Reviews

The Control of Breathing in Clinical Practice*

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The control of breathing results from a complex interaction involving the respiratory centers, which feed signals to a central control mechanism that, in turn, provides output to the effector muscles. In this review, we describe the individual elements of this system, and what is known about their function in man. We outline clinically relevant aspects of the integration of human ventilatory control system, and describe altered function in response to special circumstances, disorders, and medications. We emphasize the clinical relevance of this topic by employing case presentations of active patients from our practice. ***(CHEST 2000; 117:205–225)***

Key words: carotid body; chemoreceptors; control of ventilation; pulmonary receptors

Abbreviations: CPAP = continuous positive airway pressure; CSF = cerebrospinal fluid; CSR = Cheyne-Stokes respiration; DRG = dorsal respiratory group; $[H^+]$ = hydrogen ion concentration; HCO_3^- = bicarbonate; MVV = maximal voluntary ventilation; OSA = obstructive sleep apnea; pHa = arterial pH; PIIA = postinspiration inspiratory activity; PImax = maximal inspiratory pressure; RAR = rapidly adapting receptor; REM = rapid eye movement; Sa_{O_2} = arterial oxygen saturation; SAR = slowly adapting receptor; VC = vital capacity; $\dot{V}_E$ = minute ventilation; $\dot{V}_{O_2}$ = oxygen uptake; $\dot{V}/\dot{Q}$ = ventilation/perfusion; VRG = ventral respiratory group; V_T = tidal volume; WOB = work of breathing

This review is intended as an overview of human respiratory control. The first section will briefly describe the physiology of respiratory control including the sensors, the central controllers, and the effector systems. Subsequently, the control of breathing under special conditions and in certain common disease states will be reviewed. Throughout this discussion, we will employ selected case histories from our current outpatient population to illustrate salient, clinically relevant concepts.

Ventilation is constantly monitored and adjusted to maintain appropriate arterial pH (pHa) and Pa_{O_2}. This homeostatic control system requires a system of sensors, a central controlling mechanism, and an effector system to carry out its commands (Fig 1). Its response to changes in blood chemistry, mechanical load, metabolic rate, and respiratory neural receptors enables the respiratory system to adapt to special physiologic circumstances such as sleep, exercise, and altitude, as well as to compensate for pathologic disorders such as asthma, COPD, drug use, Cheyne-Stokes respiration (CSR), and neurologic disease.

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Components of Respiratory Control

Respiratory Sensors

The afferent input into the central system is provided primarily by four groups of neural receptors: (1) peripheral arterial chemoreceptors; (2) central (brainstem) chemoreceptors; (3) intrapulmonary receptors; and (4) chest wall and muscle mechanoreceptors.

Peripheral Arterial Chemoreceptors: The peripheral arterial chemoreceptors consist of the carotid and aortic bodies. The physiologic significance of the aortic bodies in humans is difficult to determine but likely to be small: the carotid bodies appear to have preeminent

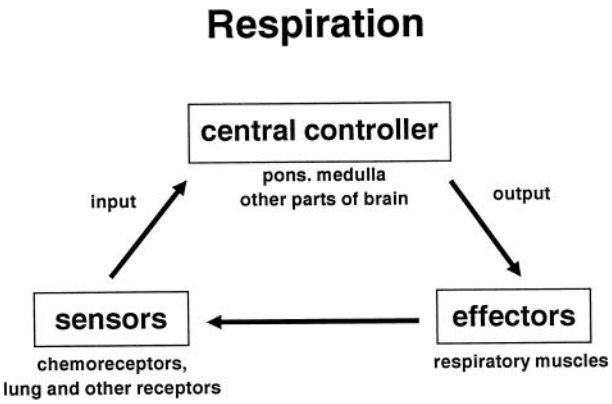

FIGURE 1. A schematic of the respiratory control system. Information from the various peripheral sensors is fed to a central control mechanism, the output of which goes to the effector muscles. By changing ventilation, the respiratory muscles reduce perturbations of the sensors (negative feedback). Reprinted with permission from West.[126]

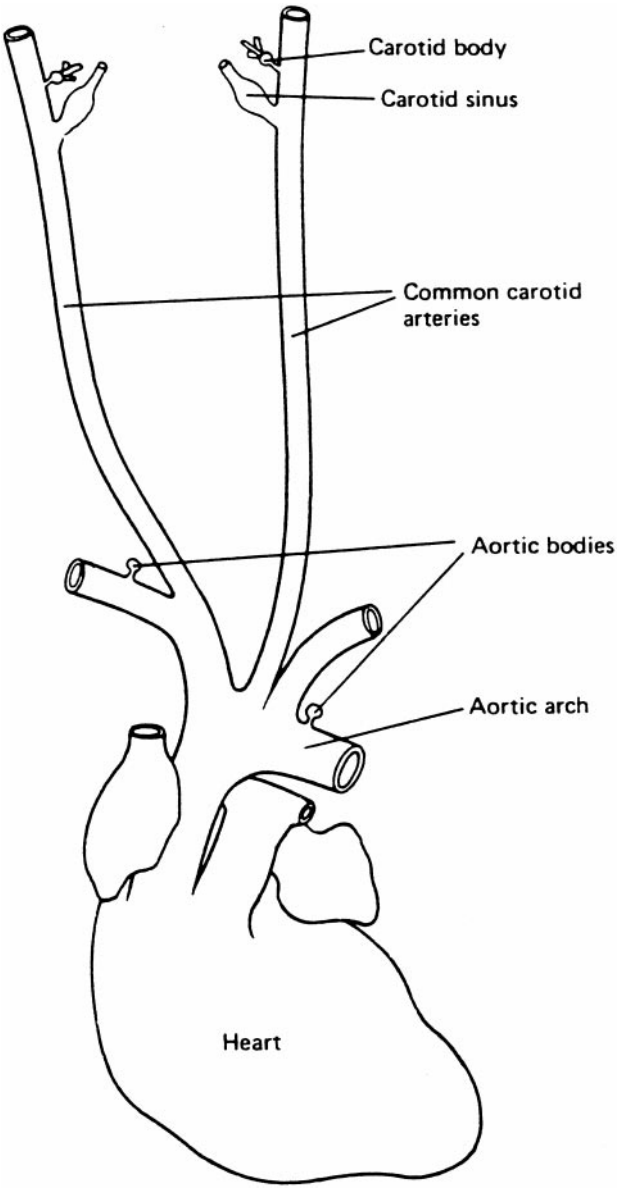

FIGURE 2. The location of the carotid and aortic bodies with respect to the common carotid arteries and aortic arch, respectively. Reprinted with permission from Ganong.[1]

importance. The carotid bodies are located at the junction of the internal and external carotid arteries, and are small, measuring $1.5 \times 2.0 \times 3.7$ mm each with a weight of 10.6 to 12.6 mg (Fig 2).[1,2] They receive their blood supply from branches of the external carotid artery, and their sensory supply from the carotid sinus branch of the glossopharyngeal nerve.[3]

The carotid bodies consist of two different cell types, glomus cells (type I) and sheath cells (type II) (Fig 3). Both cells are innervated primarily by the carotid sinus nerve, which contains both parasympathetic and sympathetic neurons with both afferent (sensory) and efferent (motor) components. The afferent neurons terminate on glomus cells. There is also an unmyelinated supply to the sheath cells. The efferent neurons or sympathetic innervation primarily supply the vasculature and regulate vessel tone and blood supply to the carotid body.[2,3] The carotid body has a uniquely high arterial blood supply (2 L/min/100 g) that allows for its oxygen needs to be met by the dissolved oxygen in the blood, unlike other tissues that depend primarily on oxygen initially bound to hemoglobin.[1] In addition, Pa_{O_2} is the specific signal sensed by the glomus cells. Therefore, the carotid body is insensitive to conditions that lower arterial oxygen content but exert little or no change on the Pa_{O_2}, such as anemia and carbon monoxide poisoning.[1] This accounts for the clinical observation that carbon monoxide intoxication, regardless of severity, does not include signs and symptoms of respiratory stimulation such as dyspnea or hypoventilation.

The carotid body responds to both Pa_{O_2} and hydrogen ion concentration ($[H^+]$). The intensity of the response of the glomus cells varies according to the severity of the arterial hypoxemia or acidosis in a nonlinear manner. The greatest increase is seen in response to hypoxemia, especially when Pa_{O_2} falls to ≤ 70 mm Hg, at which point the firing frequency and, subsequently, minute ventilation ($\dot{V}E$) increase in an accelerated fashion (Fig 4).[4] This increase in $\dot{V}E$ is manifested primarily by an increase in the depth of breathing (tidal volume, or VT) rather than by an increased respiratory rate. In mammals, the carotid bodies are responsible for about 90% of the ventilatory response to hypoxemia; the remaining 10% is from the aortic bodies. They are also responsible for 20 to 50% of the response to arterial hypercapnia and acidemia, with the remaining 50 to

80% of the response to hypercapnia and acidemia mediated by the central brainstem receptors.[4] The exact mechanism by which the carotid bodies transduce the stimulus of a low Pa_{O_2} into neurotransmitter release is still under investigation.

In humans, bilateral carotid body resection or carotid endarterectomy reduces resting $\dot{V}_E$, raising resting Pa_{CO_2} by 2 to 4 mm Hg, and essentially eliminates the ventilatory response to hypoxia both at rest and during exercise.[5,6] These patients also experience a 30% decrease in their ventilatory response to euoxic hypercapnia.[5] Unlike in cats and ponies, this loss of peripheral chemosensitivity in humans is permanent, perhaps because of the relatively minor function of the aortic bodies in man.[7] The most common clinical situation in which carotid body "resection" now occurs is as an unintended consequence of carotid endarterectomy, which may damage the carotid bodies.[6] Following unilateral surgery, peripheral chemosensitivity remains normal or is slightly decreased, but patients with bilateral endarterectomies may lose carotid body function completely, losing their ventilatory response to hypoxia and experiencing an increase in their resting Pa_{CO_2}.[6]

Case 1: Sequential Bilateral Carotid Endarterectomy in a COPD Patient. A 69-year-old white woman was admitted for an elective right carotid endarterectomy. Her medical history was significant for 40 pack-years of cigarette smoking, severe COPD, two cerebrovascular accidents, and a left carotid endarterectomy 1 year prior. Her preoperative arterial blood gas values showed a pH of 7.43; Pa_{CO_2}, 48 mm Hg; Pa_{O_2}, 50 mm Hg; and bicarbonate (HCO_3^-), 31 mEq/L while breathing room air. After an uneventful procedure, she was extubated on postoperative day 2 and received oxygen by nasal cannula at a rate of 3 L. On postoperative day 3, the nurses noticed that the patient was increasingly somnolent, and by postoperative day 5 she had developed severely altered mental status characterized by lethargy and confusion, despite the absence of any narcotic or sedative medications. There was no detectable change in her chest examination or chest radiograph. Arterial blood gas values while breathing 2 L of oxygen demonstrated a pH of 7.28; Pa_{CO_2}, 69 mm Hg; Pa_{O_2}, 62 mm Hg; and HCO_3^-, 31 mEq/L. The pulmonary service was consulted at this point and recommended treating her with nasal bilevel positive airway pressure ventilation. The patient improved clinically; 2 days later, her arterial blood gases while breathing 2 L oxygen per nasal cannula were a pH of 7.38; Pa_{CO_2}, 54 mm Hg; Pa_{O_2}, 72 mm Hg; and HCO_3^-, 36 mEq/L.

