Control of Breathing

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Abstract

Substantial advances have been made recently into the discovery of fundamental mechanisms underlying the neural control of breathing and even some inroads into translating these findings to treating breathing disorders. Here, we review several of these advances, starting with an appreciation of the importance of $\dot{V}_A$:$\dot{V}CO_2$:$PaCO_2$ relationships, then summarizing our current understanding of the mechanisms and neural pathways for central rhythm generation, chemoreception, exercise hyperpnea, plasticity, and sleep-state effects on ventilatory control. We apply these fundamental principles to consider the pathophysiology of ventilatory control attending hypersensitized chemoreception in select cardiorespiratory diseases, the pathogenesis of sleep-disordered breathing, and the exertional hyperventilation and dyspnea associated with aging and chronic diseases. These examples underscore the critical importance that many ventilatory control issues play in disease pathogenesis, diagnosis, and treatment.

Keywords

- chemoreception
- exercise hyperpnea
- plasticity
- sleep-disordered breathing
- respiratory rhythm generation
- exertional dyspnea
- COPD
- CHF
- aging

The past three decades have seen an explosion of information on the neural control of breathing. The impetus for much of this expansion of both basic and applied research has been the key roles played by the neurochemical control system in several important clinical disorders. These include the highly prevalent problem of sleep apnea, exertional dyspnea in obstructive lung diseases and congestive heart failure (CHF), elevated sympathetic vasoconstriction in cardiorespiratory diseases, and the numerous ventilatory control problems facing intensive care unit practitioners with patients in dyssynchrony with mechanical ventilation, or with CO_2 retention.

In healthy humans, ventilation is tightly controlled by a system that is concerned with both the precise constancy of alveolar and arterial blood gases and acid–base status, as well as with minimizing the work and metabolic cost of breathing. Breathing must remain largely an involuntary act of which we are not made aware. To this end, a three-component system is required, consisting of a pontomedullary rhythm/pattern generator and integrator; extensive sensory and modulatory inputs from peripheral receptors and suprapontine circuits; and, finally, synchronous distribution of motor outputs to respiratory musculature of the upper airway, thorax, and abdominal wall (►**Fig. 1**).

In this review of ventilatory control, we begin with an appreciation of the fundamental relationships of alveolar ventilation ($\dot{V}_A$) and CO_2 production rate ($\dot{V}CO_2$) in the regulation of arterial CO_2 tension ($PaCO_2$). We then discuss key advances in our understanding of the respiratory central pattern generator and chemoreceptor feedback. The application of this basic knowledge is then made to sleep and to exercise, to the plasticity of ventilatory control, and to the failure of homeostatic control of breathing and sympathetic nerve activity in select chronic diseases.

$\dot{V}_A$:$\dot{V}CO_2$:$PaCO_2$ Relationships

Appreciating the role of $\dot{V}CO_2$ and its relationship to $\dot{V}_A$ in the regulation of $PaCO_2$ is fundamental to understanding breathing control, as shown in the following equation, where $\dot{V}_A$ is

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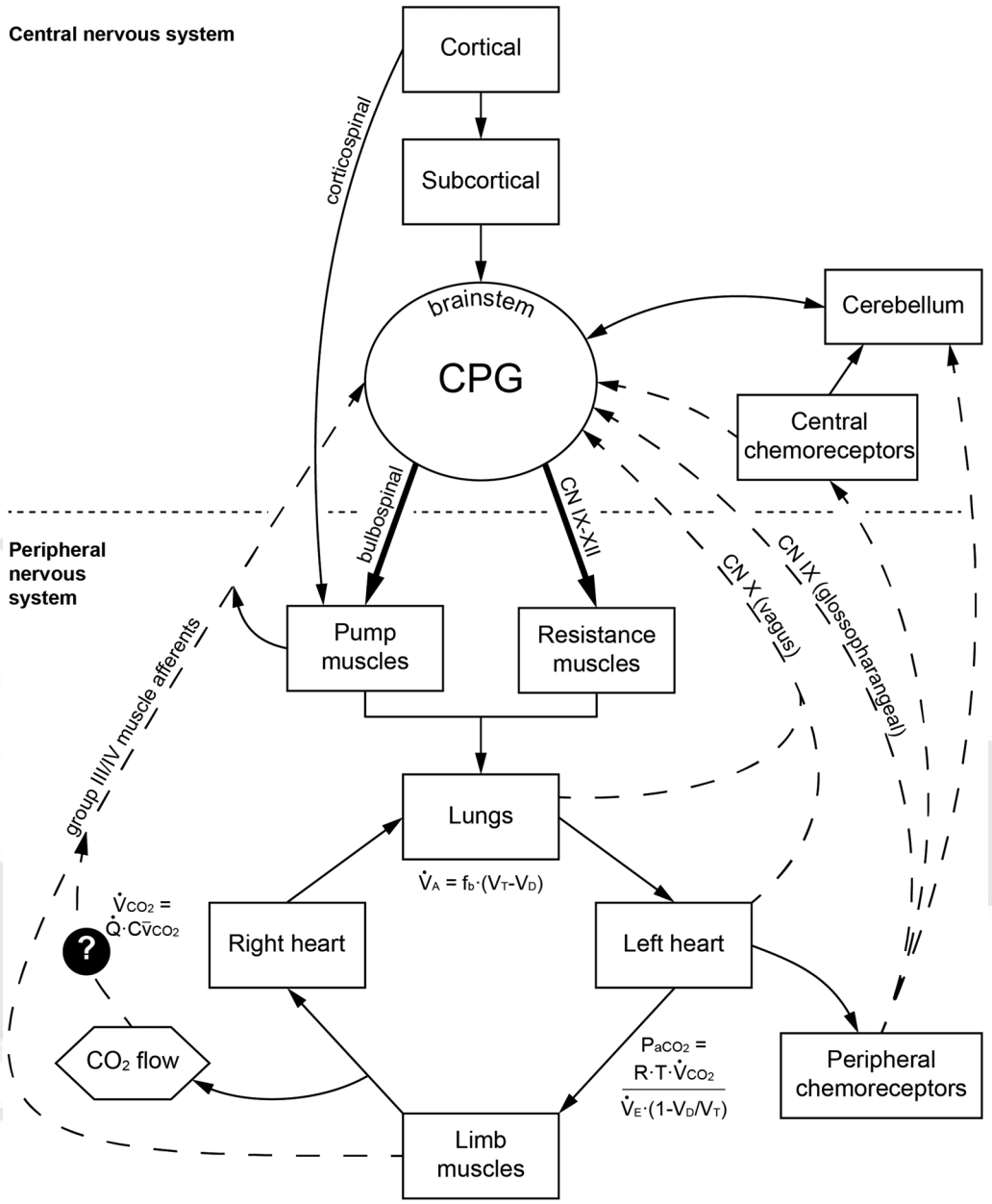

