $[OH^-]$ are equal and therefore by definition, water always has a neutral pH. Blood and intracellular fluid pH also change with temperature. The intracellular pH of various ectotherms at their normothermic temperatures is equal to the pH value of water at that temperature. In other words, intracellular pH remains virtually neutral as temperature changes. Blood pH is alkaline relative to intracellular pH, but in vivo changes in blood pH parallel changes in intracellular pH as temperature changes such that relative alkalinity (blood pH vs. intracellular pH) remains constant. A similar change in human blood pH is observed in vitro

as temperature changes. This adaptation is a reflection of the fact that pH is an important determinant for enzymatic functions in living cells (2–11).

Based on observations in animals with different core temperatures and the behavior of imidazole moiety of histidine, Reeves (4,12) advanced the α-stat hypothesis. At 37°C, intracellular pH is close to the pK of the imidazole group of histidine, and changes in the pK of imidazole parallel changes in pH, as the latter changes with temperature (7). The α-stat hypothesis states that the charge state or fractional dissociation (the ratio of protonated to total protein) of the imidazole group of histidine remains constant as pH changes with temperature (2–8). Histidine is present at the active site of key enzymes, and the charge state of these enzymes is critical for their function (5,6,9–13). Central to the regulation of ventilation, a protein conforming to the α-stat hypothesis appears to be involved in central chemosensitivity (7,9,14). In fresh water turtles, ventilation was not related to cerebrospinal fluid pH changes, induced by changing water temperature, but was a function of α-imidazole (15).

Another important benefit of maintaining intracellular pH close to neutral is that most water-soluble biosynthetic intermediates have pK values that render them fully ionized at neutrality (10). A cell pH near neutrality retains these ionized molecules inside the boundaries of cell membranes without energy expenditure.

QUANTITATIVE COMPONENTS OF VENTILATION

Minute Volume

Minute volume (also referred to as minute ventilation) is the product of respiratory rate (RR, or breathing rate) and tidal volume (VT):

$$\dot{V}I \text{ or } \dot{V}E = RR \times VT \quad (1)$$

In this equation, $\dot{V}I$ and $\dot{V}E$ stand for minute volume measured during inspiration or expiration, respectively. Tidal volume is usually measured during expiration. Therefore, the minute volume usually measured is VE. If inspiratory tidal volume is being recorded, the minute volume measured is $\dot{V}I$. Normally $\dot{V}I$ is somewhat greater than $\dot{V}E$, because O_2 consumption ($\dot{V}O_2$) is greater than CO_2 production ($\dot{V}CO_2$).

Some of the volume of each breath is distributed to areas where gas exchange does not occur (Fig. 1). This area is called the anatomical dead space and includes the nose, mouth, trachea, and bronchi up to and including terminal bronchioles. The more distal airways take part in gas exchange and are referred to as respiratory airways (Fig. 1). In various cardiopulmonary disorders (e.g., pulmonary embolism) some alveoli are ventilated but not perfused, and these unperfused alveoli act as extra dead space. The new dead space along with anatomical dead space is collectively referred to as physiological dead space.

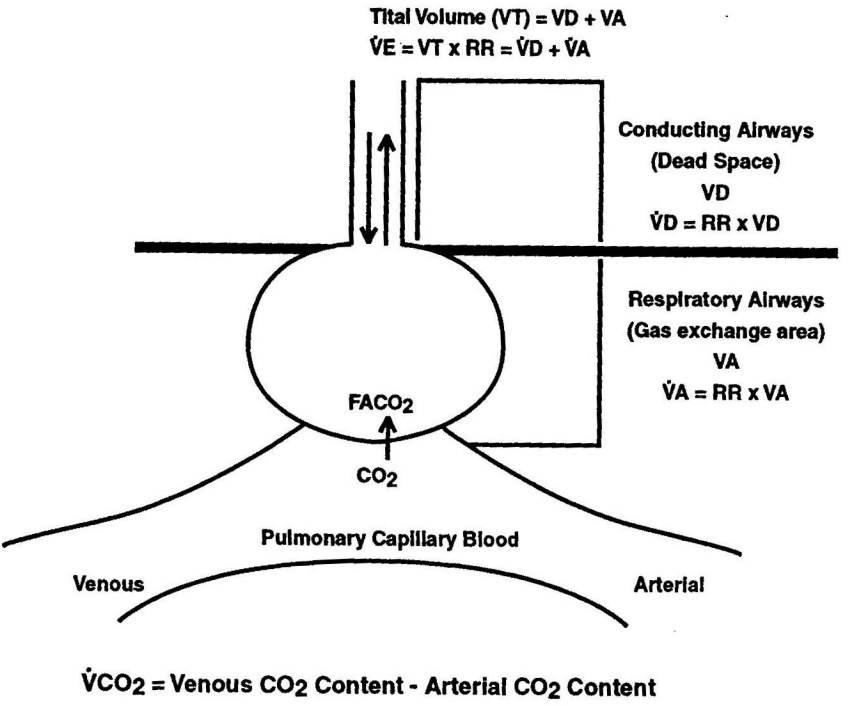

Figure 1 A simplified two-compartment model of the lung and airways. The anatomical dead space (upper part of diagram) includes the conducting airways where gas exchange does not occur. The alveolar space (lower part of diagram) contains the respiratory airways, adjacent to the pulmonary capillary bed, where gas exchange occurs. When dead space (VD) and alveolar volumes (VA) are multiplied by respiratory rate (RR), dead space ventilation (VD) and alveolar ventilation (VA) are obtained. The sum of dead space and alveolar volume is equal to the tidal volume. The sum of dead space and alveolar ventilation is equal to minute ventilation (VE).

In a simplified model, the volume of each breath consists of two components, the dead space (VD) volume and the alveolar volume (VA):

$$VT = VD + VA \tag{2}$$

Multiplying both sides of the equation by respiratory rate:

$$RR \times VT = VD \times RR + VA \times RR \text{ or} \tag{3}$$

$$\dot{V}E = \dot{V}D + \dot{V}A \tag{4}$$

As indicated by Eq. (4), minute volume ($\dot{V}E$) consists of two "separate" ventilation volumes, dead space ($\dot{V}D$) and alveolar ventilation ($\dot{V}A$). The gas composition of $\dot{V}E$ is the sum of the gas compositions of $\dot{V}D$ and

$\dot{V}A$. For a given minute volume, the higher the dead space ventilation, the lower the alveolar ventilation and the higher the $PaCO_2$.

Alveolar Ventilation

PCO_2 is determined by the balance between CO_2 production ($\dot{V}CO_2$) and excretion under steady-state conditions (16). Excretion of CO_2 is determined by its pulmonary clearance, alveolar ventilation ($\dot{V}A$):

$$PACO_2 = PaCO_2 = K \times \dot{V}CO_2 / \dot{V}A \quad (5)$$

In Eq. (5), $\dot{V}CO_2$ is CO_2 production in mL/min, $\dot{V}A$ is CO_2 clearance in mL/min, $PACO_2$ is alveolar carbon dioxide tension, which is assumed to be equal to $PaCO_2$ in mmHg, and K is a number, which relates the different units in this equation. Equation (5) is called the alveolar ventilation equation.