This case report illustrates an example of the clinical importance of the carotid bodies in the control of ventilation. This patient developed acute respiratory acidemia following the inadvertent operative denervation of her sole remaining functional carotid body. Together with her severe COPD with baseline CO_2 retention, the acute loss of the carotid body input to the respiratory center resulted in further depression of $\dot{V}_E$ sufficient to produce CO_2 narcosis.

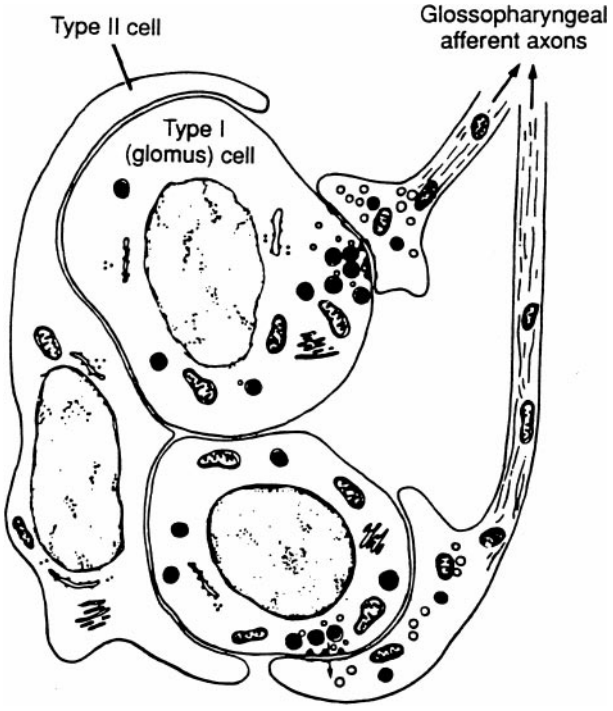

FIGURE 3. Organization of the carotid body showing the two different cell types. Glomus cells (type I) contain catecholamines (norepinephrine and dopamine). When exposed to hypoxia, they release the stored neurotransmitters that stimulate the cuplike endings of the carotid sinus nerve fibers (Hering's nerve) in the glossopharyngeal nerve. The glial-like sheath cells (type II) surround the type I cells and probably have a sustentacular function. Reprinted with permission from Ganong.[1]

The Central Chemoreceptors: The fact that a ventilatory response to added CO_2 persists in experimental animals despite peripheral chemoreceptor denervation suggests that there are chemoreceptors in the brain that are sensitive to CO_2 or hydrogen ions.[8] Although no definite chemoreceptors have been defined anatomically, results of experiments involving the local application of chemical, electrical, and thermal stimuli or the ablation of neural tissue suggest that the central chemoreceptors are located at or near the ventral surface of the medulla.[8] Stimulation of these receptors increases both the rate of rise and the intensity of the inspiratory "ramp" signal, thereby increasing the frequency of the respiratory rhythm.[9] The inspiratory ramp signal

is a nervous signal transmitted to the respiratory muscles as a weak burst of action potentials that steadily increases in a ramp-like manner.[10,11] Physiologically, these central chemoreceptors respond primarily to alterations of $[H^+]$ in the cerebrospinal fluid (CSF) and medullary interstitial fluid. The contribution of these central chemoreceptors to ventilation depends on the factors that alter hydrogen ion flux in their vicinity, causing changes in their intracellular pH. They are located in many different brainstem locations, including the ventral medullary surface, deeper sites near the nucleus tractus solitarius, and rostrally close to the locus ceruleus. Stimulation of these sites increases the whole respiratory control system output, suggesting that they respond to changes in brainstem pH via a ventilatory feedback loop. The sensing of acute pH changes, but not the steady-state ventilatory response, seems to require carbonic anhydrase. Imidazole-histidine appears to be an important molecule involved in central chemoreception and may be a pH sensor molecule. It is found in proteins located in pH-sensitive areas including ion channels, ion transport proteins, enzymes, and receptors. Thus, it may be involved in central chemoreception at sites within the ventrolateral surface of the medulla oblongata.[12]

Hydrogen ions enter and exit the CSF and extracellular fluid in the vicinity of the central chemoreceptors as a result of both CO_2 dissociation and by direct diffusion into and out of the bloodstream. Elevated arterial CO_2 rapidly penetrates the blood-brain barrier because CO_2 is highly membrane-permeable, is converted to carbonic acid (H_2CO_3), and rapidly dissociates into hydrogen ions and HCO_3^-. This causes $[H^+]$ in the CSF and interstitium to rise in parallel with $Paco_2$. This increased $[H^+]$ stimulates respiration by a direct action on the central chemoreceptors. Conversely, a decreased $Paco_2$ or $[H^+]$ inhibits ventilation.[13]

The ventilatory response to an increased $Paco_2$ is divided into an initial rapid phase (within seconds) due to the relatively rapid acidification of the CSF, and a slower phase (within minutes) due to hydrogen ion buildup in the more highly buffered medullary interstitium. In addition, when compared with the highly membrane-permeable CO_2, hydrogen ions in the arterial blood penetrate the blood-brain barrier relatively slowly (minutes to hours). As a result, changes in pHa result in relatively slower and smaller changes in ventilation (Fig 5).[14] Changes in $Paco_2$ alone have a potent acute effect on ventilation but only a weak chronic effect. This occurs because a chronically elevated $Paco_2$ is associated with renal compensation with the retention of HCO_3^-. This HCO_3^- gradually diffuses through the blood-brain barrier and into the CSF, where it binds to the excess hydrogen ions produced by the elevated $Paco_2$ and negates their effect on ventilatory drive.[13]

The central hydrogen ion chemoreceptors are somewhat redundant, sensing the same stimulus as the carotid bodies. Carotid body chemoreceptors seem to adjust for breath-to-breath changes in arterial chemistry, while the hydrogen ion-sensitive medullary chemoreceptors sustain ventilation with lesser breath-to-breath variation.[13]

Pulmonary Receptors: Pulmonary receptors are present in the airways and lung parenchyma. They are all innervated by the vagus nerve, with myelinated fibers supplying the airway receptors and un-

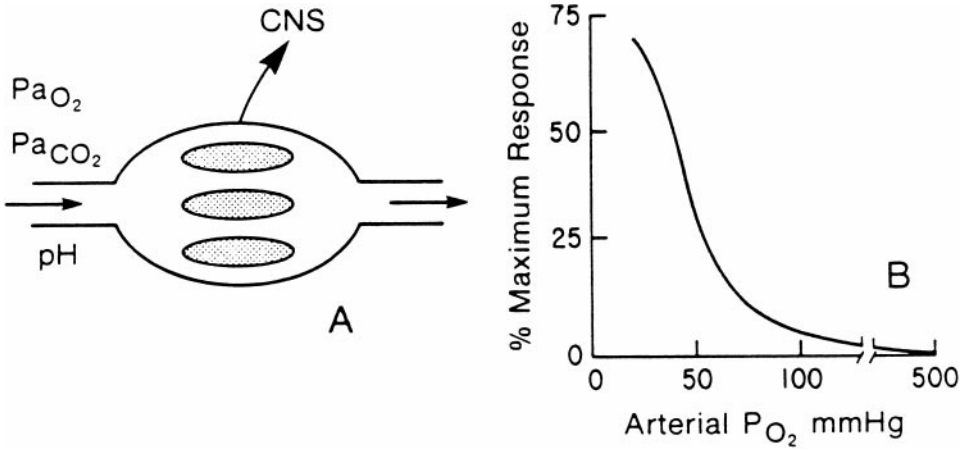

FIGURE 4. (*Left, A*: the carotid body responds to changes of Po_2, Pco_2, and pH in arterial blood. Impulses travel to the CNS through the carotid sinus nerve (Hering's nerve). *Right, B*: the percent maximum response of the firing frequency of the carotid body to arterial Po_2. Note that the maximum response occurs at a Po_2 of < 50 mm Hg and that the response varies in a nonlinear fashion. Reprinted with permission from West.[126]

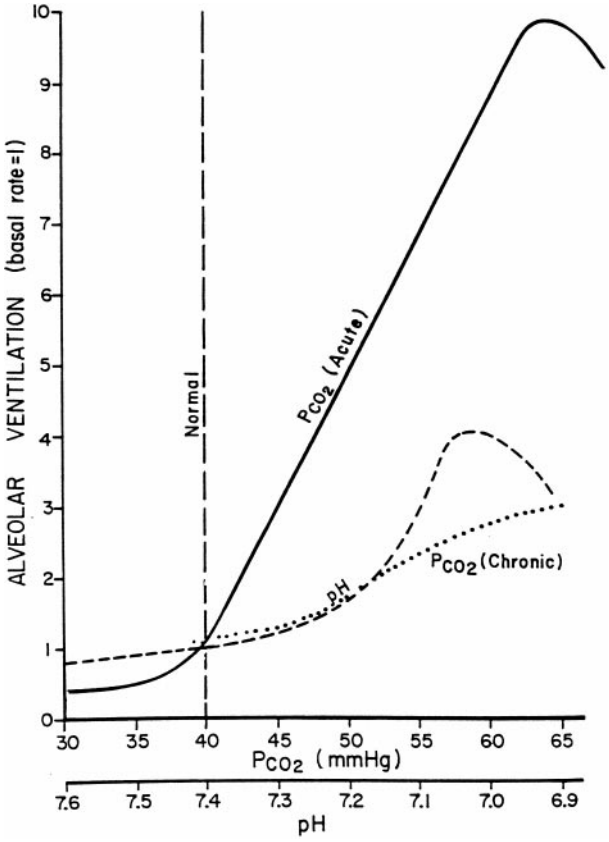

FIGURE 5. Effects of increased arterial P_{CO_2}, both acute (continuous line) and chronic (dotted line), on the rate of alveolar ventilation. The second abscissa shows the relationship of decreased pHa (broken line) to alveolar ventilation. Note that an acute change in P_{CO_2} has a greater effect on alveolar ventilation than a chronic change. Reprinted with permission from Guyton.[9]

myelinated C fibers supplying the lung parenchyma.[14,15] The airway receptors are subdivided into the slowly adapting receptors (SARs), also known to be the pulmonary stretch receptors, and the rapidly adapting receptors (RARs). The lung parenchyma receptors are called juxtacapillary receptors.