Fig. 1 Schematic outlining of the three-component system for the neural control of breathing, consisting of a brainstem central pattern generator (CPG)/integrator, afferent sensory and modulatory inputs into the CPG, and efferent outputs to muscles of the respiratory pump and airways. The schema illustrates many concepts in the integrated neural control of breathing but is not intended to convey full pathways. Brainstem CPGs (e.g., ventral respiratory group) coordinate respiratory drives to spinal pump muscles (e.g., diaphragm) and upper airway resistance muscles (e.g., genioglossus). Alveolar ventilation ($\dot{V}_A$) is determined by the pattern of respiratory motor output which in turn regulates arterial CO_2 pressure ($PaCO_2$) for a given metabolic rate ($\dot{V}CO_2$). Contracting limb and respiratory muscles activate group III/IV muscle afferents which stimulate breathing. The "vascular distension" hypothesis posits that CO_2 flux to the lung may be detected by changes in cardiac output ($\dot{Q}$) which mechanically activates muscle afferents. Changes in $PaCO_2$ and arterial PO_2 are sensed by peripheral chemoreceptors (e.g., carotid body), whereas central chemoreceptors (e.g., retrotrapezoid nucleus) are sensitive to changes in $PaCO_2$. The respiratory CPG receives many inputs from suprapontine structures such as the periaqueductal gray of the midbrain and the dorsolateral prefrontal cortex. These central neurogenic inputs are associated with behavioral/voluntary control of respiration. The cerebellum receives an array of inputs from the cortex, brainstem, and spinal cord, including chemoafferent neurons, and may be an important site in respiratory learning and memory. $C\bar{v}CO_2$ = mixed-venous CO_2 content; f_b = breathing frequency; V_D = dead-space volume; V_T = tidal volume.

alveolar ventilation, $\dot{V}CO_2$ is the CO_2 exchange at the lung, $PaCO_2$ is the arterial PCO_2, and K is 0.863.

$$P_aCO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} \cdot K$$

Consider the following observations which highlight the importance of these relationships (►**Fig. 2**). The hyperbolic shape of the $\dot{V}_A$:$PaCO_2$ relationship at any given $\dot{V}CO_2$ defines the "plant gain," which indicates system sensitivity to changes in $\dot{V}_A$ (i.e. $\Delta PaCO_2/\Delta\dot{V}_A$). Thus, a given change in

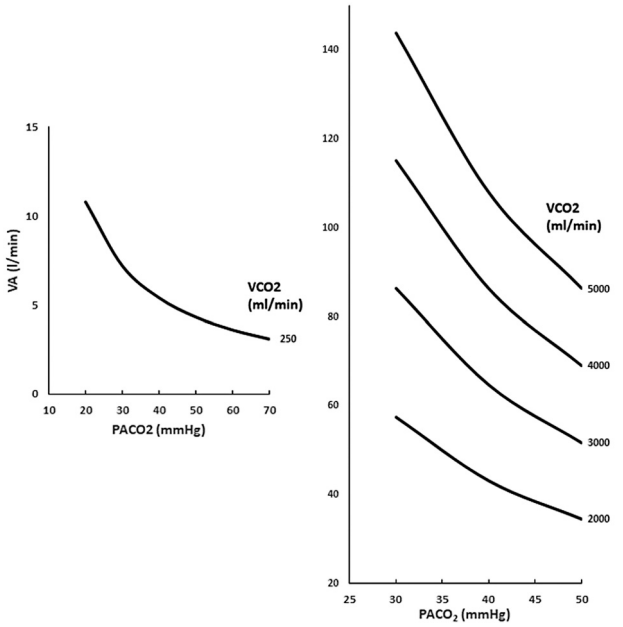

Fig. 2 Hyperbolic relationship of $\dot{V}_A$ to $PaCO_2$ at any given $\dot{V}CO_2$ dictates changing ventilatory requirements for regulating $PaCO_2$ at rest (left panel) and during exercise (right panel). At a normal resting $\dot{V}CO_2$ of 250 mL/min, a $\dot{V}_A$ of 5.4 L/min is required to maintain $PaCO_2$ at 40 mm Hg. $PaCO_2$ will increase to 50 mm Hg with a 1.1 L/min fall in $\dot{V}_A$ and to 60 and 70 mm Hg with only a further 0.7 and 0.6 L/min, respectively, further fall in $\dot{V}_A$. Conversely, lowering $PaCO_2$ by 20 mm Hg from normal requires a twofold increase in $\dot{V}_A$. These requirements for a changing $\dot{V}_A$ for raising and lowering $PaCO_2$ are magnified with increasing $\dot{V}CO_2$ as the hyperbolic slope of $PaCO_2$ to $\dot{V}_A$ steepens. So, for example, at maximal exercise in a normal untrained subject, the compensatory hyperventilatory response required to reduce $PaCO_2$ from 40 to 30 mm Hg would require an additional 21 L/min $\dot{V}_A$ at 3,000 mL/min $\dot{V}CO_2$ vs. 36 L/min at 5,000 mL/min $\dot{V}CO_2$ in a highly trained subject.