Clearance of a substance is the amount of the substance removed from plasma per unit time, divided by the average plasma concentration. Equation (5) is a clearance equation. The relationship between $\dot{V}A$ and $PaCO_2$ (assumed to be equal to $PACO_2$) is depicted in Fig. 2. In the context of clearance,

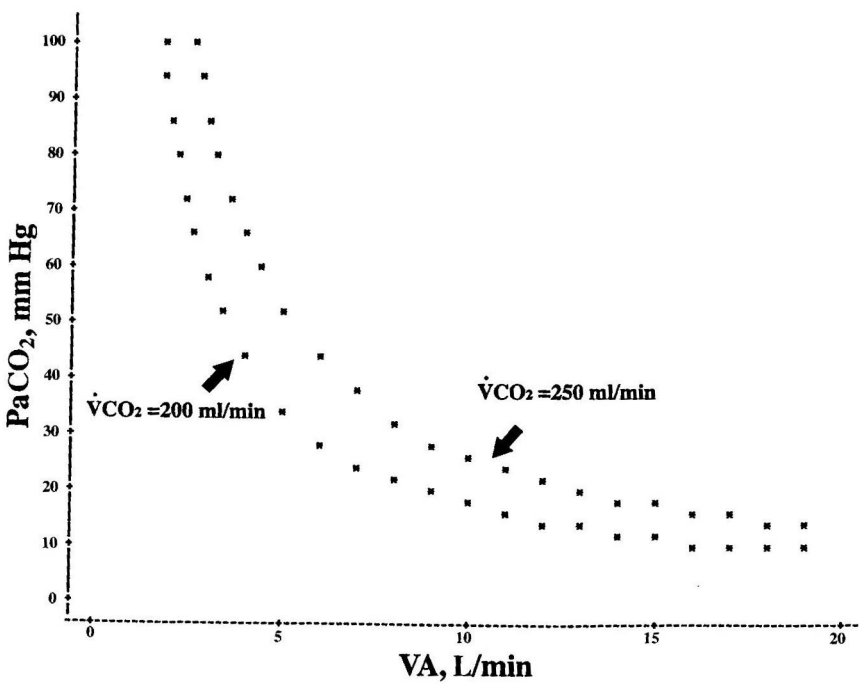

Figure 2 CO_2 clearance curves at two values for CO_2 production ($\dot{V}CO_2$), 200 and 250 mL/min. For a given level of CO_2 production, $PaCO_2$ increases as alveolar ventilation ($\dot{V}A$) falls.

alveolar ventilation is the virtual volume that removes all the CO_2 produced by the body per unit time in the steady state.

The same principle that relates serum creatinine to creatinine clearance also operates to relate $PaCO_2$ to alveolar ventilation. In this regard, the following applies:

$$\text{Creatinine production} = U_{\text{creatinine}} \times V \tag{6}$$

Because urine volume (V) is analogous to exhaled volume ($\dot{V}E$) and urine creatinine concentration ($U_{\text{creatinine}}$) is analogous to CO_2 concentration in the mixed exhaled air ($FECO_2$), CO_2 production ($\dot{V}CO_2$) is related to CO_2 excretion in the steady state as follows:

$$\dot{V}CO_2 = \dot{V}E \times FECO_2 \tag{7}$$

As noted earlier, minute ventilation ($\dot{V}E$) includes both alveolar ventilation and dead space ventilation. Because venous CO_2 is cleared only by alveolar ventilation:

$$\dot{V}CO_2 = FECO_2 \times \dot{V}E = FACO_2 \times \dot{V}A \tag{8}$$

In Eq. (8), $FACO_2$ is the fractional concentration of CO_2 in alveolar air (also analogous to serum creatinine) and can be converted to $PACO_2$, partial pressure of CO_2 in alveolar air:

$$PACO_2 = FACO_2 \times (\text{Barometric pressure} - 47\,\text{mmHg}) \tag{9}$$

In this equation, 47 mmHg is the water vapor pressure at 37°C. Normally, we assume that partial pressure of PCO_2 in the alveolar air is equal to $PaCO_2$. Therefore, $FACO_2$, $PACO_2$, and $PaCO_2$ are all analogous to serum creatinine.

The alveolar ventilation equation [Eq. (5)] shows that when metabolism is stable (constant CO_2 production), $PACO_2$ is inversely proportional to $\dot{V}A$. Thus, if $\dot{V}A$ decreases by 50%, $PACO_2$ and $PaCO_2$ will double. The alveolar ventilation equation can be applied to a single lung unit or to a homogeneous normal lung if one assumes that $PACO_2$ is equal to $PaCO_2$ (17). In the presence of ventilation–perfusion mismatch, however, this assumption is invalid, because $PaCO_2$ and $PACO_2$ diverge. Therefore, alveolar ventilation cannot be accurately assessed. Despite this problem, the equation is commonly used to calculate $\dot{V}A$ in the presence of ventilation–perfusion mismatch. Under such circumstances, it is assumed that some lung units with homogenous gas exchange are present and the equation represents ventilation of these lung units. In the presence of hypercapnia, the calculated $\dot{V}A$ will be low, but the latter does not mean that the total air movement into and out of all lung units is necessarily low. In such settings, hypercapnia should not be equated with hypoventilation (discussed later).

When $PaCO_2$ is within the normal range, large changes in alveolar ventilation are required before appreciable changes in $PaCO_2$ are observed (Fig. 2). In contrast, when $PaCO_2$ is elevated, small changes in alveolar ventilation result in major changes in $PaCO_2$. This has important consequences with regard to oxygenation, because of the reciprocal relation between alveolar PO_2 and PCO_2. Administration of small doses of respiratory depressants, for example, may result in a major rise in $PaCO_2$ and a major drop in PaO_2 in hypercapnic states such as severe asthma and chronic obstructive pulmonary disease. When ventilation decreases during sleep, $PaCO_2$ normally rises by 4–6 mmHg. In a hypercapnic subject, however, the same decrement in ventilation increases $PaCO_2$ to a much greater extent, causing clinically significant oxygen desaturation.

PATHOPHYSIOLOGY OF ALTERATIONS IN $PaCO_2$

$PaCO_2$ is determined by the balance between CO_2 production and alveolar ventilation. $PaCO_2$ will increase when either CO_2 production increases or alveolar ventilation decreases or a combination of the two, and will decrease when either CO_2 production decreases or alveolar ventilation increases. During wakefulness at sea level, normal $PaCO_2$ is 40 mmHg. When $PaCO_2$ is <36 mmHg, hypocapnia is diagnosed, and when $PaCO_2$ is >44 mmHg hypercapnia is diagnosed. The term hypoventilation is not synonymous with hypercapnia. Although hypoventilation results in hypercapnia (see earlier), it is not the only cause. In many disorders causing hypercapnia, minute ventilation and therefore air movement into and out of lung may be normal or increased. In fact, hypercapnia frequently occurs in the absence of hypoventilation in disorders such as chronic obstructive pulmonary disease. Hyperventilation and tachypnea are also often used synonymously. However, hyperventilation is defined as an increase in alveolar ventilation and tachypnea simply means rapid breathing.

Steady-state changes in CO_2 production reflect changes in metabolic rate (Table 1). Examples of increased CO_2 production include exercise, increased body weight, hyperthermia, hyperthyroidism, and carbohydrate utilization. Under normal conditions, an increase or decrease in CO_2 production does not change $PaCO_2$ because alveolar ventilation changes appropriately. For example, CO_2 production increases several folds during exercise, but $PaCO_2$ does not rise because alveolar ventilation increases in direct proportion to the increase in production [see Eq. (5)]. The mechanisms coupling CO_2 production to alveolar ventilation are complex and are not discussed further in this chapter.

If alveolar ventilation is kept constant and CO_2 production changes, $PaCO_2$ has to change proportionately [see Fig. 2 and Eq. (5)]. For example, under conditions of fixed mechanical ventilation, if CO_2 production

Table 1 Factors Altering CO_2 Production

Increased	Decreased
Exercise	Sleep, inactivity
Increased work of breathing	Decreased work of breathing; respiratory muscles rest; use of mechanical ventilation, paralyzing or sedating agents
Weight gain	Weight loss
Hyperthermia	Hypothermia
Hyperthyroidism	Hypothyroidism
Carbohydrate utilization	Fat utilization

increases, due to excessive utilization of carbohydrates, fever, use of respiratory muscles when fighting the ventilator, $PaCO_2$ will increase. Sedating agents are used to decrease excessive work of breathing and metabolic rate in order to lower CO_2 production. Maneuvers to decrease CO_2 production help to lower $PaCO_2$ and reciprocally increase PaO_2. Such maneuvers are particularly helpful when gas exchange is severely impaired. Under these conditions, high positive end-expiratory pressure, high fractional concentration of O_2 in inhaled air, or excessive ventilation may be necessary to provide acceptable levels of PaO_2 and $PaCO_2$. Lowering CO_2 production allows for decreasing the amount of inhaled O_2 to avoid O_2 toxicity, or lowering the tidal volume to avoid damage to the lung due to intermittent stretch. In the absence of fixed ventilation, alterations in $PaCO_2$ are invariably caused by alterations in alveolar ventilation rather than CO_2 production. The disorders causing hyper- and hypocapnia are discussed elsewhere (Chapters 20 and 21), but the major control mechanisms relating ventilation to $PaCO_2$ are reviewed here.