The SARs lie among the airway smooth muscle and are responsible for the Hering-Breuer inflation reflex in animals. Activation of these receptors also causes the tracheobronchial smooth muscle to relax, thus dilating the airways.[16] The Hering-Breuer reflex is the prolongation of expiratory time and the decrease in respiratory rate in response to lung inflation.[15,17] In humans, the Hering-Breuer reflex is manifest only at a VT of > 3 L and seems to play a protective role in preventing excessive lung inflation.[10,17] The SARs do not accommodate to persistent stimulation such as prolonged distention.[14] The SARs are thought to participate in ventilatory control by prolonging inspiration in conditions that reduce lung inflation, such as airway obstruction or decreased chest wall compliance, thereby allowing a normal VT to be achieved. Conversely, in conditions that prolong expiration, lung deflation is slow and the increased SAR activity increases the force of contraction of the expiratory muscles and also prolongs expiratory time. This prevents an increase in end-expiratory volume, thus decreasing the resting length of the inspiratory muscles and allowing them to function along the most advantageous portion of their length-tension curve.[18]

The RARs lie between the airway epithelial cells and are irritant receptors, responding to noxious stimuli such as dust, cigarette smoke, and histamine.[19] They are concentrated in the carina and primary bronchi, and are also believed to be cough receptors.[14] These RARs are innervated by myelinated fibers and have a more rapid rate of adaptation than SARs. During normal breathing, their discharge is independent of the phases of inspiration and expiration, and therefore these receptors do not seem to be an important influence on breathing at rest.[20] However, animal studies show that they are stimulated by conditions that increase airflow resistance and decrease lung compliance.[21] Thus, their most important function may be to detect pathophysiologic changes in the airways. RARs also seem to be responsible for the augmented breathing and sighs that occur sporadically during normal breathing that helps to prevent atelectases.[22] These receptors may be important in the sensations of chest tightness, dyspnea, bronchoconstriction, and the rapid and shallow breathing that occurs in asthma.[16,23]

The pulmonary parenchymal receptors are innervated by the unmyelinated C fibers of the vagus nerve. They are called juxtacapillary receptors because of their location near capillaries in the alveolar walls. In animals, these receptors respond both to hyperinflation of the lungs and to chemicals present in the pulmonary circulation, and may be involved in the sensation of dyspnea in conditions causing interstitial congestion (*eg*, heart failure).[17,24] Stimulation of these C fibers may also be associated with rapid shallow breathing, bronchoconstriction, and increased airway secretions.[25]

The cumulative influence of lung receptors innervated by the vagus nerve on ventilation has been determined by blocking or interrupting the vagal tracts in animals. This intervention produces a reduced ventilatory response to hypercapnic and hypoxemic stimuli in conscious dogs at rest, and a decreased respiratory frequency response during exercise.[26] The mechanism for rapid shallow breathing and hyperventilation present during acute asthma has also been studied in dogs before and after vagotomy. Although vagotomy has no effect on baseline respiratory pattern, experimental bronchoconstriction after vagotomy does not produce the char-

acteristic increase in respiratory rate and $\dot{V}_E$ present in dogs (and humans) with intact vagi, suggesting that the rapid shallow breathing pattern in response to bronchoconstriction is mediated by vagal afferent pathways.[27,28] Another study in anesthetized dogs demonstrated that the rapid shallow breathing response to severe inspiratory resistive loading was abolished by bilateral vagectomy and was not mediated by diaphragm fatigue or hypoxia.[28] Similar results have been found in limited experiments in man.[29,30]

Overall, these studies suggest that the abnormal breathing pattern associated with certain diseases (*eg*, asthma, pneumonia, heart failure, and pulmonary thromboembolism) in humans may be related primarily to lung receptor stimulation rather than derangements in lung mechanics or arterial blood gases.

Chest Wall and Muscle Mechanoreceptors: Mechanoreceptors are sensors that respond to changes in length, tension, or movement. The primary mechanoreceptors in the chest are the muscle spindle endings and tendon organs of the respiratory muscles and the joint proprioceptor. Muscle spindles are primarily influenced by changes in length and are responsible for reflex contraction of the skeletal muscles in response to stretching. Afferent information from these receptors is carried in the anterior columns of the spinal reticular pathway and terminates in the region of the respiratory centers in the medulla.[31] Muscle receptor afferents are involved in the level and timing of respiratory activity.[32] These receptors may also play a role in the increase in ventilation occurring during the early stages of exercise.

Tendon organs sense changes in the force of contraction exerted by the muscles of respiration. Tendon organ receptors are involved in monitoring the force of muscle contraction and have an inhibiting effect on inspiration. They may be important in coordinating respiratory muscle contraction during breathing at rest or with a respiratory load.[32]

Joint proprioceptors sense the degree of chest wall movement and may also influence the level and timing of respiratory activity. Proprioceptor afferents project to the phrenic motor neurons and affect their firing rate. They also ascend to the medullary respiratory neurons in the dorsal respiratory group and nucleus retroambiguus, where they affect the timing of inspiration and expiration.[32]

These mechanoreceptors may also be important in the sensation of dyspnea when respiratory effort is increased by the mechanism of length-tension inappropriateness.[16] This is illustrated by the following case history.

Case 2: Large Pleural Effusion Associated With Dyspnea. A 74-year-old white man presented with dyspnea on minimal exertion for several weeks. His medical history was significant for stage IV non-Hodgkin's lymphoma treated with radiation and chemotherapy several years previously. Physical examination demonstrated left cervical lymphadenopathy and decreased vocal fremitus, dullness to percussion, and poor air entry on the right side of the chest. A chest radiograph showed a large (> 50% of the hemithorax) right pleural effusion with mediastinal shift to the contralateral side. Spirometry showed an FVC of 3.0 L (60% of predicted) and a FEV_1 of 2.4 L (82% of predicted). Arterial oxygen saturation (Sa_{O_2}) on room air was 94% at rest, with mild desaturation ($Sa_{O_2} < 88\%$) occurring with informal exercise testing (1 to 2 min of ambulation in the clinic hallway). A 1.5-L therapeutic thoracentesis was performed, with dramatic improvement in the patient's symptoms. The patient returned to the clinic several weeks later with recurrence of his symptoms of shortness of breath with minimal exertion. Physical examination confirmed reaccumulation of the pleural fluid. Right-sided pleurodesis was ultimately performed with no pleural fluid recurrence and excellent long-term relief of his dyspnea.

This patient had dyspnea primarily resulting from the presence of a large pleural effusion. This appears to arise primarily by the mechanism of length-tension inappropriateness caused by a pleural effusion stretching the chest wall.[33] According to this hypothesis, inspiratory muscle activation produces muscle contraction and a degree of tension in the muscles that is sensed by the tendon organs. If the respiratory muscles are inefficient for mechanical reasons (in this case because of the thoracic distention produced by the pleural effusion), the magnitude of tension in the muscle produced by a given amount of muscle contraction is proportionately lower than in the normal state. This discrepancy between the degree of neural input to and contraction of the respiratory muscles and the tension produced by that muscle contraction is sensed by the cerebral cortex as dyspnea. Removal of the pleural fluid in this case had the effect of reducing end-expiratory muscle fiber length and restoring the relationship of muscle contraction and muscle tension to normal, thereby immediately reducing dyspnea.[33] This scenario does not exclude the possibility that other mechanisms may be contributing to this patient's symptoms. It is possible that the relief of dyspnea following thoracentesis may have resulted from the decreased work of breathing (WOB) that occurs because of the removal of the mechanical load of the pleural effusion, or possibly because of improved gas exchange from improved ventilation/perfusion ($\dot{V}/\dot{Q}$) matching.

The Central Respiratory Controllers

The central respiratory controllers are divided into the brainstem group (involuntary) and the cerebral cortex group (voluntary). The former is further subdivided into pneumotaxic, apneustic, and medullary centers.

The pneumotaxic center consists of the nucleus parabrachialis and the Kolliker-Fuse nucleus in the pons. This center is important in influencing the timing of the inspiratory cut-off by providing a tonic input to the respiratory pattern generators located in the inspiratory center. Thus, this center may modulate the respiratory response to stimuli such as hypercapnia, hypoxia, and lung inflation, and is of importance in regulating the duration of inspiration.[31,34]

The apneustic center is found in the lower pons and seems to function as the source of impulses that terminate inspiration, an "inspiratory cut-off switch."[34] Inactivation of this center results in apneustic breathing, which is rhythmic respiration with a marked increase in inspiratory time and a short expiration phase.[35] Apneustic breathing can be experimentally induced in animals by transecting the spinal cord between the pneumotaxic center and the lower brainstem in combination with bilateral vagotomy. Clinical information from patients with multiple sclerosis with brainstem involvement and clinical pathologic correlations suggest that the pneumotaxic center may function similarly in man.[35,36]

The medullary center is divided into an inspiratory dorsal respiratory group (DRG) of neurons and an expiratory ventral respiratory group (VRG). The DRG is located in the nucleus of tractus solitarius in the medulla and is important in integrating impulses from visceral afferents from the upper airways, intraarterial chemoreceptors, and lung parenchyma through the fifth, ninth and 10th cranial nerves, respectively.[34] It may also be the site of projection of proprioceptive afferents from the respiratory muscles and chest wall. The DRG is a processing center for respiratory reflexes and is the site of origin of the normal rhythmic respiratory drive consisting of repetitive bursts of inspiratory action potentials.[34] The exact mechanism by which this rhythm is generated is unknown.