$\dot{V}_A$ will elicit relatively large changes in $PaCO_2$ when resting $PaCO_2$ is high (e.g., respiratory failure) and much smaller changes when resting $PaCO_2$ is low. Differences in plant gain of the respiratory control system have substantial clinical relevance. For example, a patient move readily in and out of severe CO_2 retention with only small changes in $\dot{V}_A$, whether these changes are made in total ventilation ($\dot{V}_E$) or in the ratio of dead-space to tidal volume (V_D/V_T). Thus, in severe chronic obstructive pulmonary disease (COPD), CO_2 retention is exacerbated by relatively small decreases in $\dot{V}_A$ resulting from nonuniform ventilation-perfusion ($\dot{V}_A$:$\dot{Q}$) distribution and high V_D/V_T, even at abnormally high levels of neural respiratory drive, tachypnea, and $\dot{V}_E$. Conversely, chronic stimulation of ventilatory drive can relieve all or most of the CO_2 retention via small increases in V_T and $\dot{V}_A$.[1–3] Transient increases in $\dot{V}_A$ during sleep will elicit sufficient transient reductions in $PaCO_2$ to reach the apneic threshold when the baseline, steady-state $PaCO_2$ is normal or high (i.e., high plant gain) but not when the baseline steady-state $PaCO_2$ is low (i.e., low plant gain; see section "Pathogenesis of Sleep-Disordered Breathing"). Third, the slope of the hyperbolic $\dot{V}_A$:$PaCO_2$ relationship steepens with rising $\dot{V}CO_2$ so that any compensatory reductions in $PaCO_2$ during exercise require a much larger increase in $\dot{V}_A$, the higher the exercise intensity and $\dot{V}CO_2$.

These few examples are intended to underscore the importance of considering $\dot{V}_A$:$\dot{V}CO_2$:$PaCO_2$ relationships when assessing the changing requirements placed on the ventilatory control system that have consequences for both the maintenance of blood–gas and acid–base homeostasis and the work of breathing. We will revisit these fundamental concepts as we discuss the mechanisms controlling breathing and breathing stability in various conditions.

Central Rhythm Generation and Integration

As with locomotion and other rhythmic behaviors, the basic breathing pattern is generated within the brainstem without the need for peripheral or suprapontine input. This central pattern generator always features active inspiration, commonly postinspiratory activity, and sometimes active expiration. At the core of the respiratory central pattern generator is the pre-Bötzinger complex (PBC),[4,5] where the inherent rhythm of breathing appears to be dependent on reciprocal synaptic inhibition, in which many PBC neurons become hyperpolarized following inspiratory bursts. In a network which relies on recurrent excitation for inspiratory burst initiation, any change in excitability during the refractory period determines the duration of periods between breaths. Inhibitory neurons active during inspiratory bursts are prevalent within the PBC.[5] Not acting in isolation, the PBC works with other rhythm generators located at the postinspiratory complex and retrotrapezoid nucleus (RTN) of the medulla to produce a synchronous and rhythmic breathing cycle. Importantly, vagal sensory feedback sensitive to lung stretch also shortens the refractory period of inspiratory neurons, thereby facilitating PBC inhibition. Accordingly, vagal blockade in a resting or exercising animal or human prolongs inspiratory time, reduces breathing frequency, and augments V_T.[6,7]

Research into how abnormalities or mutations of medullary neuronal networks responsible for rhythm and pattern generation may impact human disease is underway in animal models of select chronic diseases. Abnormal breathing patterns, often with CO_2 retention and especially during sleep, have been documented in neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis, and post-polio syndrome with bulbar involvement, and are linked to deficits in neurons in the PBC, pontine raphe, and adjacent areas.[8,9] Furthermore, the PBC has been identified as a major site of action mediating the depressive effect of opiate agonists on respiratory rhythm and the reversal of depressive effects via μ-opiate antagonists.[10]

Chemoreceptors

Physiology

Chemoreceptors in both the central (CNS) and peripheral nervous systems serve primarily as feedback "error" detectors that "fine-tune" breathing, regulating arterial blood–gases and pH within normal limits. Carotid chemoreceptors are the body's primary PaO_2 sensor and drive ventilation in a

synergistic manner when hypoxemia is combined with hypercapnia.[11] Carotid chemoreceptors are polymodal receptors that also sense K^+, temperature, osmolarity, norepinephrine, and insulin.[12] Medullary chemoreceptors, principally the RTN, are highly sensitive to changes in brain extracellular fluid PCO_2 and pH.[13]

Both peripheral and central chemoreceptors regulate both sympathetic and phrenic motor nerve activity in response to hypoxemia and hypercapnia. Carotid body (CB) afferents project to multiple sites in the CNS via the nucleus of the solitary tract (NTS). Some NTS neurons relay to the respiratory central pattern generator that determines respiratory motor output, whereas other carotid chemoafferent neurons project to the rostral ventrolateral medulla (RVLM) that determines sympathetic outflow.[14] Additional evidence in rodents reveals differential regulation of respiratory *versus* sympathetic responses via the carotid chemoreceptor.[15] This differential regulation likely explains recent findings in healthy and hypertensive humans which revealed noncongruence in the sensitivity of sympathetic and ventilatory responses to hypoxia or to transient hyperoxia.[16,17]

The *PHOX2B* gene is expressed in an uninterrupted chain of neurons in a circuit that includes the CB, CB afferents, as well as the NTS and RTN; thus, CO_2-sensitive RTN neurons respond to CB stimulation.[18] Evidence obtained using an extracorporeal circuit to perfuse the CB in isolation from the CNS in the unanesthetized canine and goat revealed the functional nature of central and peripheral chemoreceptor interdependence. Inhibition of the isolated CB with hyperoxic, hypocapnic blood caused a marked depression of the central respiratory response to hypercapnia while hypoxemic or hypercapnic stimulation of the isolated CB increased the slope of the central CO_2 ventilatory response.[19–21] This interdependence was also shown in CB denervated humans and canines by a reduced slope of ventilatory responses to inhaled hyperoxic-hypercapnia[22,23] (►**Fig. 3A, B**). These isolated CB preparations revealed that exposing the extra-CB systemic circulation and the CNS to hypoxia (or hyperoxia) while maintaining normoxic/normocapnic tonic input from carotid chemoreceptors elicits hyperventilation in a dose–response manner.[24–27] Furthermore, in awake CB-denervated animals, hyperventilation increases with increasing levels of systemic hyperoxia with reductions in $PaCO_2$ that are likely sufficient to elicit CNS alkalosis.[22,28]

These collective findings have several implications for our understanding of human ventilatory control—especially attempts to quantify separately the sensitivities of central and peripheral chemoreceptors in humans with intact CBs. First, while the ventilatory response to hypoxia requires the presence of intact carotid chemoreceptors, extracarotid chemoreceptor hypoxic stimulation also contributes significantly to the total ventilatory response to hypoxia. Second,