NORMAL CONTROL OF BREATHING

Overview

The respiratory apparatus controlling breathing has three components: sensors, controllers, and effectors (Fig. 3) (1). The controllers are the respiratory centers, which are the sites of respiratory rhythmogenesis, the most basic function underlying automatic breathing. The centers receive inputs from sensors located at various sites (Fig. 3). The sensors perceive changes in PCO_2, PO_2, $[H^+]$ and lung inflation and send information (in the form of increased or decreased activity) to the controllers. After processing this information, the controllers alter the level of activity via efferent pathways (cranial, spinal, and phrenic nerves) to multiple effectors to modify their level of function (Figs. 3 and 4).

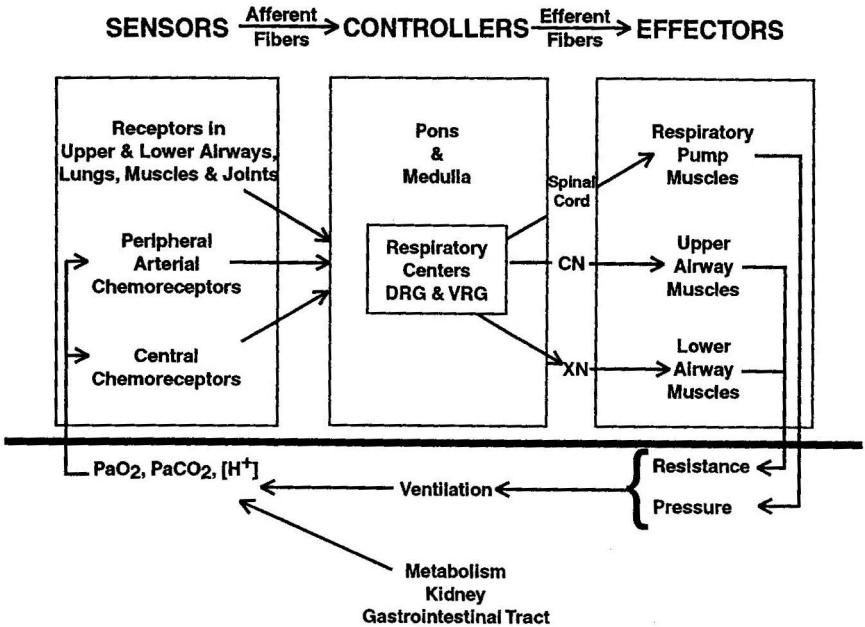

Figure 3 A simplified diagram of respiratory control system with its three major components. DRG = Dorsal respiratory group; VRG = Ventral respiratory group; CN = Cranial nerves; XN = 10th Cranial nerve.

The effectors are the thoracic inspiratory pump muscles, the muscles of the upper and lower airways, and expiratory abdominal muscles. The main inspiratory pump muscle is the diaphragm. The major respiratory muscles of the upper airways are the so-called upper airway dilators that regulate cross-sectional area and resistance. The activity of thoracic pump muscles provides the force behind inspiration (pressure, P), and the activity of muscles of the upper and lower airways determine airway resistance (R). Flow of air into the lung is determined according to

$$\text{Airflow} = P/R \tag{10}$$

Inspiration is an active process. Contraction of the inspiratory muscles (primarily the diaphragm) causes airflow into the lung by decreasing intrathoracic pressure. The rate of airflow, however, is determined by force of contraction reflected as Δ pressure, and the resistance of the respiratory system [Eq. (10)]. Normally, expiration is passive. During inspiration, the lung progressively increases in volume (and in its recoil) and when the diaphragm begins to relax at the end of inspiration, the unopposed inward recoil (created by inspiration) increases intrathoracic pressure and results in airflow

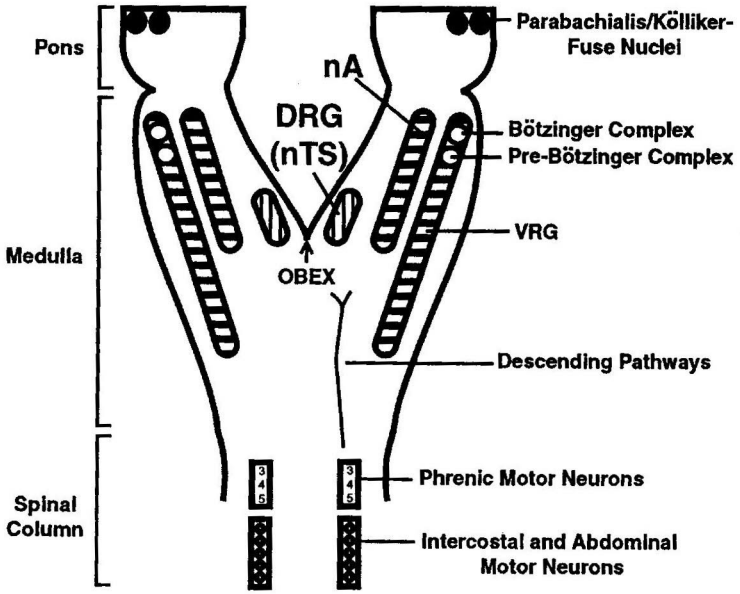

Figure 4 A cross-section of brainstem and spinal cord showing respiratory centers and some of the descending pathways. VRG, ventral respiratory group; DRG, dorsal respiratory group; NA, nucleus ambiguus.

out of the lung. During active expiration, contraction of the internal intercostal and abdominal muscles further facilitates airflow out of the lungs.

Pontomedullary Respiratory Centers

Breathing ceases in the absence of efferent output from the central nervous system. Respiratory rhythm persists after removal of the brain above the brainstem, but ceases after transection of the brainstem at the medullary-spinal level (18). Thus, rhythmogenesis is localized to the brainstem. The brainstem contains multiple neural aggregates located bilaterally (Fig. 4), whose activities have an oscillation linked to respiratory output (e.g., phrenic nerve motor activity) (19–23).

The pontine respiratory group (PRG) consists of two pairs of rostral pontine nuclei, the parabrachialis medialis and Kolliker–Fuse nuclear complex (NPBM-KF), corresponding to the pneumotaxic center. The function of these nuclei is to facilitate an earlier cut-off of inspiration, similar to that of vagal afferent pathway originating in the lung. Lesions of PRG in man cause apneustic breathing.

The medullary centers consist of two separate groups of nuclei, the dorsal (DRG) and ventral (VRG) respiratory groups (Fig. 4). The DRG

is located in the dorsomedial part of the medulla, corresponding to the ventrolateral nucleus of the tractus solitarius (nTS in Fig. 4) and contains mainly inspiratory-related neurons. They receive afferent information from the peripheral arterial chemoreceptors, via the glossopharyngeal nerves, and from intrathoracic receptors, via the vagus nerves. The axonal projections of DRG exhibit discharge patterns similar to those of the phrenic or inspiratory intercostal activities. These projections cross the midline of medulla and terminate in the cervical and thoracic anterior spinal motor neurons of the phrenic and intercostal nerves.

The VRG is more diffuse than the DRG, consisting of many neural aggregates extending from the rostral to the caudal medulla. The VRG consists of the Bötzinger complex, pre-Bötzinger complex, nucleus ambiguus (NA), nucleus paraambigualis (NPA), and nucleus retroambigualis (NRA) (Fig. 4). The pre-Bötzinger complex is probably the site of respiratory rhythm generation (22). The VRG contains neurons that are active both during inspiration and expiration, projecting to inspiratory and expiratory motor neurons.

Destruction of respiratory centers may result in respiratory failure. However, because these centers are bilateral, a pathological process, such as an infarct, would have to be bilateral or otherwise very extensive, in order to cause complete cessation of respiration.

Efferent Pathways

The inspiratory and expiratory pump muscles and the muscles of the upper airway all receive rhythmic activity from the respiratory centers via descending neural pathways (Figs. 3 and 4). The pump muscles provide the pressure and the airway muscles determine the resistance. Pressure and resistance are the two determinants of airflow through airways [Eq. (10)].