A theory to explain the breathing rhythmicity of the central pattern generator is as follows. Inspiration begins by the abrupt removal of inhibitory impulses to the DRG. This is followed by increased inspiratory motoneuron activity in the form of a slowly augmenting ramp of signals that is suddenly terminated by an off-switch mechanism. This termination of inspiratory activity occurs when a critical threshold is attained. During early expiration, there is another burst of inspiratory neuronal activity that is referred to as postinspiration inspiratory activity (PIIA). PIIA does not prolong inspiration, but rather slows down the rate of exhalation during the first part of the expiratory phase. The neurons that generate the PIIA may depend on mechanisms that are different from those responsible for the main inspiratory ramp activity.[11]

The VRG consists of both inspiratory and expiratory neurons and is located within the nucleus ambiguus rostrally and nucleus retroambiguus caudally. The VRG innervates respiratory effector muscles through the phrenic, intercostal, and abdominal respiratory motoneurons.[34] Its output increases with the need for forceful expiration such as in exercise or in any condition of increased airway resistance to breathing (*eg*, COPD or asthma).[37]

The cerebral cortex plays a role in ventilatory control and can also influence or bypass the central respiratory control mechanism in order to accomplish behavior-related respiratory activity such as cough, speech, singing, voluntary breath holding, and other such activities.[38]

Effector System

The effector system consists of those pathways and muscles that are involved in the actual performance of inspiration and expiration. The spinal pathways connect the respiratory centers in the brain and spinal cord to the respiratory muscles and are divided into the descending and ascending pathways. The descending pathways connect the DRG and VRG to the ventrolateral columns of the spinal cord, the phrenic nerves, and the intercostal and abdominal muscles of respiration. These pathways are used for the inhibition of the expiratory muscles during inspiration and inhibition of inspiratory muscles during expiration to prevent opposing muscles from contracting at the same time.[34] The ascending pathways connect the respiratory muscles to the higher brainstem levels. Impairment of the ascending spinal pathways (*eg*, following bilateral percutaneous cervical cordotomy or anterior spinal operations) may lead to respiratory dysfunction in the form of apnea during sleep that is reversed by arousal. This condition may be caused by damage of ascending spinoreticular fibers, lessening brainstem reticular formation activity and causing a general depression of respiration.[34]

The respiratory muscles consist of the diaphragm and the intercostal, abdominal, and accessory muscles of respiration. The diaphragm is responsible for the majority (75%) of air movement during quiet inspiration, while the intercostal, abdominal, and accessory muscles (sternocleidomastoid and other

neck muscles) account for the remainder.[39] Inspiration at rest is active and expiration is a passive event in patients with normal lungs. During exercise or in patients with airway obstruction, both inspiration and expiration become active, with expiratory contraction of the abdominal wall and internal intercostal muscles.[40] The clinical importance of the diaphragm is illustrated by the following case history.

Case 3: Bilateral Hemidiaphragm Weakness. A 77-year-old white man was transferred to the medical ICU for failure to wean off mechanical ventilation after the repair of a type 1 thoracic aortic dissection. His postoperative course had been uncomplicated until he was extubated 48 h later. Within 15 min of extubation, he became tachypneic, hypercapnic, and acidotic (pHa of 7.13; $PaCO_2$, 85 mm Hg; and PaO_2, 66 mm Hg), and required reintubation. Initial evaluation included a brief interval of spontaneous breathing off the ventilator, during which paradoxical inward inspiratory motion of the abdomen was observed. A chest radiograph showed bilateral small but clear lung fields with minimal pleural effusions. Fluoroscopy of the diaphragm demonstrated bilateral failure to descend with rapid inspiratory efforts (sniff test).

This patient has respiratory failure due to bilateral hemidiaphragm paralysis, presumably caused by intraoperative phrenic nerve injury.[41] Less common than previously believed, this is nevertheless an easily overlooked cause of ventilator dependence after thoracic surgery. One reason it may be overlooked is that positive pressure ventilation masks the characteristic paradoxical diaphragm/abdominal wall movement and the pulmonary restriction, which would otherwise be obvious. In our experience, it presents as prolonged postoperative ventilator dependence following either complex or multiple intrathoracic operations. Typically, the patient has good gas exchange and a favorable clinical course until the ventilator is totally discontinued, when acute ventilatory decompensation occurs within a short time. Once the diagnosis is considered, measuring maximal inspiratory pressure (PImax), maximum voluntary ventilation (MVV), and supine and sitting vital capacities (VCs) will confirm it. In bilateral diaphragm paralysis, both PImax and MVV are decreased and there is a $> 50\%$ reduction in VC in the supine vs the upright position.[42]

Integrated Responses of the Ventilatory Control System

The categorization of the respiratory control system employed above is a useful means of organizing and outlining the anatomic and physiologic information available regarding its various components. However, all normal physiologic functions and derangements of respiratory control must consider the integrated function of the entire system. Considerable information of clinical significance is best understood as it relates to the integrated ventilatory response to the various chemical stimuli.

Respiratory Response to Increased CO_2

The integration of the central respiratory centers is normally coordinated, and thus arterial CO_2 is maintained constant with relatively little variation. Therefore, ventilation increases in a directly proportional manner to increasing CO_2 production. This response is reflected in the ventilatory response to experimentally induced arterial hypercapnia (Fig 5). During exercise, this occurs without arterial hypercapnia occurring. There is an important interaction between hypercapnic and hypoxemic ventilatory responses. The slope of the ventilatory response to increases in $PaCO_2$ is greater in the presence of a lower PaO_2 (Fig 6).[43] Although the majority of normal subjects maintain a resting $PaCO_2$ of 40 mm Hg, there is substantial genetic variation in CO_2 and oxygen sensitivity.[44] Genetic variation in drive may explain some of the differences in blood gas tensions in patients with COPD.[45] Both hypercapnic and hypoxemic ventilatory responses tend to decrease with increasing age or formal exercise training.[46,47] Pregnancy is associated with an increase in resting $\dot{V}E$ primarily because of an increased VT. This begins

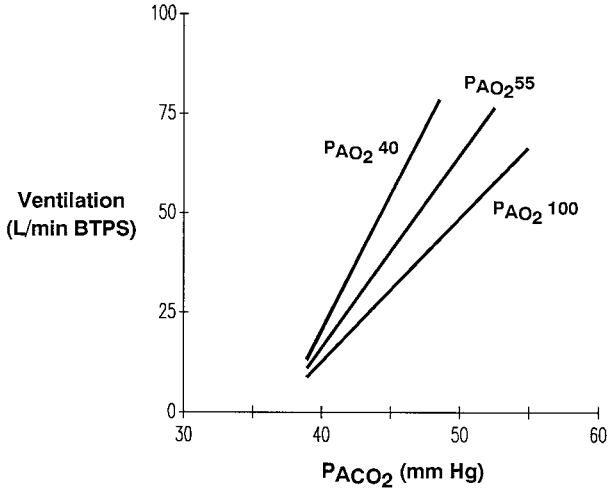

Figure 6. Fan of lines showing the difference in ventilatory response to $PaCO_2$ at various fixed values for alveolar P_{O_2}. Note that hypoxemia increases the slope of the ventilatory response to $PaCO_2$. BTPS = corrected for physiologic body temperature, pressure, and water saturation. Reprinted with permission from Ganong[1]; see original source for references within Figure.

in the first trimester but then remains relatively constant thereafter. The hyperventilation is thought to be secondary to the rise in progesterone blood levels.[48]

Abnormalities of the response of the central control system's to CO_2 may occur (*eg*, central alveolar hypoventilation when lesions of the CNS are present). If no lesions are detected, the condition is called primary alveolar hypoventilation; the following case history describes this condition.

Case 4: Primary Alveolar Hypoventilation. A 47-year-old woman was referred for asymptomatic respiratory acidosis with a pH of 7.35; $Paco_2$, 49 mm Hg; and Pao_2, 67 mm Hg. Her medical history included sick sinus syndrome, for which a pacemaker was inserted, and postural hypotension secondary to autonomic dysfunction. The physical examination revealed a nonobese patient with a BP of 110/80 mm Hg supine and 80/60 mm Hg standing, but the findings were otherwise normal. A urine toxicology screen showed no illicit drug use, and thyroid function tests and chest radiograph were normal. Spirometry, lung volumes, diffusing capacity, MVV, and negative inspiratory pressure were normal. A nocturnal polysomnogram demonstrated minimal central apneas/hypopneas associated with mild desaturation by pulse oximetry. A neurologic workup (including a CT scan of the brain) was normal, and a provisional diagnosis of primary alveolar hypoventilation was made by exclusion. This was confirmed by the arterial blood gas values after 5 min of voluntary hyperventilation: pH of 7.52; $Paco_2$, 29 mm Hg; and Pao_2, 93 mm Hg.

The diagnosis of primary alveolar hypoventilation is ordinarily based on finding hypercapnia, hypoxemia, and chronic respiratory acidosis in the absence of respiratory muscle weakness, mechanical ventilatory defects, or an underlying neurologic disease.[49] These patients, although often asymptomatic, may have symptoms secondary to the combination of hypercapnia and resulting hypoxemia. These may include symptoms of cor pulmonale, morning headaches, daytime fatigue, somnolence, confusion, and sleep disturbances. However, alveolar-arterial gradient, airflow rates, and lung volumes are usually normal, as are MVV and PImax. In contrast, patients' ventilatory and occlusion pressure responses to hypercapnia are reduced or absent, and they have an abnormal ventilatory response to exercise associated with further increases in their $Paco_2$ and a decrease in Pao_2.[49] Their breath-holding time is also markedly prolonged without the accompanying sensation of dyspnea.[50] Typically, these patients can voluntarily hyperventilate to a normal or low $Paco_2$.

This case illustrates an important method that may be useful to differentiate the cause of hypercapnia in a patient. If the patient can, during voluntary hyperventilation, lower $Paco_2$ to normal or below, then a central mechanism depressing ventilation is at least partially responsible for the hypercapnia. However, if voluntary hyperventilation fails to lower $Paco_2$ to normal, an alternative cause of the hypercapnia should be sought. Primary alveolar hypoventilation was diagnosed in this patient, as she effectively hyperventilated on command, and no central lesions effecting her central respiratory drive were identified.