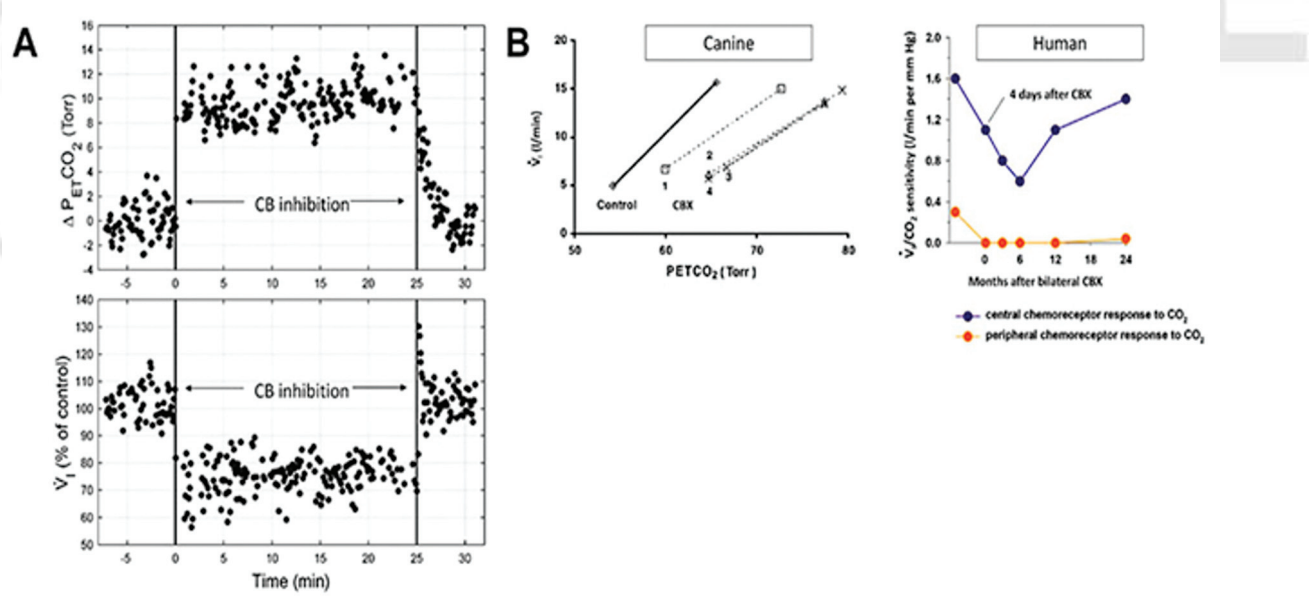

Fig. 3 The hyperadditive effect of carotid body (CB) sensory input on central CO_2 sensitivity is illustrated by two types of findings. (**A**) In awake (or sleeping) canines, one CB was denervated and the remaining CB vascularly isolated from the CNS and perfused extracorporeally. When the isolated CB was inhibited by hyperoxia plus hypocapnia, a marked alveolar hypoventilation and CO_2 retention occurred, which persisted despite substantial, sustained CNS acidosis. Note the immediate 60% increase in $\dot{V}_E$ at minute 25 when the tonic CB inhibition was removed, thereby further revealing the critical dependence of central CO_2 chemosensitivity on CB sensory input. Further experiments showed that the (extra-CB) central CO_2 ventilatory response slope was markedly depressed with CB inhibition and enhanced via CB stimulation using variations in CB PO_2, PCO_2, or their combination (not shown).[19,21] (**B**) In awake humans (right) and canines (left), bilateral CB denervation resulted in significantly reduced ventilatory response slopes to hyperoxic-hypercapnia as determined within a few days following CB denervation.[22,23] Several months following denervation, the "early" peripheral response to CO_2 remains eliminated, but the "late" central CO_2 response has risen to normal levels. These findings confirm those in other species and reveal the importance of quantifying the CB contribution to CO_2 chemosensitivity very early following CB denervation. To date, evidence for hyperadditive interdependence of central CO_2 chemosensitivity on CB input is limited to experimental preparations with physiologic levels of CO_2 chemosensitivity and in which the peripheral and central chemoreceptors are anatomically isolated (see explanation in Smith et al[21]). (Modified from Dempsey and Smith.[102])

the moderate hyperventilation associated with prolonged steady-state hyperoxia in intact animals and humans[28–30] likely reflects the effects of increased reactive oxygen species (ROS) in neural tissue, primarily the brainstem.[27] Third, the common use of hyperoxic CO_2 rebreathing tests to quantify chemoreflex sensitivity in humans reflects both the peripheral and central chemosensitivity, not just the latter as commonly presumed.

Extracarotid Body O_2 Sensors

Recent evidence points to three potential extra-CB sites of hypoxic sensing that might work cooperatively with varying levels of CB sensory input to impact the respiratory and sympathetic networks. First, release of ATP from PBC astrocytes contributes to hypoxic-induced ventilatory and sympathetic excitation via Ca^{2+}-dependent purinergic receptor mechanisms.[27] Second, in the kidney, hypoxia activates the cell bodies of renal afferent fibers which project to the ipsilateral horn of the spinal cord where they synapse with neurons projecting to the NTS and RVLM cardiorespiratory cells.[31] Further, erythropoietin released from the hypoxic kidney has been shown to stimulate the CB to increase ventilation.[32] Finally, sympathetic preganglionic neurons in the isolated thoracic spinal cord of the rodent responded to local hypoxia, triggering increases in sympathetic nerve activity.[33] Given that alterations in extra-CB PO_2 elicit bimodal stimulation of breathing i.e., in both hypoxia and hyperoxia, it is noteworthy that ROS also shows a similar bimodal response in many tissues, including the brainstem.[34,35] Increased ROS activates phospholipase-C and IP_3 receptors, thereby eliciting release of Ca^{2+} and enhancing vesicular release of ATP.[27]

Role of Chemoreceptors in Health

The chemoreceptors' principal role in the control of breathing is as feedback detectors of errors in PCO_2, pH, and PO_2 in the arterial blood, and, to a lesser extent, as contributors to the tonic control of breathing. Use of the isolated CB preparation in unanesthetized canines and humans (►**Fig. 3**) showed that acute, complete inhibition of the CB decreased the tonic steady-state drive to eupneic breathing by 25 to 35%, reflecting the effect of CB sensory input on the respiratory central controller plus its effect on central CO_2 chemosensitivity.