The diaphragm, intercostal and abdominal muscles are activated by spinal α-motor neurons (Fig. 4). Phrenic motor neurons lie in the third, fourth, and fifth cervical segments and motor neurons of intercostal and abdominal muscles extend from thoracic to upper lumbar spinal cord. Because the diaphragm is the main inspiratory muscle (see below), cervical pathology involving third, fourth, and fifth segments results in hypoventilation and respiratory failure.

Cranial nerves innervate muscles of the upper and lower airways. The neural mechanisms controlling upper airway muscles are of critical importance in upper airway occlusion and obstructive sleep apnea–hypopnea. The vagus nerves control the tone of the smooth muscles of the intrathoracic airways. Increases in vagal activity to these muscles decrease airway cross-sectional area, resulting in airway constriction and bronchospasm. In severe asthma and exacerbation of chronic obstructive pulmonary disease,

increased airway resistance could contribute to hypercapnia by increasing work of breathing.

Peripheral Arterial Chemoreceptors (PCR) and PO_2 Homeostasis

The peripheral arterial chemoreceptors include the carotid and aortic bodies, which show chemosensitivity to changes in blood PO_2, PCO_2, and $[H^+]$. The carotid bodies are located in the tissue between the internal and external carotid arteries and the aortic bodies are located at the arch of aorta (Fig. 5). The carotid bodies should not be mistaken for the carotid sinuses, which are located in the wall of the internal carotid arteries and are baroreceptors sensing changes in blood pressure.

The carotid bodies are the predominant arterial chemoreceptors, stimulating ventilation in response to decreased PaO_2 (hypoxemia) (Fig. 5). In the absence of carotid bodies, hypoxemia causes ventilatory depression (23,24). There are two cell types in the carotid bodies, type I and II cells. Type I cells (the glomus cells) are the cells involved in chemotransduction (25) via transmission to the sensory endings of the carotid sinus nerve, a branch of the glossopharyngeal nerve. The afferent information from the carotid body goes to the nucleus tractus solitarius in the medulla (Fig. 4).

The feedback loop involving the carotid bodies is illustrated in Fig. 6. Hypoxemia stimulates the carotid bodies causing an increase in afferent impulses to the brainstem respiratory centers (nTS). Increased activity from the respiratory centers to the upper airway muscles decreases airway

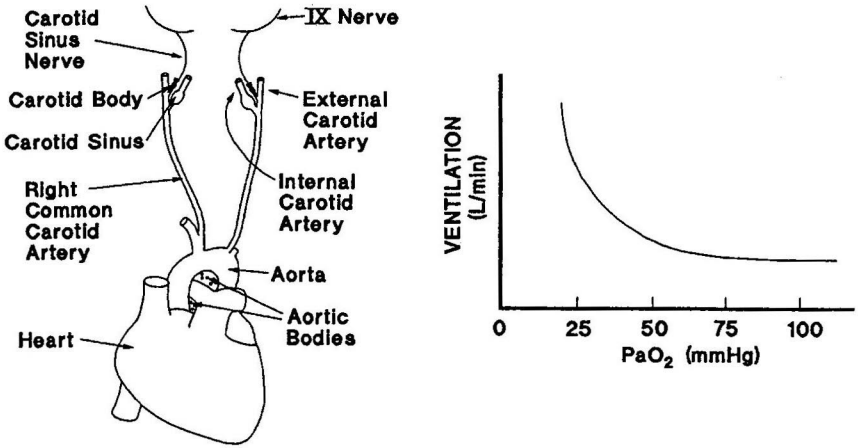

Figure 5 Diagram showing locations of peripheral arterial chemoreceptors and the related ventilatory response to hypoxemia mediated primarily by carotid bodies. Note the hyperbolic nature of ventilatory response, and that arterial PO_2 must decrease considerably before appreciable changes in ventilation are noted.

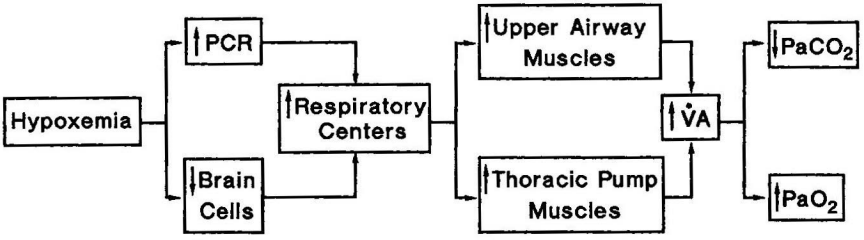

Figure 6 The feedback loop involving carotid bodies (PCR) in the response to hypoxemia. Hypoxemia results in both an increase in the force of breathing and a decrease in airway resistance, increasing airflow into the lung. Increased ventilation increases the clearance of CO_2 and therefore $PaCO_2$ decreases as PaO_2 increases.

resistance, and to the thoracic pump muscles increases the force of breathing. Alveolar ventilation thus increases [see Eq. (10)], delivering more O_2 and removing more CO_2. As a result, PaO_2 increases (and $PaCO_2$ decreases), removing the initial stimulus of hypoxemia.

The importance of the carotid and aortic bodies in O_2 homeostasis is demonstrated by travel to high altitude. Despite a progressive drop in atmospheric PO_2, compensatory hyperventilation allows for maintenance of adequate PO_2 for survival (26). In various cardiopulmonary disorders the ventilation–perfusion mismatch results in impairment of gas exchange across alveolar-capillary membrane (17,27,28). If no ventilatory compensation occurred, severe hypoxemia and hypercapnia would ensue. These adverse events are minimized by the actions of the peripheral chemoreceptors.

As shown in Fig. 5, PaO_2 falls to 55–60 mmHg before the receptors are stimulated to increase ventilation. Thus, hyperventilation cannot be ascribed to hypoxemia unless $PaO_2 \leq 55$–60 mmHg. As PaO_2 decreases further, ventilation progressively increases. These characteristics are due to the hyperbolic nature of the changes in the rate of discharge of afferent nerve fibers from the carotid body, and are reflected in the hyperbolic changes in ventilation when PO_2 decreases. The carotid bodies sense PaO_2, not hemoglobin saturation or the O_2 content of the arterial blood. Thus, anemia and carbon monoxide inhalation are not associated with compensatory hyperventilation.

The ventilatory response to hypoxemia is quite variable, but the scatter diminishes within family members, suggesting that genetic factors may play an important role (29–31). Individuals with diminished O_2-chemosensitivity could be prone to develop hypercapnia in the face of ventilatory stress, such as asthma or chronic obstructive pulmonary disease (32–36).

Although the carotid bodies show chemosensitivity to changes in $PaCO_2$ and $[H^+]$ in addition to changes in PaO_2, their most important function is O_2 chemosensitivity. In metabolic acidosis, for example, the ventilatory response to an increase in arterial $[H^+]$ is preserved in animals with

peripheral chemodenervation (37–40). This is not to say that the peripheral arterial chemoreceptors are H^+-insensitive; indeed they may be involved in initiating hyperventilation in metabolic acidosis (see later).

A low $PaCO_2$ can be seen in a variety of cardiopulmonary disorders in the absence of sufficient hypoxemia to stimulate the carotid bodies, and is due to stimulation of pulmonary airway and parenchymal receptors by pathological processes in the lung (Fig. 3) (41,42). This information is transferred from intrapulmonary receptors via vagus nerves to the nucleus tractus solitarius (Fig. 3), resulting in an increase in respiratory rate and ventilation.

Central Chemoreceptors and PCO_2 Homeostasis

The central chemoreceptors are located in the brain within the medulla (43–45), but are different from the respiratory centers discussed above. Evidence for their existence stems from the observation that infusion of acidic solution into cerebral ventricles stimulates ventilation (45–47). This response is maintained in animals with peripheral arterial chemodenervation (37–40). The central chemoreceptors are exquisitely sensitive to changes in $[H^+]$; small changes induced either by acid infusion or changes in PCO_2 elicit a brisk ventilatory response (46,47).

This information is signaled to respiratory centers (Fig. 2) and causes changes in alveolar ventilation and $PaCO_2$ that mitigate the changes in $[H^+]$ induced initially by the acid–base perturbation. This feedback loop is similar to that described earlier for peripheral chemoreceptors when PO_2 changes. However, the ventilatory response of central chemoreceptors to changes in $[H^+]$ is linear (Fig. 7).