Respiratory Response to Decreased Oxygen

The ventilatory response to hypoxemia varies depending on the level of CO_2 and also varies between individuals on a genetically determined basis.[43,45] It also decreases with age and training.[46,47] The response to a falling Pao_2 demonstrates an exponential type of curve rather than the linear relationship of increasing ventilation in response to increasing $Paco_2$ (Fig 7). There is little increase in $\dot{V}E$ until the Pao_2 falls to < 60 mm Hg.[51] At this point, any further decrease in Pao_2 causes a marked increase in $\dot{V}E$. However, if CO_2 is added to the inspired gas during testing to cause hypercapnia, then the resultant ventilatory response is markedly increased (Fig 7). Conversely, if the $Paco_2$ is decreased during

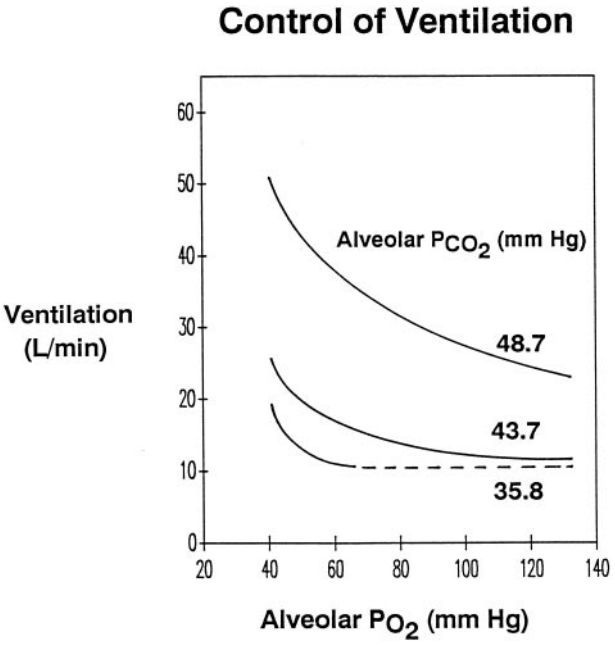

FIGURE 7. Shown are the ventilatory response curves at three different levels of alveolar CO_2. Note that when $PAco_2$ is 36 mm Hg, almost no increase in ventilation occurs until the Pao_2 is reduced to about 50 mm Hg. Reprinted with permission from West.[126]

testing, the ventilatory response to hypoxemia is blunted.[43] The clinician should be alerted when the patient is not dyspneic in the face of significant hypoxemia, particularly when hypercapnia is also present. In these patients, a low ventilatory drive should be suspected, and reversible abnormalities (*eg*, ventilatory-depressant drug use—opiates and sedatives) or hypothyroidism should be considered.

Response to pH

Ventilation is stimulated by a primary metabolic acidosis/acidemia and inhibited by alkalosis/alkalemia (Fig 5). This response is mediated primarily through the peripheral chemoreceptors.[4] At any level of Pa_{O_2}, the carotid body responds to an increase in hydrogen ions by increasing the firing rate of the glomus cells and vice versa. In the clinical setting, hyperventilation in response to metabolic acidosis is easy to overlook. This is because the primary mechanism of compensation involves an increase in VT, which is more difficult to detect clinically than an increase in respiratory rate.

In metabolic alkalosis, respiratory compensation for the increased serum HCO_3^- occurs with a decrease in minute alveolar ventilation. This elevates Pa_{CO_2} to cause a respiratory acidosis, and tends to normalize pH. This compensation is ultimately limited by the carotid chemoreceptors once Pa_{O_2} begins to decrease.[52]

Control of Breathing in Special Physiologic Circumstances

Sleep

At sleep onset, the behavioral and cognitive influences on ventilatory control are largely eliminated. $\dot{V}_E$ and respiratory responses to exogenous (and presumably endogenous) stimuli such as the response to hypoxia and hypercapnia are generally reduced.[53,54] In addition, an increase in airflow resistance typically occurs at sleep onset because of relative hypotonia of the upper airway dilatory muscles.[55] Ventilatory compensation to both added and intrinsic resistance to breathing is also severely reduced during rapid eye movement (REM) sleep; this explains why the majority of sleep-related ventilatory disturbances are most severe during this phase of sleep.[56] These effects are summarized in Table 1. Hypoventilation during slow-wave sleep is a product of a decreased VT and respiratory rate resulting in a 2- to 7-mm Hg increase in Pa_{CO_2} and a reciprocal fall in Pa_{O_2}. A periodic breathing pattern following sleep onset commonly occurs in stages 1 and 2 of sleep. The respiratory pattern is notably most regular in stages 3 and 4.[57] Another notable change related to the sleep state is the marked reduction in skeletal muscle tone during REM sleep, sparing only the diaphragm and ocular muscles. This decreased muscle activity is thought to be caused by REM-related supraspinal inhibition of the alpha motor drive and the specific depression of fusimotor function, causing attenuation of the stretch and polysynaptic reflexes with decreased muscle tone.[58] The diaphragm is relatively spared because it contains very few muscle spindles and is therefore much less affected by these inhibitory impulses.[59] However, during phasic REM sleep, the contraction of the diaphragm becomes uncoordinated (so-called "diaphragmatic fragmentation").[60] In fact, respiration during phasic REM sleep is very irregular and consists of sudden changes in both respiratory amplitude and frequency, which are linked to the rapid eye movements. Sa_{O_2} is also lowest during this period.[61] Ventilation during REM sleep is primarily maintained through diaphragmatic contraction. It follows

Table 1—*Effects of Sleep on Breathing

Characteristics	Slow-Wave Sleep	REM Sleep
Alveolar ventilation	Decreased due to ↓ VT and ↓ F	Variable
Arterial P_{CO_2}	↑ 4–6 mm Hg	Variable
Arterial P_{O_2}	↓ 4–8 mm Hg	Variable
Breathing pattern		
Stages 1 and 2	Periodic	Irregular
Stages 3 and 4	Regular	↑ F plus ↓ VT
Diaphragmatic contraction	No change	No change
Intercostal contraction	↓	↓
Upper airway muscle contraction	↓	↓
Ventilatory response to CO_2	↓	↓
Ventilatory response to hypoxemia	↓	↓
Response to lung afferents	↓	↓
Response to respiratory muscle afferents	↓	↓

*F = respiratory frequency.

that any respiratory impairment in which diaphragmatic dysfunction is prominent (*eg*, paralysis, weakness, or the hyperinflation of severe COPD) can cause severe nocturnal hypoventilation, especially during REM sleep.

Exercise

The usual ventilatory response to exercise is a well-known and extensively studied phenomenon consisting of four phases (Fig 8). However, the exact mechanism involved in the control of this response is unclear. It now seems likely that there are several potential biological control mechanisms, and that a number of them combine together in a complex fashion to coordinate the overall response.

Phase I consists of an immediate increase in baseline $\dot{V}E$ that occurs within seconds of the onset of exercise, preceding any detectable changes in PaO_2 or $PaCO_2$. This response is thought to be neurally mediated by impulses originating from the muscle spindles in the exercising muscles, tendons, and proprioceptors in the joints. There may also be stimuli that originate from a region of the brain rostral to the pons and medulla (possibly the hypothalamus and motor cortex) and operate independently of the other stimuli.[62] This phase is unaltered by carotid body resection, hypoxia, or hypercapnia.[63–65]

Phase II of the ventilatory response to exercise occurs within 20 to 30 s of exercise initiation, an interval that approximates the circulation time for venous blood from the exercising muscles to reach the respiratory centers. This phase consists of a slower and exponential increase in $\dot{V}E$, oxygen uptake ($\dot{V}O_2$), and CO_2 elimination. This increased ventilation lags behind CO_2 production, and consequently the respiratory exchange ratio and PaO_2 decrease in association with an increase in $PaCO_2$ during this period.[66]

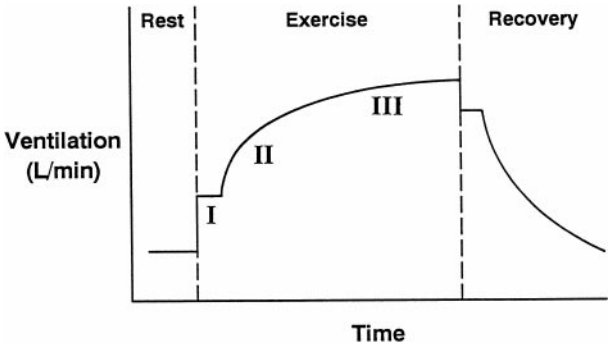

FIGURE 8. The ventilatory response to exercise showing the initial rapid increase that occurs at the onset (phase I), followed by the slower and exponential increase (phase II), the steady state (phase III), and the rapid decrease that occurs with cessation of activity. Reprinted with permission from Wasserman et al.[71]

Phase III of the respiratory response to exercise is a steady state characterized by pulmonary gas exchange that matches the metabolic rate to maintain a stable arterial $PaCO_2$, pHa, PaO_2, and respiratory exchange ratio that are similar to resting values.[67] It normally occurs within 4 min of exercise initiation and is characterized by a generally constant respiratory frequency and VT, and a ventilatory response to exercise that is linearly related to CO_2 output. The magnitude of the steady-state ventilatory response appears to be inversely related to the resting $PaCO_2$, and the lower the $PaCO_2$, the greater the ventilatory response to a given level of exercise. There is little change in blood lactate concentration during this phase. Patients who have undergone carotid body resection show no impairment in their ability to regulate $PaCO_2$ during phase III.[68] Phase III ends once the anaerobic threshold is reached.

Phase IV is the final ventilatory response to exercise. It begins at the point at which the anaerobic threshold is reached. It is also known as the first ventilatory threshold. At this point, oxygen consumption exceeds oxygen delivery, and lactic acid accumulates in arterial blood as a product of anaerobic metabolism. This lactic acidosis produces an exponential rise in $\dot{V}E$, which is usually accompanied by a decrease in $PaCO_2$.[69,70] The second ventilatory threshold is a second nonlinear increase in ventilation that occurs when the subject reaches 70 to 90% of their maximal $\dot{V}O_2$. At this point, ventilation increases disproportionately to both $\dot{V}O_2$ and CO_2 elimination. This threshold is accompanied by prominent arterial hypocapnia until exhaustion finally occurs.[67]

Termination of exercise is associated with an abrupt decrease in ventilation followed by an exponential decay to resting levels. This abrupt decrease is usually of a lesser magnitude than the abrupt increase seen at the onset of exercise. It may be secondary to the removal of neural stimuli from the higher neural centers and exercising limbs, while the slow decay may be related to the removal of the remaining stimuli (hypoxia, hypercapnia, and short-term potentiation) present during steady-state exercise.[67] The measurement of the ventilatory response to exercise is a useful clinical tool that is often used to evaluate the cause of dyspnea or exercise limitation.