What stimuli comprise the large remaining drive to air-breathing ventilation that so precisely controls the link of $\dot{V}_A$ to $\dot{V}CO_2$ such that $PaCO_2$ varies little with changes in respiratory quotient or body mass, or even with several-fold increases in $\dot{V}CO_2$ and $\dot{V}_A$ during steady-state exercise?[36] Medullary CO_2 chemoreceptors are commonly viewed as major tonic inputs to eupnea, but there are several examples among rodents and other species or with pharmaco-genetic lesioning, in which the hypercapnic ventilatory response is reduced or even negligible while the eupneic air-breathing $PaCO_2$ is normal.[37–39] Acute optogenetic lesioning of RTN CO_2-sensitive neurons resulted in a significant CO_2 retention in the awake rodent, but this was due only to increased breathing frequency and dead-space ventilation with no significant reductions in V_T or $\dot{V}_E$.[40] This tachypneic response is not usually indicative of a chemoreceptor influence. Alternatively, perhaps pulmonary CO_2 exchange itself (i.e., $\dot{V}CO_2$) may be a major source of the "error-free" drive to breathe as is suggested by the precise link of $\dot{V}_A$ to $\dot{V}CO_2$ when venous CO_2 is raised or lowered.[41,42] While the mechanisms of $\dot{V}CO_2$ sensing is unknown, there is convincing evidence in anesthetized canines using separate pulmonary and systemic extracorporeal circulations to show the existence of a vagally innervated CO_2 sensor in the mammal's pulmonary circulation.[43] In this preparation, the ventilatory sensitivity to PCO_2 in the pulmonary circulation approximated that in the arterial systemic circulation. These CO_2 sensitive receptors exposed to mixed venous blood returning to the lung, might be sufficiently sensitive to account for modest changes in $\dot{V}_A$ due to changes in CO_2 flow to the lung.

Role of Chemoreceptors in Chronic Diseases

Accumulating evidence in animal models and human patients over the past two decades has demonstrated highly sensitized carotid chemoreceptors with augmented tonic activity—even in the presence of normal arterial oxygenation—in several disease states. In each of the following cases, this heightened tonic activity is associated with disease exacerbation.

Congestive Heart Failure

In humans with CHF, heightened chemoreflex sensitivity manifests as augmented sympathetic outflow, ventilatory instability, and augmented ventilatory responses to exercise.[44] Experimental heart failure in rats, canines, and rabbits produces carotid chemoreflex hypersensitivity leading to increased tonic levels of sympathetic outflow under normoxic conditions, enhanced sympathetic and ventilatory responses to acute hypoxemia, and vasoconstriction of locomotor muscle vasculature during exercise.[45,46] This form of CB plasticity is critically dependent on increases in locally produced angiotensin II, upregulation of angiotensin II type 1 receptors, increased expression of NADPH oxidase subunits, and enhanced superoxide production.[47] Thus, the CHF-induced increase in CB sensitivity is caused by a shift in redox balance toward oxidative stress. CHF-induced declines in CB blood flow, reduced shear stress, and resultant endothelial dysfunction are likely contributors to CB plasticity in this setting.[48,49]

Hypertension

In human hypertension, augmented neurocirculatory and ventilatory responses to transient hyperoxia provide evidence for tonically elevated chemoreflex drive.[50,51] Blood pressure elevation in the spontaneously hypertensive rat, an animal model of neurogenic hypertension, is dependent on excessive tonic input from the CB.[52] An important role for CB P2X3 receptors in causing chemoreflex hypersensitivity, heightened tonic sympathetic activity, and hypertension in this model has recently been demonstrated.[53] An interesting postulate is that the CB, via its own autonomic innervation, is a target of the widespread increase in sympathetic outflow observed in hypertensive states.[54] This local increase in

sympathetic outflow could have an excitatory effect on the CB, caused at least, in part, by reductions in CB blood flow.[55]

Chronic Obstructive Pulmonary Disease

In patients with COPD, several findings provide evidence for CB hypersensitivity: (1) heightened basal sympathetic outflow, even in the absence of overt arterial hypoxemia[56–58]; (2) larger decreases in ventilation and sympathetic nerve activity during transient hyperoxia and during low-dose dopamine infusion; and (3) augmented increases in ventilation during exposure to acute hypoxia, relative to control subjects.[59] The origins of COPD-associated CB plasticity are unknown; however, COPD may impose an insult analogous to high altitude exposure—that is, continuous hypoxia-induced chemoreflex hypersensitivity leading to high tonic levels of sympathetic outflow and ventilatory instability, especially during sleep.[60,61]

In the chronically hypercapnic and hypoxemic COPD patient with acute exacerbation, even moderate amounts of supplemental O_2 will correct hypoxemia but often lead to worsening respiratory acidosis for multiple reasons. Reduced neural drives to breathe via suppression of high tonic levels of carotid chemoreceptor activity will reduce $\dot{V}_E$ transiently, but in the steady-state of hyperoxia, this reduction in ventilatory drive makes only a minor contribution to the reduced $\dot{V}_A$ and CO_2 retention. C~ The major reason $\dot{V}_A$ is reduced and CO_2 retention occurs with hyperoxia is that hypoxic pulmonary vasoconstriction is inhibited in low $\dot{V}_A$:$\dot{Q}$ areas, thereby diverting blood flow from high $\dot{V}_A$:$\dot{Q}$ areas of the lung and increasing V_D/V_T.[2,62–64] Over reliance on oximetry monitoring of O_2 saturation (SpO_2) can contribute to this problem because respiratory acidosis can develop and worsen via small reductions in $\dot{V}_A$ (►**Fig. 2**) with little detectable change in SpO_2. Rather, frequent monitoring of $PaCO_2$ is important during gradual addition of supplemental O_2.[2]