Early studies (43,44) identified superficial areas on the ventrolateral aspect of the medulla, designated M, S, and L for the scientists who discovered them (Fig. 7). Areas M and L are chemosensitive and presumably their outputs converge into area S which is not chemosensitive. Deeper chemoreceptors are present as well (48–50).

The stimulus to the central chemoreceptors is the $[H^+]$ in their environment, although PCO_2 may have an independent effect (51–53).

The central chemoreceptors are separated from the blood by the blood–brain barrier, which is formed anatomically by the tight junctions between the endothelial cells of the cerebral capillaries (54). Because the blood–brain barrier resists ionic diffusion, it takes several minutes for changes in plasma $[H^+]$ to be reflected in cerebral fluids (55,56). As noted earlier, it is therefore conceivable that the initial hyperventilatory response to metabolic acidosis, particularly if the process is mild, is mediated via carotid bodies.

Changes in brain extracellular fluid $[H^+]$ are smaller than corresponding changes in plasma $[H^+]$ in both metabolic acidosis and alkalosis (55,56). This difference occurs because the blood–brain barrier can transport various

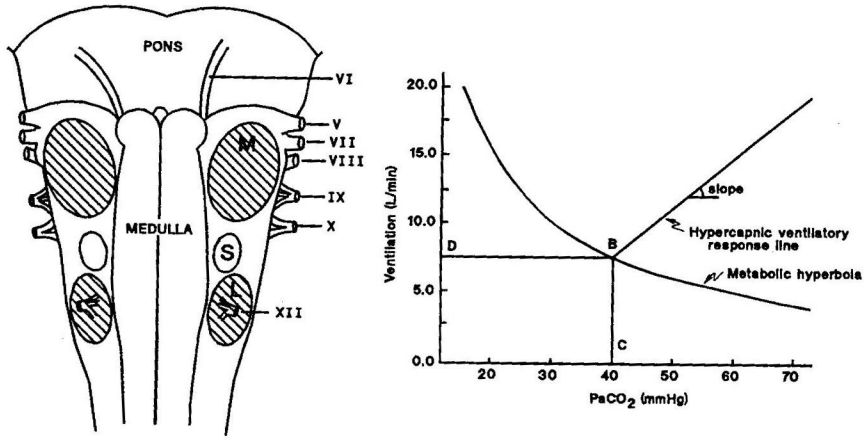

Figure 7 Location of the central chemoreceptors (labeled M, S, and L) and the related ventilatory response to CO_2. Note that resting $PaCO_2$ is at the point where the line defining ventilatory response and the curve defining the CO_2 hyperbola meet. Also note that ventilatory response to CO_2 is linear and any increment in PCO_2 elicits a response.

ions into and out of extracellular fluid, thereby regulating ionic composition of the brain extracellular fluid (57–59).

In contrast to somewhat slow changes in cerebral fluid $[H^+]$ during metabolic acid–base changes in plasma, brain extra- and intracellular fluid $[H^+]$ increases rapidly with acute increases in $PaCO_2$ (55,60). This rapid increase in $[H^+]$ occurs because CO_2 diffuses quickly across the blood–brain barrier. In brain fluids, CO_2 is hydrated to form carbonic acid, which is dissociated to H^+ and HCO_3^-. The excess $[H^+]$ stimulates the central chemoreceptors. The opposite occurs with hypocapnia.

The sensitivity or gain of the central chemoreceptors to changes in PCO_2 exceeds that of the peripheral chemoreceptors. Overall, most of the steady-state ventilatory response to changes in $[H^+]$ (metabolic or respiratory) is mediated by the central chemoreceptors. As noted earlier, in response to severe metabolic acidosis, hyperventilation occurs equally before and after denervation of the peripheral chemoreceptors (37–40).

Carbon dioxide chemosensitivity varies considerably among normal individuals. There are the so-called low and high responders. In low responders the rise in ventilation as PCO_2 increases is smaller than in high responders. Diminished CO_2 chemosensitivity may predispose an individual to CO_2 retention in the face of asthma and chronic obstructive pulmonary disease (31–35) when gas exchange abnormalities occur. In contrast, high responders may be predisposed to instabilities in breathing. For example, patients with heart failure and increased CO_2 chemosensitivity may be

predisposed to develop central apnea during sleep (Cheyne–Stokes respiration) (61).

OVERVIEW OF MECHANISMS CAUSING CHANGES IN $PaCO_2$

Hypercapnia

Hypercapnia occurs when the rate of alveolar ventilation is insufficient for elimination of CO_2. Four pathogenetic mechanisms can cause hypercapnia (Table 2): (1) ventilation–perfusion inequality (V/Q mismatch), (2) hypoventilation (decreased $\dot{V}E$), (3) a pattern of breathing characterized by shallow breaths (low tidal volume), and (4) increased CO_2 production. In three of these, V/Q mismatch, shallow breathing, or increased CO_2 production, "compensatory" increases in ventilation may occur that can ameliorate or eliminate the hypercapnia. For example, the increase in CO_2 production that accompanies exercise is coupled with a parallel increase in $\dot{V}A$, such that $PaCO_2$ remains constant.

Clinical causes of hypercapnia can be divided into three categories: (1) pathophysiological processes affecting chemoreflex system, (2) disorders of neuromuscular system, and (3) disorders of ventilatory apparatus (airways, lung parenchyma, and chest wall). Hypoventilations due to metabolic alkalosis or administration of respiratory depressants are examples of reversible processes affecting the chemoreflex system. Severe asthma, severe acute respiratory distress syndrome, and kyphoscoliosis are, respectively, examples of disorders of airways, lung parenchyma and chest wall causing hypercapnia. Table 3 shows some of the processes mediating hypercapnia in part based on factors controlling respiration shown in Fig. 3. For further details of disorders causing hypercapnia, see Chapter 20.

Hypocapnia

Hyperventilation occurs when alveolar ventilation exceeds the amount necessary for elimination of CO_2. Alveolar hyperventilation is caused by an abnormally excessive ventilatory drive, persisting despite the resultant

Table 2 Pathogenic Mechanisms of Hypercapnia

1.	V/Q mismatch (most common)	Various CP disorders
2.	Hypoventilation	Respiratory depression
3.	Shallow breathing	Various CP disorders
4.	Increased CO_2 production	Unlikely cause of hypercapnia

In 1, 3, and 4, "compensatory" mechanisms may occur that can prevent development of hypercapnia.

V/Q, ventilation/perfusion; CP, cardiopulmonary.

Table 3 Some Disorders and Their Mechanisms Mediating Hypercapnia

Sites	Stimuli/factors	Conditions
I. Controllers (DRG/VRG)	Necrosis, inflammation	Brainstem infract (usually bilateral), encephalitis
II. Descending pathways, spinal cord, nerves, neuromuscular junction	Inflammation, injury, autoimmune drugs	ALS, GBS, C_{3-5} trauma, MG, procainamide toxicity
III. Effectors		
Muscles	Inflammation, energetics	Muscular dystrophy, diaphragmatic fatigue
Chest wall	Congenital/genetic	Kyphoscoliosis, obesity, and OSAHS
Airways	Bronchospasm	Severe asthma, COPD
Lungs	V/Q mismatch	Severe asthma or COPD, severe pulmonary edema, severe ARDS
IV. PCR	a. Hyperoxia	COPD with hypercapnia
	b. Alkalemia	Metabolic alkalemia
	c. Decreased hypoxic chemosensitivity	COPD, asthma
V. CCR	a. Alkalemia	Metabolic alkalemia
	b. Drugs	Opiates, benzodiazepines
	c. Decreased CO_2 chemosensitivity	Primary alveolar hypoventilation syndrome COPD, asthma, OSAHS

DRG, dorsal respiratory groups; VRG, ventral respiratory group; ALS, amyotrophic lateral sclerosis; MG, myasthenia gravis; GBS, Gillian Barre syndrome; V/Q, ventilation/perfusion; PCR, peripherial arterial chemoreceptors; CCR, central chemoreceptors; CNS, central nervous system; CSF, cerebrospinal fluid; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea–hypopnea syndrome.

fall in PCO_2, which should decrease ventilation by the feedback loop discussed earlier in this chapter.