Altitude

The ventilatory response to altitude is largely dependent on the degree of altitude and rate of ascent. As altitude increases, barometric pressure decreases; although the partial pressures of oxygen and nitrogen remain unchanged, their absolute pres-

sures decrease. Inspired oxygen tension is 150 mm Hg at sea level and approximately 120 mm Hg at 5,200 feet; thus, the expected arterial Pa_{O_2} decreases from 100 to 70 mm Hg. This mild hypoxemia results in an increase in alveolar ventilation and a lower arterial Pa_{CO_2} (respiratory alkalosis).[71]

Acute mountain sickness may develop following rapid ascent to moderate altitude as a result of hypoxemia that causes cerebral vasodilatation with increased perfusion pressure, leading to the development of cerebral edema. Symptoms include headache, nausea and vomiting, lethargy, and sleep disturbances. Hypoxemia-induced hyperventilation and pulmonary hypertension are probably important in the common complaint of dyspnea at altitude. Twenty-five percent of visitors to Rocky Mountain ski resorts developed symptoms of acute mountain sickness, usually within the first 12 h of arrival. Persons who are younger, are less physically fit, live at sea level, have a history of acute mountain sickness, or have underlying lung problems are more likely to develop this syndrome.[72] Symptoms may be diminished or abolished either by slow ascent, (*eg*, over a 5-day period) or by 2 days of prophylaxis with acetazolamide. This drug induces a HCO_3^- and sodium diuresis, causing a hyperchloremic metabolic acidosis. This leads to compensatory hyperventilation with subsequent improvement in oxygenation and normalization of breathing pattern during sleep.[73]

High-altitude pulmonary edema is a form of noncardiogenic pulmonary edema secondary to hypoxia of high altitudes that may develop in normal subjects without preexisting cardiac or pulmonary disease. It occurs after 6 to 48 h at altitudes of $>$ 8,000 feet and is more common with cold exposure and after exercise. The symptoms of this illness consist of cough, severe dyspnea, chest pain, and fatigue. On examination, these patients may be febrile, tachypneic, tachycardic, and cyanotic; their chest examination may reveal crackles and wheezes. A chest radiograph initially shows prominent pulmonary arteries and patchy, diffuse infiltrates. The ECG shows sinus tachycardia and a right ventricular strain pattern. Pulmonary artery catheterization reveals elevated pulmonary artery pressures, with a low pulmonary capillary wedge pressure. Sa_{O_2} is 40 to 70%, and the mortality rate is 4 to 11%. Treatment is centered on increasing the fraction of inspired oxygen with supplemental oxygen or increasing barometric pressure by rapid descent. Nifedipine, a calcium-channel antagonist, may be utilized in acute treatment and also for prophylaxis in susceptible subjects.[74]

Normal Adaptations to Stress

Important insight into the capacity of the integrated respiratory control system to respond to acute disease states can be gained by experimentally inducing acute respiratory muscle fatigue in subjects with a normal respiratory apparatus. Following a brief interval of breathing against a high resistance, normal subjects develop respiratory muscle fatigue, measured by a reduction in their ability to reach or sustain normal high (negative) inspiratory pressures.[75] When exposed to the stimulus of CO_2 rebreathing while in this fatigued state, these subjects maintain their ventilatory response to CO_2, but do so at lower inspiratory pressures with smaller, more frequent breaths (*ie*, rapid shallow breathing).[75] In addition, if these subjects with experimentally induced acute respiratory muscle fatigue are subjected to heavy exercise, ventilation is also maintained at prefatigue exercise values, but again with smaller, more frequent breaths.[76] This is accomplished by recruitment of abdominal muscles to augment the efforts of the fatigued respiratory apparatus.[77] As can be surmised by this information, these experimental observations correspond to the well-known pattern of rapid shallow breathing and accessory muscle use employed to sustain $\dot{V}E$ in acute asthmatics. Thus, the ventilatory control system rapidly employs a variety of compensatory mechanisms in the service of its ultimate function.

Control of Breathing in Various Disease States

Asthma

Symptomatic asthmatics normally breathe at a normal or increased frequency.[78] Their ventilatory drive (as measured by mouth occlusion pressure) increases during exacerbations, probably in response to the resistive load imposed by increased airflow resistance.[79] This compensation is usually excellent, as most asthmatics hyperventilate during an episode of wheezing with dyspnea. Although asthmatics are usually hypoxemic during attacks, supplemental oxygen does not significantly raise the low Pa_{CO_2}, suggesting that hypoxemia is not the cause of the hypocapnia. The hyperventilation during acute asthma attacks is primarily caused by an increased respiratory rate and is not accompanied by an increased V_T.[79] This is the reverse of the respiratory pattern response seen in asthmatics during bronchoconstriction iatrogenically induced by either methacholine or exercise, where $\dot{V}E$ increases because of increases in V_T alone, with no increase in the respiratory rate. A possible explanation for these

different responses is the presence of severe airway inflammation during an acute asthma attack that is absent in the bronchoconstrictor challenge induced by methacholine or exercise.[79]

The clinical importance of increased respiratory drive in severe asthma is well known to physicians, as the majority of asthmatics have a low $Paco_2$ on presentation for emergency care. A normal or increased $Paco_2$ signifies severe airway obstruction, patient fatigue, and incipient ventilatory failure. These attacks may be fatal and mandate careful observation and monitoring of the patient.

A final issue of potentially life-saving clinical importance is that asthmatic patients with histories of acute asthma and respiratory failure (near-fatal asthma) may have an inherently blunted perception of the resistance to their breathing imposed by worsening bronchospasm. Thus, they are unable to sense when they are reaching the point of critical airflow obstruction.[80] It is of utmost importance that these patients routinely monitor some objective measure of lung function, such as peak expiratory flow rate, to determine when their airflow obstruction is progressing. In this way, they can modify their treatment early and prevent life-threatening exacerbations.

COPD

The clinical importance of the ventilatory response to CO_2 in COPD is illustrated by the following cases of normocapnic vs hypercapnic COPD patients. In this section, we will also discuss several other ventilatory control issues unique to these patients.

Case 5: Severe COPD Without CO_2 Retention. A 50-year-old white woman presented to the pulmonary clinic with complaints of progressive dyspnea on exertion and weight loss for the past 5 years. She denied any cough, phlegm, or peripheral edema. Her medical history was significant for a 60–pack-year history of cigarette smoking. Examination of her chest revealed hyperinflation with poor air entry bilaterally but no wheezing. Extremities showed no clubbing, cyanosis, or edema. Her chest radiograph showed evidence of hyperinflation with bullous changes and a small heart. Spirometry demonstrated an FEV_1 of 0.47 L (18% of predicted) and an FVC of 2.8 L (86% of predicted). Arterial blood gas analysis on room air showed a pH of 7.42; $Paco_2$, 36 mm Hg; Pao_2, 68 mm Hg; and serum HCO_3^-, 24 mEq/L.

This woman has severe COPD, yet nonetheless manages to maintain a normal $Paco_2$ and pH. She can be contrasted to the following patient from our practice.

Case 6: Severe COPD With CO_2 Retention. A 72-year-old white woman with a 40–pack-year history of cigarette smoking presented with cough, increasingly purulent sputum, dyspnea and paroxysmal nocturnal dyspnea, worsening lower extremity edema, and weight gain. Physical examination revealed cyanosis, increased jugular venous pressure, decreased breath sounds, wheezing, prolonged expiration, and bilateral lower extremity edema. Her chest radiograph showed increased bronchovascular markings and an enlarged heart. Spirometry demonstrated an FEV_1 of 0.74 L (31% of predicted) and an FVC of 2.43 L (73% of predicted). Arterial blood gas analysis on room air showed a pH of 7.35; $Paco_2$, 52 mm Hg; Pao_2, 60 mm Hg; and serum HCO_3^-, 29 mEq/L. These values were consistent with a compensated respiratory acidosis.

These cases juxtapose two patients from our practice with severe COPD. The most notable fact is that the first patient (case 5) with the greater airflow obstruction (FEV_1, 0.46 L) has a normal arterial CO_2, while the second, with less severe obstruction (FEV_1, 0.74 L), has hypoventilation and a respiratory acidosis. The causes of hypercapnia in COPD are multiple and complex, and include the degree of airflow obstruction, inspiratory muscle function, the native ventilatory response to CO_2, the coexistence of nocturnal hypoventilation, and other less well-defined features. The most important determinant of arterial CO_2 retention in these patients is the magnitude of airflow obstruction. This has been studied previously in a group of COPD patients.[81] Very few patients with an FEV_1 of ≥ 1 L had $Paco_2$ values > 40 mm Hg. However, this study also demonstrated great variability in the degree of CO_2 retention for any level of FEV_1 reduction of < 1 L. Therefore, the degree of CO_2 retention in patients with COPD with lung function in this range seems to be determined by other factors.

Another possible explanation for chronic hypercapnia is inspiratory muscle dysfunction or weakness in association with an increase in lung resistance.[82] This decrease in inspiratory muscle strength is probably caused by a combination of increased lung volumes together with shortening of the diaphragm and other inspiratory muscles or generalized muscle weakness affecting the respiratory muscles. This combination of inspiratory muscle weakness and increased lung resistance is associated with hypercapnia and may be a protective strategy to avoid overloading the inspiratory muscles, thereby causing fatigue and ultimately irreversible respiratory failure.[83]

One interindividual factor that may contribute to this variable hypercapnia in COPD patients is the native ventilatory response to $Paco_2$. This concept of inherent differences in the ventilatory response to

CO_2 arose from the observation that considerable variability existed in the magnitude of the ventilatory response to experimentally induced increases in arterial P_{CO_2} in normal subjects. In accord with this concept, subjects with high ventilatory responses to abnormal blood gases who went on to develop even severe COPD would adapt to their disease by maintaining normal blood gases by increasing total $\dot{V}_E$, thereby preserving alveolar ventilation and reasonable blood gas values. Those with native low ventilatory responses to CO_2 would, alternatively, adapt to increasing airflow obstruction by tolerating arterial CO_2 retention, and therefore hypoventilate and develop respiratory acidosis. According to this paradigm, COPD patients have been classified into those with high ventilatory responses to abnormal blood gases (type A; pink puffers) and those with low responses (type B; blue bloaters), with additional distinguishing characteristics (Table 2). A genetic basis for attenuated respiratory drive is supported by the observation that adult children of pink puffers have higher ventilatory chemosensitivity than offspring of blue bloaters do.[45]

Another factor that may account for variable arterial CO_2 retention (hypoventilation) in severe COPD patients is a correspondingly variable coincidence of sleep-related hypoventilation: those with the most sleep-disordered breathing having daytime hypoventilation and those with normal ventilation during sleep having the least hypoventilation. In support of this hypothesis, hypercapnic COPD patients have a higher association of sleep-related upper airway compromise compared with those who are eucapnic.[84] In addition, patients with obstructive sleep apnea (OSA) syndrome and concurrent COPD have higher daytime Pa_{CO_2} values than those without COPD.[85] Although we neither perform nor recommend nocturnal polysomnograms in COPD patients *per se*, we try to keep the coincidence of these conditions in mind.