Renal disease

Several sequelae of chronic kidney disease, such as metabolic acidosis and chronic anemia,[65,66] are potent chemoreflex stimuli. Patients with renal failure exhibit excessive basal sympathetic outflow[67,68] and augmented carotid chemoreflex-induced sympathoexcitation,[69,70] but the mechanisms leading to CB plasticity remain obscure. One potential instigator is increased vasoconstrictor sympathetic outflow to the CB, which is triggered reflexively by activation of renal afferents in response to hemodynamic and/or chemical derangements, including hypoxia in the failing kidney.[71]

Obstructive Sleep Apnea

The cyclical nature of sleep apnea elicits chronic intermittent hypoxemia (CIH; ►**Fig. 4**). ROS are generated primarily during the reoxygenation cycle of CIH, creating an imbalance in pro- versus antioxidant isoforms of the protein, hypoxia-inducible factor-1α (HIF-1α). The resultant oxidative stress increases [Ca^{2+}] which depolarizes CB glomus cells and triggers sensory neuronal activity.[72–74] Thus, in the CB, oxidative stress begets more oxidative stress, leading to enhanced sensory input and oxidative stress in other components of the extended chemoreflex pathway (e.g., NTS and RVLM) which results in increased sympathetic vasoconstrictor outflow and ventilation under baseline normoxic conditions and during hypoxia.

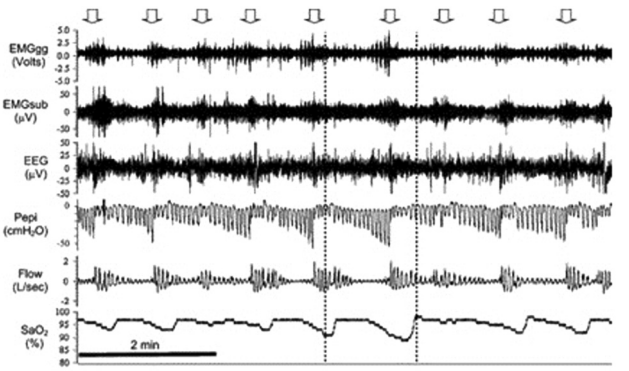

Fig. 4 Polysomnographic tracings of obstructive sleep apnea (OSA) in a patient with severe disease (apnea–hypopnea index = 56 events/hour). Note: (1) the reduction in the upper airway dilator genioglossus muscle EMG (EMG_{gg}) accompanying each airway obstruction; (2) the repeated O_2 desaturations as a result of severely impaired (hypopnea) or absent (apnea) airflow despite continued breathing efforts (P_{epi}); and (3) the cyclical breathing pattern that ensues as the patient oscillates between sleep and transient arousal (downward pointing arrows). (Reprinted with permission from Dempsey et al.[83])

Is Carotid Body Hypersensitization Reversible?

Studies in experimental animals point to potential benefits of strategies aimed at reducing chemoreflex hyperexcitability (e.g., CB resection, exercise training, statins, purinergic receptor blockade). In human CHF, surgical resection of the CB (both bilateral and unilateral) reduced muscle sympathetic nerve activity (MSNA) and produced a modest improvement in quality of life.[75] In patients with drug-resistant hypertension, unilateral CB resection reduced MSNA and blood pressure only in approximately 50% of individuals treated; moreover, these improvements were not maintained at 1-year follow-up.[76]

These observations in animals and humans demonstrate the capacity to eliminate, or at least suppress, excessive chemoreceptor drive, but is bilateral CB resection safe? In Japan,[63] extensive research in patients with asthma who underwent bilateral CB resection to relieve dyspnea suggests that the procedure is relatively benign; however, near-total suppression of the hypoxic ventilatory response persisted in some patients 30 years after resection.[77] Thus, of concern is the possibility that bilateral CB resection could lead to unsafe S_pO_2 levels with air travel, sojourns at high altitude, and via apnea prolongation during sleep-disordered breathing. A more pragmatic treatment would reduce tonic sympathetic hyperactivity while maintaining a normal ventilatory response to acute hypoxia. In this regard, one such treatment shown to be effective in rodents is selective pharmacologic blockade of ATP-gated ion channels (P2X3 receptors) in the CB.[53] The safety and efficacy of this treatment in humans with chronic disease has not been established.

Carotid Chemoreception and the "Silent Hypoxemia" of COVID-19

During the COVID-19 pandemic, many anecdotal reports surfaced of infected patients who were hypoxemic without dyspnea prior to hospitalization, leading to delayed treatment. While dyspnea perceptions have multiple causes with poorly defined central neural pathways, it is generally accepted that dyspnea occurs with dissociation between the "expectations" of the medullary control centers in terms of the ventilation produced for a given drive to breathe, and those outputs that the respiratory system is mechanically capable of producing. This concept of "neuromechanical uncoupling" is supported by experimental evidence demonstrating that when the spontaneous increase in V_T is mechanically constrained during rest or exercise in the face of increased chemostimulation, unpleasant sensations such as "air hunger" or "unsatisfied inspiration" are consistently provoked.[78] Thus, it is important to appreciate that moderate levels of hypoxemia (in the absence of coincident hypercapnia) and the attending hyperventilation, per se, are unlikely to elicit significant dyspneic sensations, as shown in healthy subjects at rest exposed acutely to hypoxic inspired gases or high altitudes.[79] It is more plausible that perceptions of dyspnea in the presence of COVID-19 infection would develop when the raised drive to breathe attending hypoxemia was combined with proinflammatory-induced lung injury which negatively impacts breathing mechanics and raises the work of breathing. Exacerbation of dyspnea might also be expected with lung vascular inflammation due to additional sensory stimulation of the drive to breathe and breathing frequency elicited through lung unmyelinated C-fibers via increases in pulmonary vascular pressures.[80] It has also been suggested that CB sensitivity might be enhanced via COVID-induced inflammation or immune reactions and/or an imbalance of ACE1/ACE2 (angiotensin-converting enzyme) occurring systemically or locally at the CB.[81] If the ventilatory response was coincidentally enhanced, this might be sufficient to promote dyspneic sensations, especially during exercise.