The excessive ventilatory drive is mediated by disorders affecting either the metabolic or behavioral control system. Engagement of the automatic metabolic pathway in hyperventilation occurs via stimulation of peripheral arterial or central chemoreceptors or pulmonary airway or parenchymal receptors (Fig. 3). Psychogenic hyperventilation is an example of a behavioral (cortical) mechanism of hyperventilation. Using Fig. 3 as a model, some of the causes of hyperventilation are depicted in Table 4. For further details of the disorders causing hypocapnia, see Chapter 21.

Table 4 Some Disorders and Their Mechanisms Mediating Hypocapnia

Sensors	Stimuli/factors	Conditions
I. PCR	a. Hypoxemia	High-altitude cardiopulmonary disorders[a]
	b. Acidemia	Metabolic acidemia
	c. Drugs	Almitrine, doxapram
II. CCR	a. Hormones & drugs, progesterone, salicylate	Pregnancy; liver disease, salicylate poisoning
	b. Acidemia	Metabolic acidemia
	c. CSF lactacidosis	Central neurogenic hyperventilation, intracranial hemorrhage, CNS malignancy
III. Cortical	Anxiety	Psychogenic hyperventilation
IV. Pulmonary receptors (J or irritant)	Inflammatory mediators, increased interstitial pressure	Cardiopulmonary disorders

[a]Cardiopulmonary disorders such as pulmonary congestion/edema, pulmonary embolism, pneumonias, interstitial lung disorders, and mild asthma.
PCR, peripheral arterial chemoreceptors; CCR, central chemoreceptors; CSF, cerebro spinal fluid; CNS, central nervous system.

CHANGES IN $PaCO_2$ IN METABOLIC ACID–BASE DISTURBANCES

Metabolic Alkalosis

Metabolic alkalosis increases $PaCO_2$ in a predictable fashion (62,63). The fall in $[H^+]$ in the blood and brain caused by metabolic alkalosis decreases the activity of the peripheral and central chemoreceptors (Fig. 8). As a result, medullary respiratory output to inspiratory muscles decreases and minute and alveolar ventilation decrease, increasing alveolar and arterial PCO_2. The rise in $PaCO_2$ increases $[H^+]$, which mitigates the initial drop in $[H^+]$ due to metabolic alkalosis (see Chapter 16).

Metabolic alkalosis causing hypercapnia is an example of hypoventilation (Table 2). The decreased minute and alveolar ventilation is brought about primarily by a reduction in tidal volume (Table 5) (62). Assuming a constant dead space, a fall in tidal volume decreases alveolar ventilation. As an example, with dead space of 150 mL and tidal volume of 450 mL, VD/VT ratio is 1/3 and alveolar volume of each breath is 300 mL (Fig. 1). With respiratory rate of 15/min, alveolar ventilation is 4.5 L/min. If tidal volume is decreased to 300 mL per breath (about 30% reduction from

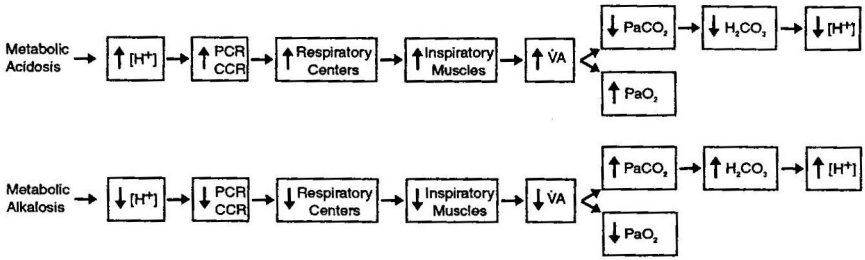

Figure 8 Diagram of the negative feedback loop involving the carotid bodies (PCR) and central chemoreceptors (CCR) in mediating hyper- or hypoventilation as $[H^+]$ changes in metabolic acid–base disorders.

baseline), then VD/VT ratio is 1/2 and alveolar volume of this breath is 150 mL. With the same respiratory rate of 15/min, alveolar ventilation becomes 2.25 L/min, doubling arterial PCO_2. In order to decrease alveolar ventilation by the same amount with only a reduction in respiratory rate, the respiratory rate would have to fall from 15 to 7.5 breaths/min (50% reduction). Therefore, decreasing tidal volume is a very efficient way to decrease alveolar ventilation.

Metabolic Acidosis

Metabolic acidosis decreases $PaCO_2$ in a predictable fashion (62,64) (see Chapter 9). The rise in $[H^+]$ caused by metabolic acidosis is reflected in the environment of the peripheral and central chemoreceptors, which collectively increase afferent activity to respiratory centers. This, in turn, causes augmented output to the respiratory muscles (Fig. 8), causing a rise in alveolar ventilation and a fall in $PaCO_2$. The fall in PCO_2 reduces extra- and intracellular $[H^+]$ mitigating the initial rise due to metabolic acidosis.

In response to metabolic acidosis, $PaCO_2$ is decreased primarily by increasing tidal volume. As discussed earlier, this is a more efficient way to achieve a given change in alveolar ventilation than is an increase in respiratory rate (Table 6). For example, to increase alveolar ventilation from 4.5 to 6.7 L/min, the respiratory rate has to increase from 15 to 22.5 if tidal volume remains constant (Table 6). However, the same increment in alveolar ventilation can be achieved by increasing tidal volume form 450 to 600 mL without changing respiratory rate.

Because small increases in tidal volume can decrease $PaCO_2$ considerably, it is often difficult to notice the compensatory hyperventilation at the bedside, unless metabolic acidosis is so severe to make the increase in the depth of breathing visually apparent (Kussmaul's sign). The difficulty in appreciating an increase in the depth of breathing contrasts with the easily recognizable tachypnea observed in various diseases such as pneumonia,

Table 5 Ventilation Under Baseline, Acidotic, and Alkalotic Conditions in Six Normal Subjects

	$[H^+]$ (nmol/l)	$PaCO_2$ (mmHg)	$[HCO_3^-]$ (mmol/L)	PaO_2 (mmHg)	$\dot{V}E$ (L/min)	RR (/min)	VT (ml)	$\dot{V}A$ (L/min)	VD (ml)	VD/VT (%)	$\dot{V}CO_2$ (ml/min)
Baseline	38 ± 1	38 ± 1	24 ± 0.4	94 ± 4	6 ± 0.2	12 ± 2	522 ± 72	4.4 ± 0.3	90 ± 10	18 ± 3	177 ± 18
Metabolic alkalosis	31* ± 1	44* ± 1	34* ± 2	85* ± 4	5* ± 0.1	13 ± 2	422* ± 55	3.2* ± 0.2	101 ± 6	29* ± 3	156 ± 14
Metabolic acidosis	46* ± 1	32* ± 1	17* ± 0.2	109* ± 4	7* ± 0.1	12 ± 2	624* ± 92	—	—	—	—

Values are means ± 1SE. There were 14 episodes of metabolic alkalosis and seven episodes of metabolic acidosis.
$\dot{V}E$ = exhaled volume; RR = respiratory rate; $\dot{V}CO_2$ = carbon dioxide production; VT = tidal volume; $\dot{V}A$ = alveolar ventilation; VD = dead space.
*Significant vs. baseline. *Source*: Modified from Ref. 62.

Table 6 Theoretical Examples Showing Differences in Respiratory Rate vs. Tidal Volume to Achieve the Same Alveolar Ventilation

	VT (mL)	RR (/min)	$\dot{V}E$ (mL/min)	VD (mL)	$\dot{V}A$ (mL/min)	$\dot{V}D$ (mL/min)
Baseline	450	15	6750	150	4500	2250
Increased RR	450	22.5	10125	150	6750	3375
Increased VT	600	15	9000	150	6750	2250

A higher minute ventilation is necessary to achieve the same alveolar ventilation with tachypnea than by increasing tidal volume. In this example, dead space was kept constant, though with an increase in tidal volume and lung stretch, the anatomical dead space also increases slightly. VT = tidal volume; RR, respiratory rate; VD = dead space; $\dot{V}A$ = alveolar ventilation; $\dot{V}E$ = minute ventilation; $\dot{V}D$ = dead space ventilation.

pulmonary embolism, congestive heart failure, or interstitial lung diseases. As is discussed below, the rise in respiratory rate in these disorders is almost always due to stimulation of pulmonary airway and parenchymal receptors brought about by the pathological process in the lung (Fig. 3).