Some COPD patients with CO_2 retention will develop worsening respiratory acidosis when given supplemental oxygen that raises their Pa_{O_2} to > 70 mm Hg, an effect that is usually attributed to the loss of their hypoxic stimulus to breathe. However, reduction in hypoxic ventilatory drive may not be the sole mechanism causing increasing hypercapnia in this group. A second potential explanation for the arterial hypercapnia associated with supplemental oxygen administration in this patient group is worsening $\dot{V}/\dot{Q}$ mismatch resulting in a significant increase in the dead space–to-V_T ratio.[86,87]

$\dot{V}/\dot{Q}$ mismatch occurring under these circumstances may be explained as follows. Before supplemental oxygen use, areas of local alveolar hypoxia produce pulmonary hypoxic vasoconstriction, thereby diverting the flow of CO_2-rich blood from poorly ventilated to better ventilated lung segments. When supplemental oxygen reverses local hypoxemia, pulmonary hypoxic vasoconstriction reverses

Table 2—*Differentiating Features in Advanced Chronic Airflow Obstruction

Features	Type A (Pink Puffer)	Type B (Blue Bloater)
Symptoms	Dyspnea (first and predominant symptom); patients are usually thin, and weight loss is common; minimal or no cough; hyperinflated lung fields; no signs of cor pulmonale	Cough and sputum production with frequent chest infections; stocky build; recurrent or persistent signs of right heart failure
Routine laboratory studies		
Chest radiograph	Hyperinflation; decreased vascular markings	Normal or increased markings at lung bases (so-called dirty-chest appearance)
Arterial blood gases	Mildly reduced Pa_{O_2}; normal or decreased Pa_{CO_2}	Marked reduction in Pa_{O_2}; increased Pa_{CO_2}
Total lung capacity	Increased	Normal or slightly increased
D_{LCO}	Decreased	Normal
Hematocrit	Normal	Increased
Specialized laboratory studies		
Inspiratory resistance	Normal	Increased
Pulmonary compliance	Increased	Normal
$\dot{V}/\dot{Q}$ distribution	Increased V_D/V_T	Increased regions of low $\dot{V}_A/\dot{Q}$
Hemodynamics	Normal or decreased cardiac output Mild pulmonary hypertension	Normal cardiac output Marked pulmonary hypertension
Ventilatory performance and gas exchange during exercise	Increased ventilatory equivalent ($\dot{V}_E/\dot{V}_{O_2}$) D_{LCO} fails to increase normally Decreased Pa_{O_2}; small rise in Pa_{CO_2}	Decreased $\dot{V}_E/\dot{V}_{O_2}$ D_{LCO} increases normally Pa_{O_2} may increase; moderate rise in Pa_{CO_2}
Gas exchange during sleep	Moderate degree of oxygen desaturation	Frequent periods of profound oxygen desaturation

*D_{LCO} = diffusing capacity of the lung for carbon monoxide; V_D/V_T = physiologic dead space ventilation; $\dot{V}_A/\dot{Q}$ = ventilation/perfusion ratio.

and allows for perfusion of very poorly ventilated lung segments, increasing the proportionate amount of dead space and reducing effective alveolar ventilation, thus allowing arterial CO_2 to rise. Finally, $PaCO_2$ may increase with supplemental oxygen administration because of a concurrent decrease of the CO_2 carrying capacity of the hemoglobin molecule secondary to the increasing oxygenation. This results in an altered steady-state relationship between carboxyhemoglobin and $PaCO_2$, which raises the latter by several millimeters of mercury. This is known as the Haldane effect.[88]

COPD patients have an increased neural drive to their respiratory muscles, as measured by surface electromyographic activity of the diaphragm associated with an increased respiratory rate and low VT.[89] This increased drive seems to be greater in hypercapnic COPD patients than in normocapnic patients, and may be related to mechanical (pulmonary and chest wall) and chemical (hypoxic) afferents. This theory is in contrast to the concept of an inherited decreased ventilatory response to CO_2 in patients who develop CO_2 retention.[45] This increased respiratory drive is probably needed to overcome both increased airway resistance and mechanically disadvantaged respiratory muscles. The latter is a product of several factors: flattening of the diaphragm (muscle shortening) causes the muscle to operate on a less favorable portion of its length-tension curve. There is also a decreased radius of curvature of the diaphragm, which requires an increased motor input to generate the same transdiaphragmatic pressure. Lastly, hyperinflation of the lungs and chest wall reverses the normally outwardly directed chest wall recoil forces, which assist inspiration. These factors together contribute to a reduction in inspiratory muscle strength that can be measured as a decrease in the PImax.[83,90] For these reasons, an increased neural drive to breathe is required to maintain the same level of alveolar ventilation in patients with COPD compared with normal subjects.[89]

Obesity-Hypoventilation Syndrome

Obesity-hypoventilation syndrome is another sleep-related disorder affecting the control of ventilation. This is illustrated by the following case history.

Case 7: Obesity-Hypoventilation Syndrome. A 65-year-old woman was evaluated for bilateral knee replacement surgery. During her preoperative assessment, she was noted to be cyanotic with an SaO_2 of 80% by pulse oximetry. The patient admitted to cough, shortness of breath with exertion, and swollen ankles for several years. She had daytime hypersomnolence but was not noted to be a loud snorer. Her medical history included hypertension and gout, for which she was taking medications. She was a nonsmoker and had no previous history of pulmonary disease. On examination, she was 5 feet, 2 inches tall, and weighed 252 lb. Mental status, chest, cardiovascular system, and abdominal examinations were normal. She had 2+ pitting edema of both lower extremities up to the level of the knees associated with venous stasis dermatitis. Initial laboratory data included a hematocrit of 58%; arterial blood gas assessment showed a pH of 7.36; PCO_2, 55 mm Hg; PaO_2, 45 mm Hg; and HCO_3^-, 34 mEq/L. Spirometry showed mild obstruction with an FEV_1 of 1.3 L (70% of predicted) and an FEV_1/FVC of 0.68. A chest radiograph showed prominent pulmonary arteries bilaterally. An echocardiogram showed a severely dilated right atrium and right ventricle with an estimated pulmonary artery systolic pressure of 80 mm Hg. A diagnosis of obesity-hypoventilation syndrome was made. The patient was treated with nocturnal bilevel continuous positive airway pressure (CPAP) ventilation by nasal mask and dramatically improved over a period of 3 months.

Patients with obesity-hypoventilation (pickwickian) syndrome usually have hypersomnolence, daytime hypoventilation, hypoxemia with the development of pulmonary hypertension, and subsequent right-sided cardiac failure.[91] The daytime hypersomnolence is related to their disturbed sleep.[92] These patients have marked depression of both their hypercapnic and hypoxic respiratory drives, accompanied by an abnormal and irregular pattern of breathing during sleep that persists during the waking state.[93] They have an increased respiratory rate (25%) and a decreased VT (25%) compared with subjects with simple obesity. In contrast to subjects with simple obesity, the inspiratory muscles are weak and ventilatory drive is not increased to meet the extra WOB. Both VC and expiratory reserve volume are reduced.[94] The cause of their daytime arterial hypercapnia is believed to be increased mechanical impedance to breathing related to severe obesity combined with a decreased central respiratory drive.[95,96] This daytime hypercapnia differentiates them from OSA patients. Although obesity-hypoventilation syndrome is often associated with OSA or central sleep apnea, this is not always the case; this combination is associated with worse hypoxemia and hypercapnia. The primary treatment involves weight loss combined with improving oxygenation through the use of supplemental nocturnal oxygen and the relief of any concurrent OSA through the use of nocturnal nasal CPAP or tracheostomy.[97,98] Weight loss is effective by reducing the mechanical impedance to breathing. Nasal CPAP alone or bilevel

CPAP ventilation corrects abnormal ventilatory drive and nocturnal hypoventilation with subsequent improvement in daytime blood gases.[99,100] The enhancement of central respiratory drive by drugs such as medroxyprogesterone is sometimes effective.[101]

CSR

CSR is a disorder of breathing pattern characterized by a progressive increase in VT followed by a decrease, occurring in a cyclical pattern associated with intervening periods of apnea. It is a form of periodic breathing that may occur in a variety of situations in adults, such as neurologic disease, congestive heart failure, and ascent to altitude.[102] CSR is illustrated by the following case history.

Case 8: CSR in a Patient With Neurologic Disease. A 68-year-old white man fell off the roof of a barn and landed on his right side. On admission, a CT scan revealed fractures of the right skull base, parietal bone, and zygomatic arch, with a small epidural hematoma. He required a tracheostomy initially for airway protection and ventilatory support, but was weaned off the ventilator 6 days later. He then developed mental status changes and left lower extremity weakness. A repeat CT scan showed a hypodense area in the right temporo-occipital lobe thought to be the result of an ischemic cerebrovascular accident. The patient improved, and his tracheostomy was removed. He was transferred to a rehabilitation program, where desaturation during sleep and breathing pauses lasting up to 23 s associated with a fall in Sa_{O_2} were noted. An overnight polysomnogram demonstrated frequent episodes of central apnea, each associated with significant oxygen desaturation approaching 80%, producing an apnea/hypopnea index of 43/h. Very rare obstructive apneic events and no snoring were noted. A trial of CPAP resulted in no improvement in the frequency or duration of the apneas. Supplemental nocturnal oxygen at 2 L/min markedly improved his sleep-disordered breathing.