Pathogenesis of Sleep-Disordered Breathing

Sleep renders the ventilatory control system highly vulnerable to disordered breathing by removing the wakefulness drives to breathe, unmasking a critical dependence of ventilatory drive on chemoreception and reducing upper airway dilator muscle tonicity. These fundamental effects of sleep are manifested in cyclical sleep apnea when present in individuals with enhanced controller (i.e., $\Delta\dot{V}_A/\Delta PaCO_2$) and/or plant (i.e., $\Delta PaCO_2/\Delta\dot{V}_A$) gains, and pharyngeal airways susceptible to closure[82,83] (►**Fig. 4**).

Sleep-Induced Suppression of the Wakefulness Drive to Breathe and Ventilatory Stability: The Loss of Vigilance

Regulation of chemoresponsiveness, upper airway patency, and ventilatory stability is dependent on "wakefulness" drives to breathe.[84,85] The origins of these tonic facilitatory drives have been localized to several highly state-dependent areas of the CNS, including (1) orexinergic neurons in the hypothalamus[86,87]; (2) premotor cortex and supplementary motor area neurons[88]; and (3) parallel neuronal systems that link H^+ chemosensitivity to both breathing and arousal.[89,90]

Physiologically, the loss of tonic wakefulness neurogenic drives is manifest throughout sleep in the (1) increased collapsibility of the extrathoracic upper airway due to loss of pharyngeal dilator muscle tone; (2) varying degrees of alveolar hypoventilation secondary to both increased airway resistance and a resetting of the $PaCO_2$ set-point,[91] the latter likely due to NREM sleep-induced reductions in medullary inspiratory neuronal activity[92]; and (3) critical dependence on CO_2 chemosensitivity above and below eupnea on breathing stability. In turn, the breathing instability that occurs during NREM sleep is characterized by repeated, excessive ventilatory undershoots and overshoots (►**Fig. 4**), demonstrating a "loss of vigilance" of the respiratory control system for protecting stability and arterial blood gas homeostasis—characteristics it displays so precisely during wakefulness.

Transient Ventilatory Undershoots and Overshoots

During wakefulness, transient hyperventilation rarely culminates in apnea or hypopnea, but does so consistently and in a dose–response manner in NREM sleep.[93,94] DuBois et al[94] have associated maintained ventilation (i.e., absence of apnea) following active or passive hyperventilation with respiratory-related EEG activity—cortical activity that was absent when apnea was accompanied by hypocapnia. This association suggests a "cortical-subcortical cooperation" to preserve ventilation during wakefulness that would be lost during NREM sleep. Similarly, during wakefulness when inspiratory resistive or elastic loads are imposed on the airway, inspiratory drive is immediately augmented and inspiratory time prolonged to preserve V_T and $\dot{V}_A$. In contrast, during NREM sleep, this immediate load compensation is absent, precipitating a reduced V_T until CO_2 accumulates to such a degree that chemoreceptors stimulate inspiratory and expiratory muscle EMG activity to restore $\dot{V}_E$.[95] Studies in the sleeping canine have shown that apneas following transient hyperventilation require (1) intact carotid chemoreceptors[96]; (2) intact vagally mediated lung stretch receptors[97]; (3) transient hypocapnia acting at both peripheral and central chemoreceptor sites[98]; and (4) a hyperadditive interdependence of central CO_2 sensitivity on peripheral chemoreceptor sensory input.[21]

Transient ventilatory overshoots, on the other hand, commonly occur at the termination of an apnea or hypopnea during sleep due to the synergistic effect of hypercapnia plus hypoxemia acting at the CB and augmenting ventilatory drive. These effects of chemostimulation at apnea termination are further augmented because (1) the drive to breathe following cessation of respiratory rhythm is delayed until $PaCO_2$ rises to a value that exceeds the preapneic eupneic $PaCO_2$[99] and (2) the common occurrence of transient cortical arousals at end-apnea both restores upper airway patency (thereby reducing the resistive load on ventilation) and

substantially augments the prevailing chemosensitive drive to breathe.

In summary, loss of wakefulness drives to breathe in NREM sleep unmask an apneic threshold sensitive to transient hypocapnia plus lung stretch. Equally, a sufficiently brisk synergistic responsiveness to hypercapnic/hypoxemic combinations is retained which, along with frequent transient arousals, mediates transient ventilatory overshoots at apnea termination. These combined effects above and below eupnea promote cyclical ventilatory instability. In phasic REM sleep, sporadic increases in medullary inspiratory neuronal activity augment breathing frequency[85] and oppose the occurrence of both hypocapnia-induced ventilatory undershoots/apneas and chemoreceptor-driven ventilatory overshoots.[100]

Loop Gain and Ventilatory Instability in Sleep

Excessive chemosensitivity to transient increases and decreases in CO_2 contributes importantly to central, obstructive, and mixed repeated apneas and hypopneas in health and in chronic diseases by enhancing the controller, plant, and "loop" gains of the respiratory control system. Loop gain is a dynamic measure of how close the respiratory control system is to instability[101–103] (see details in ►**Fig. 5** legend).

Lowering chemosensitivity/controller gain reduces sleep-disordered breathing instability, as shown via use of nocturnal hyperoxia in CHF patients,[104] and CB denervation or gaseous excitatory neurotransmitter blockade in rodent models of CHF.[105,106] Further, lowering of plant gain via acetazolamide-induced steady-state hypocapnic hyperventilation, or raising inspired CO_2 fraction and $PaCO_2$, reduces breathing instability and central apneas in CHF patients and in sojourners to high altitude, and even obstructive apneas in selected patients with OSA.[61,107–109]

Obstructive Sleep Apnea Links to a Declining Neural Drive to Breathe

Classically, OSA is thought to occur at sleep onset via a state-related decline in pharyngeal dilator muscle tone, precipitating pharyngeal/airway obstruction and hypoxemia. Obstructive apneas elicit a chemoreflex-induced rise in ventilatory drive which usually fails to reopen the airway until arousal occurs, resulting in transient ventilatory overshoots.[110,111] In contrast, several small physiologic studies have demonstrated that variations in neural ventilatory drive can have profound influences on upper airway patency and resistance, with complete airway obstruction occurring at the nadir of diaphragmatic EMG activity or during central apnea in subjects with airways susceptible to collapse[83,112–114] (►**Fig. 6A**). Furthermore, as shown in experimental studies with relatively small number of OSA patients, raising or preventing transient reductions or oscillations in ventilatory drive in many OSA patients (using supplemental CO_2, metabolic acidosis, or hyperoxia) significantly reduces airway obstruction.[109,115,116]