CHANGES IN $PaCO_2$ IN CARDIOPULMONARY DISORDERS

Decreased $PaCO_2$

Hypocapnia occurs in a variety of cardiopulmonary disorders, including pulmonary edema, asthma, interstitial lung diseases, and pulmonary embolism. Assuming that these disorders do not alter or minimally affect CO_2 production, the fall in $PaCO_2$ is primarily due to an increase in alveolar ventilation [Eq. (5)]. The increase in alveolar ventilation in these disorders is due to an increase in respiratory rate. Increasing alveolar ventilation primarily by a change in rate (Table 6), tachypnea, is easily recognizable at the bedside and is characteristic of a pathological process in the lung. Typically, the pattern of breathing is rapid and shallow.

In all these disorders, ventilation and perfusion are increasingly mismatched. In lung units with a low ventilation/perfusion ratio, the amount of ventilation is inadequate for the corresponding blood flow, resulting in inadequate O_2 delivery and insufficient CO_2 removal. Consequently, regional alveolar PO_2 (and therefore regional capillary PO_2) is reduced, and regional alveolar PCO_2 (and therefore regional capillary PCO_2) is increased. Without an increase in ventilation, hypoxemia and hypercapnia will develop (17,27,28). However, alveolar ventilation typically increases by a variety of signaling and effector mechanisms (discussed earlier). When PCO_2 increases because of the $\dot{V}/\dot{Q}$ mismatch, ventilation is stimulated primarily by central chemoreceptors. The ventilatory response to CO_2 is linear and any small increment in PCO_2 will increase ventilation. This feedback mechanism is an attempt to maintain PCO_2 close to normal and should not cause

hypocapnia. However, when PaO_2 decreases, ventilation is stimulated by peripheral chemoreceptors. As noted earlier, hypoxemia must be relatively severe before noticeable chemostimulation occurs, but this feedback mechanism can result in hypocapnia. Alveolar ventilation may also increase due to an increase in respiratory rate. Tachypnea is caused by stimulation of intrapulmonary receptors by the pathological process in the lung. Depending, collectively, on the severity of *V/Q* mismatch, CO_2 production and the three compensatory mechanisms to increase alveolar ventilation, $PaCO_2$ may be normal or decreased, or rarely increased.

Although patients with *V/Q* mismatch commonly have normal or a low $PaCO_2$, hypoxemia is invariably present. PaO_2 decreases because the O_2 content of the blood leaving areas with high *V/Q* ratios is not sufficiently increased to compensate for the low O_2 content of the blood emanating from low *V/Q* areas. Therefore, the characteristic arterial blood gas findings in these disorders are hypoxemia with either normal $PaCO_2$ or chronic hypocapnia (chronic respiratory alkalosis).

In the presence of hypocapnia, the severity of gas exchange abnormalities is commonly underestimated. As noted earlier, when PCO_2 decreases (or increases), the PO_2 should rise (or decrease) almost equally. A PaO_2 of 75 mmHg thus signifies a considerably greater abnormality in gas exchange across the alveolar capillary membrane if $PaCO_2$ is 20 rather than 40 mmHg.

Increased $PaCO_2$

Hypercapnia is observed in the course of a variety of cardiopulmonary disorders as the severity of the pathological process intensifies. In chronic obstructive pulmonary disease and asthma, hypercapnia is observed when forced expiratory volume in 1 sec (a surrogate of severity of the disorder) has decreased to values approaching 1 L/sec, about 20–30% of predicted (Fig. 9) (65–79). Milder obstructive defects are not associated with hypercapnia unless additional factors contribute. For example, a eucapnic individual with moderate chronic obstructive pulmonary disease may develop hypercapnia if pneumonia or congestive heart failure develops, increasing ventilation–perfusion mismatch.

The mechanisms of hypercapnia in severe asthma and chronic obstructive pulmonary disease are multifactorial and relate to a complex interaction of severity of ventilation perfusion mismatch, work of breathing and CO_2 production, pattern of breathing, and O_2–CO_2 chemosensitivity. The role of diminished O_2–CO_2 chemosensitivity in predisposing an individual with chronic obstructive pulmonary disease (34–36) or asthma (32,33) to hypercapnia has already been discussed (see earlier). Increased work of breathing due to elevated airway resistance and mechanical impediment results in excessive CO_2 production and contributes to hypercapnia [Eq. (6)].

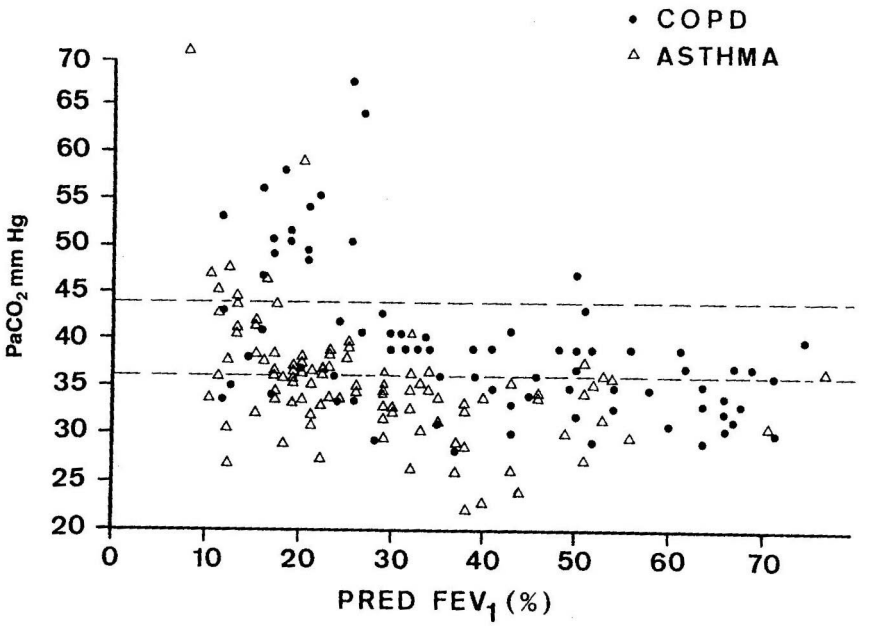

Figure 9 Diagram showing that in both chronic obstructive pulmonary disease and asthma, CO_2 retention occurs mostly when mechanical impairment, as measured by forced expiratory volume in one second (FEV_1), is severe. PRED = Predicted.*Source*: Modified from Refs. 65, 66.

The two major reasons for hypercapnia, however, are probably ventilation–perfusion mismatch impairing CO_2 clearance (26–28) and shallow tidal volume (71,72). When hypercapnic and eucapnic subjects are matched for severity of mechanical impairment and CO_2 production, the breathing pattern appears to be the main factor determining $PaCO_2$ (72). Both groups had similar minute ventilation, metabolic rate (CO_2 production), and absolute volume of dead space (Table 7). Hypercapnic subjects, however, breathed faster and shallower than eucapnic subjects and the lower tidal volume resulted in lower alveolar ventilation (Table 7). Recall that for any given minute ventilation and dead space, a reduction in tidal volume due to shallower breathing causes an increase in VD/VT, resulting in "wasted" breathing, that is, a decrease in alveolar ventilation. Thus, for any minute ventilation, dead space volume and CO_2 production rate, low tidal volume causes CO_2 retention, as the proportion of alveolar ventilation decreases.

Although not well studied, shallow breathing may also contribute to hypercapnia in severe pulmonary edema, acute respiratory distress syndrome, and during exacerbation of chronic obstructive pulmonary

Table 7 Chronic Hypercapnia in Chronic Obstructive Pulmonary Disease

$PaCO_2$ (mmHg)	RR (min)	VT (mL)	$\dot{V}E$ (L/min)	VD (mL)	$\dot{V}D$ (L/min)	$\dot{V}A$ (L/min)	$\dot{V}CO_2$ (mL/min)
40	16	463	7.6	179	3.0	4.7	212
50*	22*	355*	7.8	181	4.0*	3.8*	222

In the face of similar minute ventilation ($\dot{V}E$), dead space volume (VD), and CO_2 production ($\dot{V}CO_2$), hypercapnia occurred. This was due to shallow breathing resulting in decreased alveolar ventilation. Note that in each group, the sum of alveolar and dead space ventilation is equal to minute ventilation. *Source*: Values have been rounded from Ref. 72.
*$P < 0.05$.

disease. As these disorders are appropriately treated with antibiotics, bronchodilators and diuretics, the depth of breathing increases, the VD/VT ratio and wasted ventilation decrease while alveolar ventilation increases. Treatment also improves ventilation–perfusion mismatch, facilitating effective gas exchange.