This classic case of CSR caused by CNS dysfunction illustrates how a neurologic disease such as a cerebrovascular accident can affect the control of breathing. In this setting, CSR is usually associated with bilateral supramedullary damage in conjunction with a depressed level of consciousness, such as occurs during sleep, sedation, or diffuse cortical injury.[102] Periodic breathing is most obvious during non-REM sleep, and is often misdiagnosed as typical OSA unless a sleep study is performed to differentiate the cause of the irregular breathing.

CSR is also associated with congestive heart failure and an increased mortality in these patients.[103] This may be the result of the associated unusually high sympathetic nervous system activity present during sleep as a consequence of these apneas. When patients with congestive heart failure and CSR are treated with nocturnal nasal CPAP, a significant improvement in left ventricular ejection fraction occurs over a 3-month period, possibly related to an associated decrease in sympathetic nervous activity resulting from the diminution in CSR.[104] This novel treatment remains experimental, as others have not reproduced these findings.[105] Supplemental oxygen may be used as treatment and tends to eliminate or decrease CSR in congestive heart failure by eliminating hypoxemia, which contributes to respiratory cycling.[106]

CSR secondary to heart failure may also be treated with oral theophylline. This results in a significant reduction in the number of episodes of apnea and hypopnea per hour and also decreases the total percentage of sleep time during which Sa_{O_2} is $< 90\%$. These beneficial effects occur without deterioration in sleep quality or increase in ventricular arrhythmias. It is believed that theophylline improves periodic breathing because it competes with adenosine receptors in the CNS. Adenosine is known to be a respiratory depressor.[107] Thus, by inhibiting adenosine receptors, theophylline stimulates respiration and results in a decreased number of central apneas.[108] Although theophylline is a somewhat effective treatment for CSR in heart failure, it is not generally recommended for patients with underlying neurologic diseases because it may induce seizures.[109] Although periodic breathing may not require therapy, treatment is indicated for severe oxygen desaturation or if there is compromise in sleep quality resulting from the arousals that occur during maximal hyperpnea.

Sleep at altitude is associated with periodic breathing.[71] Sleep at an altitude of 14,000 feet was characterized by central apneas in normal subjects in a study investigating sleep and respiratory patterns at sea level and following a stay of several days on a mountain summit.[110] Acetazolamide can be used to reduce periodic breathing at altitude and often results in improved sleep quality. Interestingly, CO_2 will eliminate periodic breathing induced by hypoxia, probably as a result of the elimination of hypocapnia, thus preventing Pa_{CO_2} from falling below the apneic threshold.[111] This has been used in experimental situations only.

Neuromuscular Disease

Neuromuscular diseases are often associated with abnormalities of ventilatory control with associated hypoventilation, particularly during sleep, and a reduced ventilatory response to CO_2 and oxygen.[112] Of

important clinical significance is the fact that patients with certain neuromuscular diseases may have severe derangements in arterial blood gases without impressive symptoms. These patients increase their respiratory rate rather than VT in response to hypercapnia and hypoxemia.[113] This rapid and shallow breathing response is thought to be an attempted compensation aimed at increasing ventilation with minimal increase in the WOB. This is a particularly important feature of patients with chest wall deformities (kyphoscoliosis) in whom thoracic compliance is low. Accordingly, there is a less impressive increase in total alveolar ventilation due to increased dead space ventilation. This is in comparison with the normal response of increased VT in response to hypercapnia or hypoxemia. The tachypnea may then cause worsening respiratory muscle fatigue leading to further reduction in VT. Respiratory failure typically complicates advanced neuromuscular disease by compromising effective respiratory muscle function. Death in these patients is usually caused by progressive respiratory failure and superimposed infections secondary to aspiration as a result of pharyngeal dysfunction. One method of preventing decompensation of alveolar ventilation during sleep is with the use of either nasal bilevel ventilation or through the placement of a tracheostomy and mechanical ventilation.[114,115] This is illustrated by the following case history.

Case 9: Respiratory Failure Due to Duchenne's Muscular Dystrophy. A 24-year-old white man with Duchenne's muscular dystrophy presented with progressive shortness of breath at rest over 2 months. On physical examination, he was tachypneic. Chest examination revealed thoracic spine scoliosis and tachypnea with shallow respiration but otherwise normal breath sounds. He had diffuse muscle wasting and profound weakness of both his upper and lower extremities with pseudohypertrophy of his calves and contractures of his ankles. Arterial blood gas analysis on room air showed a pH of 7.32; $Paco_2$, 79 mm Hg; and Pao_2, 42 mm Hg. His chest radiograph showed mild cardiomegaly with prominent pulmonary arteries and increased vascular markings. Maximum inspiratory force was -25 cm H_2O. A diagnosis of chronic respiratory failure due to Duchenne's muscular dystrophy was made. The patient was treated with nasal bilevel positive airway pressure ventilation during sleep. Two weeks later, arterial blood gas analysis off ventilation improved to a pH of 7.39; $Paco_2$, 55 mm Hg; and Pao_2, 71 mm Hg; his dyspnea at rest resolved. Over the course of the day while the patient was off bilevel ventilation, repeat sequential blood gas analyses showed a rising $Paco_2$, a falling pH, and a slow decrease in Pao_2.

It is now known that nocturnal hypoventilation precedes resting daytime gas exchange abnormalities, probably accounting for the presenting symptoms of disturbed sleep, increasing daytime hypersomnolence, morning headaches, and features of cor pulmonale despite reasonably normal daytime gas exchange.[116] These patients typically have generalized muscle weakness of a proportionately severe degree, including pharyngeal airway dysfunction. Therefore, the impending respiratory failure is a conspicuous, rather than an unexpected, feature of their illness. However, disproportionate respiratory muscle dysfunction with respiratory failure can occur, especially in patients with associated kyphoscoliosis. Regardless of the status of the associated muscle weakness, respiratory failure can be anticipated when the VC falls to $< 55\%$ of predicted, and the maximum inspiratory force falls to $< 30\%$ of predicted.[117] Patients with neuromuscular disease typically have a rapid, shallow breathing pattern with accessory muscle use, especially under respiratory duress.[113] A variety of ventilatory control abnormalities have been suggested in patients with neuromuscular disease.[112] However, as a rule, all important abnormalities in the ventilatory response to blood gases with chest wall mechanical dysfunction and in breathing during sleep are best viewed as a direct consequence of the primary abnormality of respiratory muscle. We routinely follow patients with progressive neuromuscular diseases (*eg*, muscular dystrophy, amyotrophic lateral sclerosis) with spirometry and pulse oximetry, and occasionally obtain arterial blood gases. The onset of symptoms such as dyspnea at rest, disturbed sleep, morning headaches, and daytime hypersomnolence is the usual indication for the initiation of treatment, which is usually bilevel positive airway pressure delivered noninvasively by nasal mask. Ventilatory treatment is initiated empirically and titrated using nocturnal arterial blood gases and pulse oximetry. The commonplace occurrence of a dramatic relief of symptoms as well as improved daytime respiratory function is very gratifying to these patients.[118] In addition, abnormalities of daytime arterial blood gases are frequently reversed by effective noninvasive nocturnal ventilatory support.[114] This occurrence lends some credence to the hypothesis that respiratory muscle fatigue, which has been reversed by "resting" the respiratory muscles at night, is a major factor contributing to the terminal chronic respiratory failure in these patients. Other authors dispute this conclusion with good reason.[118]

Drugs and the Control of Breathing

From a clinical standpoint, the most important classes of drugs that influence ventilatory control are the inhalational anesthetics, narcotics, and minor tranquilizers. Inhalational anesthetics such as halothane, ether, and nitrous oxide cause respiratory depression in normal subjects by decreasing resting $\dot{V}E$ and the response to increasing $PaCO_2$ or hypoxemia.[119] In patients with severe COPD but without CO_2 retention, there is substantially more hypoventilation during light halothane anesthesia than in normal subjects. Characteristically, such COPD patients display a decrease in VT, producing an increase in the ratio of dead space to VT. The degree of hypoventilation in COPD patients is inversely related to preoperative FEV_1.[120]

Narcotics such as morphine, meperidine, fentanyl, and methadone typically cause mild arterial hypercapnia in clinically recommended doses. For example, morphine caused an increase in arterial $PaCO_2$ of 4.0 ± 1.8 mm Hg 45 min after a slow IV injection of 10 mg in normal-sized subjects.[121] Barbiturates have similar but less severe effects, but are comparatively rarely used in recent years. Benzodiazepines (*eg*, diazepam, lorazepam, and midazolam) have respiratory-depressant properties. With oral administration, this effect is usually mild compared with their sedative properties, unless another substance such as ethanol is present concurrently. In one study, both midazolam, 7.5 mg, and diazepam, 5 mg, given orally had no effect on either ventilation at rest or on the ventilatory responses to hypoxia and hypercapnia in normal subjects.[122] Although oral benzodiazepines do not usually cause an increase in $PaCO_2$ in COPD patients, very cautious use is recommended during exacerbations, as hypoventilation may occur. By contrast, when administered parenterally, benzodiazepines suppress ventilatory responses to hyperoxic hypercapnia and isocapnic hypoxia. In a study of patients with COPD, an IV dose of diazepam of 0.11 mg/kg caused a significant decrease in VT, a reduced response to CO_2, and an increased $PaCO_2$ and physiologic dead space ventilation.[123]

Alcohol alone tends to depress the ventilatory response to CO_2 and will shift the response curve to the right. However, $PaCO_2$ remains unchanged unless serum ethanol concentration is > 350 mg/dL.[124]

Respiratory stimulants include doxapram, aminophylline, and progesterone. All increase $\dot{V}E$ and decrease $PaCO_2$.[119] Methylprogesterone can be used to stimulate ventilatory drive in patients with obesity-hypoventilation syndrome.[101] Drugs such as the opioid antagonist naloxone and the benzodiazepine antagonist flumazenil may be used to counter the respiratory depressive effects of these drugs. They are particularly useful in the acute treatment of the overdose patient.[125]

Conclusion

Our knowledge of the control of ventilation is constantly evolving through continued clinical and basic research. Abnormalities of respiratory drive are often overlooked in clinical practice. They should be considered whenever the level of respiratory muscle weakness, intrapulmonary gas exchange abnormalities, or lung mechanical dysfunction cannot explain deranged blood gases. Breathing abnormalities tend to be more severe during sleep than during wakefulness, and they have serious consequences. The effective management of ventilatory control abnormalities has important prognostic implications in the setting of both acute and chronic disease.

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