Stable patients with interstitial lung diseases rarely develop hypercapnia, despite hypoxemia (66). In 60 subjects mostly diagnosed by lung biopsy, only two had a $PaCO_2 > 44$ mmHg (66). Hypercapnia in interstitial lung disease is rare for a variety of reasons. The main reason is that the decrease in tidal volume is counterbalanced by an increase in respiratory rate, so that adequate minute and alveolar ventilation are maintained. In addition, CO_2 production does not increase as mechanical impairment worsens (66).

HYPERCAPNIA IN NEUROMUSCULAR DISORDERS

Neuromuscular disorders comprise a major category of diseases causing hypercapnia (73). These disorders may involve the brainstem respiratory centers, the motor neurons located in the anterior horns of the spinal cord or their axons, the neuromuscular junctions or the muscle cells themselves (Fig. 3). The common final pathway in diseases causing hypercapnia, however, is diaphragmatic weakness or paralysis.

If respiratory centers are damaged by medullary infarction, hypoventilation may ensue. Because respiratory centers are widespread and bilateral (see earlier), the infarct must be extensive. Neuromuscular disorders involving the spinal cord (e.g., multiple sclerosis, amyotrophic lateral sclerosis), nerves (C_3–C_5 trauma causing phrenic nerve injury and diaphragmatic paralysis) or neuromuscular junction (Guillain Barre syndrome) are common causes of hypercapnia (Fig. 5).

Patients with neuromuscular disorders involving the diaphragm may present with orthopnea because diaphragmatic dysfunction is worse in the

supine position. Therefore, they may be misdiagnosed as having congestive heart failure (74). An important physical finding is paradoxical thoracoabdominal excursions, which should alert the clinician that diaphragmatic weakness is present (74). Subjects with neuromuscular disorders may first manifest hypercapnia only during sleep, or when another pathological process such as pneumonia stresses the respiratory system.

If hypercapnia is due solely to hypoventilation, hypoxemia should be proportional to hypercapnia and alveolar–arterial PO_2 difference should remain normal. If hypoxemia is greater than predicted by the rise in $PaCO_2$, the presence of a parenchymal process such as aspiration pneumonia or pulmonary embolism should be suspected. Subjects with neuromuscular disorders are prone to develop aspiration pneumonia (due to involvement of pharyngeal muscles) or pulmonary embolism (due to sedentary status).

OBESITY–HYPOVENTILATION SYNDROME

The obesity–hypoventilation syndrome is characterized by obesity and hypercapnia. Subjects with the syndrome commonly have excessive daytime sleepiness, high hematocrit and, in more advanced cases, cardiovascular complications such as right heart failure. Although the disorder is called obesity–hypoventilation syndrome, no systematic studies measuring minute and alveolar ventilation have been reported.

Most subjects with obesity–hypoventilation syndrome have obstructive sleep apnea–hypopnea syndrome. Characteristically, repetitive episodes of complete (obstructive apnea) or incomplete upper airway occlusion (obstructive hypopnea) occur during sleep and are terminated by arousal (75). On awakening, upper airway patency is restored and normal ventilation resumes until sleep recurs. Occlusive episodes are due to relaxation of dilator muscles of the upper airway during sleep, occurring in an individual with an anatomically small upper airway, most commonly due to obesity. Obesity is the most important risk factor for of obstructive sleep apnea–hypopnea syndrome. Episodes of apnea and hypopnea may be repeated hundreds of times during sleep in the form of periodic breathing. As a result, hypoxemia and hypercapnia develop, which eventually can cause cardiovascular complications such as hypertension, heart failure, and stroke. Daytime sleepiness is due to repetitive arousals and poor sleep quality.

A minority of patients with obstructive sleep apnea–hypopnea syndrome have daytime hypercapnia. Daytime hypercapnia in this disorder is probably multifactorial in pathogenesis (Fig. 10) (75). While asleep, hypercapnia occurs when ventilation ceases or decreases. The magnitude and duration of this nocturnal hypercapnia depends on the number and duration of these episodes. Upon termination by arousal, hyperpnea occurs correcting the blood gas abnormalities. The magnitude of hyperpnea required to excrete

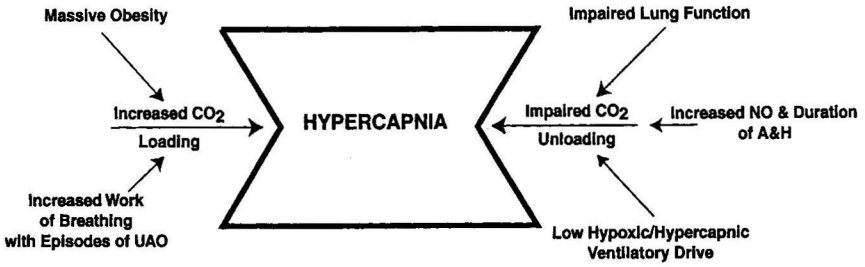

Figure 10 Mechanisms mediating CO_2 retention in obstructive sleep apnea–hypopnea syndrome. There is an imbalance between CO_2 loading and unloading processes during sleep. Eventually, nocturnal hypercapnia leads to diurnal hypercapnia. *Source*: Modified from Ref. 75.

the accumulated CO_2 (and replenish O_2) depends on the ability to increase ventilation, intrinsic chemosensitivity, and normal gas exchange. Mechanical impediments, due to chronic obstructive pulmonary disease or severe obesity (restrictive defect), may decrease the ability to respond appropriately to hypercapnia and hypoxemia and thereby limit CO_2 excretion (the "cannot breathe" mechanism). A subject with diminished hypoxic and hypercapnic chemosensitivity may not unload the accumulated CO_2 (and replenish O_2) during the intervals between apneic periods when hyperpnea should occur (the "won't breathe" mechanism). In parenchymal lung disorders with V/Q mismatch, CO_2 unloading is further impaired during hyperpnea. Excessive CO_2 production due to massive obesity also increases the CO_2 load and may contribute to hypercapnia (Fig. 10) (75).

With sustained impairment in CO_2 unloading during sleep, nocturnal CO_2 retention leads eventually to daytime CO_2 retention, perhaps due to a resetting in central chemosensitivity (76). A resetting of peripheral chemoreceptors may also occur as demonstrated in other disorders with chronic hypoxemia (77). Familial variations in chemosensitivity do not appear to be contributing to the likelihood of sustained hypercapnia in the obesity–hypoventilation syndrome (78).

A subset of patients with obesity but without evidence of obstructive sleep apnea–hypopnea may also develop hypercapnia. The mechanisms of hypercapnia in these patients remain unclear, but probably include high CO_2 production, reduced chest wall compliance, V/Q mismatch and decreased respiratory muscle strength. Subjects with obesity and hypercapnia should always undergo testing to determine if obstructive sleep apnea–hypopnea is present, because this problem can be treated effectively with mechanical ventilatory devices such as nasal continuous positive airway pressure or bilevel ventilation. In some of these patients, hypercapnia may improve or be reversed and morbidity decreased (79–82).

SUMMARY

The major function of the lungs is to regulate the partial pressures of both O_2 and CO_2 in the arterial blood in the face of varying metabolic and environmental conditions. From an acid–base perspective, this regulation acts to maintain intracellular pH close to neutrality, resulting in an arterial blood pH of 7.40. Arterial PCO_2 is regulated by a complex hierarchical system of peripheral and central nervous system sensors that respond to changes in pH and signal appropriate changes in alveolar ventilation. This regulation requires an intact neuromuscular signal-effector pathway, as well as an appropriate match between ventilation and perfusion of the lungs. Hypocapnia and hypercapnia can be the result of a normal adaptive response to superimposed acid–base disorders, or disruption of normal regulation by pulmonary, cardiopulmonary, neurologic, or neuromuscular disorders.

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