Most recently, Gell and colleagues[117] used multiple electrode high-resolution diaphragm EMG measurements to quantify neural inspiratory drive during sleep in a sample of 50 OSA patients, the majority of who had moderate-to-severe OSA. The authors demonstrated that most of the several hundred obstructive events studied exhibited drive-dependent event pathophysiology, whereby airflow was lost at the nadir of a gradually declining inspiratory drive (►**Fig. 6B**). A decline in genioglossus EMG was also shown to accompany the falling diaphragmatic EMG leading to airway obstruction. These data in a large OSA patient population confirm several prior physiologic studies supporting the importance of neural respiratory drive in the control of upper airway caliber in those with collapsible upper airways. Importantly, these data strongly reinforce the need for in-depth exploration of practical, patient-friendly ways to prevent ventilatory drive decline and instability in OSA without disrupting normal sleep states.

Control of Breathing during Exercise

The ventilatory response to steady-state exercise is characterized by proportional increases in $\dot{V}_A$ and $\dot{V}CO_2$[118–120] (►**Fig. 7**). The exercise ventilatory response must not only regulate $PaCO_2$ in the face of 10-fold increases in $\dot{V}CO_2$ but must also optimize respiratory mechanics to minimize the work, metabolic and circulatory costs of breathing. Below, we briefly describe the neural control of breathing with respect to respiratory muscle $\dot{V}O_2$ (mechanics) and $PaCO_2$ (hyperpnea) regulation during exercise.

Respiratory Mechanics

►**Fig. 8** shows ensemble averaged flow-volume and esophageal pressure-volume relationships during incremental exercise, which can be used to quantitatively assess respiratory mechanics.[118] The exercise ventilatory response is governed by the "principle of minimum effort." As workload increases, inspiratory pump muscles contract more forcefully, generating greater negative pleural pressures, and expiratory muscles are recruited to force air out of the lungs. Thus, increases in V_T are accomplished by lowering end-expiratory lung volume and increasing end-inspiratory lung volume[121,122] (►**Figs. 7** and **8**). This breathing strategy is important for two reasons: (1) increased V_T versus breathing frequency reduces V_D/V_T, thereby improving $\dot{V}_A$, and (2) breathing takes place on the linear portions of the lung and chest wall compliance curves which minimizes the increase in the elastic work of breathing as VT rises. In addition, relaxation of airway smooth muscle due to β_2-adrenergic receptor activation increases airway patency, reduces turbulent airflow, and lowers the resistive work of breathing as flow rate rises. Metaboreflexes from contraction of limb locomotor muscles contribute importantly to this exercise-induced bronchodilation.[123] Thus, in the healthy untrained individual, ventilatory demand rarely exceeds capacity to increase flow and volume, even at maximum exercise (►**Fig. 8**).

Exercise Hyperpnea

Exercise hyperpnea is $PaCO_2$ regulation about its set-point due to proportional changes in $\dot{V}_A$ and $\dot{V}CO_2$ ($\Delta\dot{V}_A \propto \Delta\dot{V}CO_2$). An important feature of exercise hyperpnea is that the gain of the exercise ventilatory response (i.e., $\Delta\dot{V}_E/\Delta\dot{V}CO_2$) is

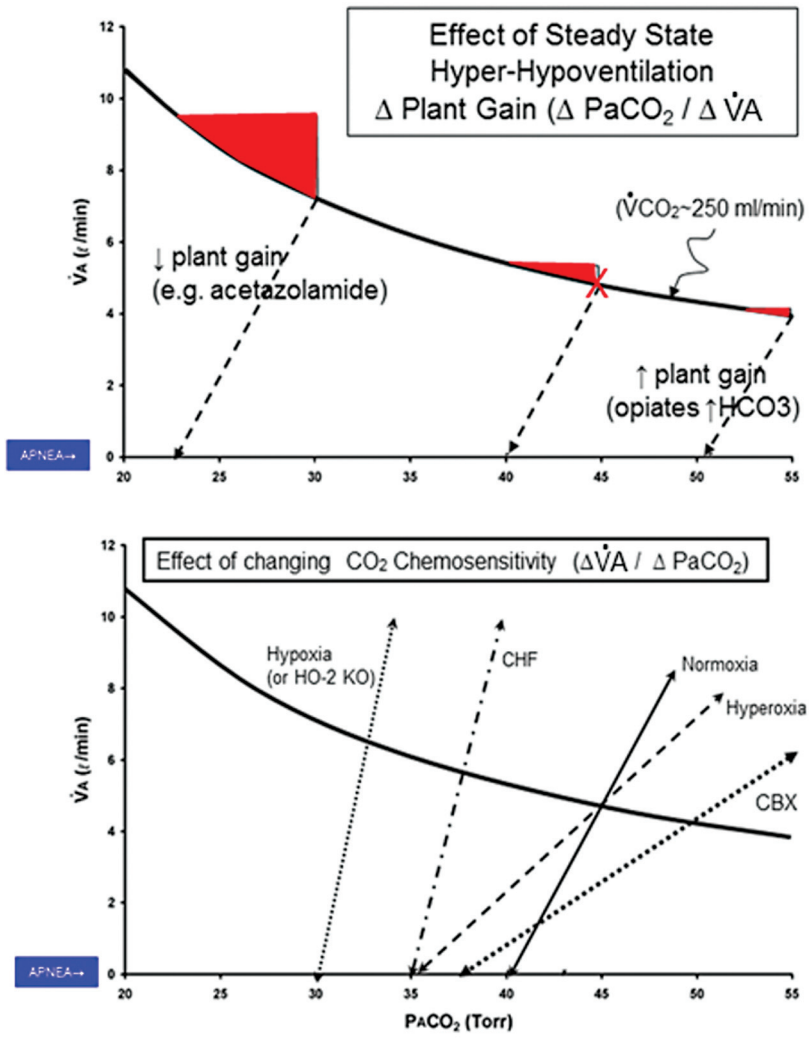

Fig. 5 Diagram of the alveolar gas equation to illustrate the effects of loop gain components on the propensity for apnea and ventilatory instability during NREM sleep. The equation is $PaCO_2 = \dot{V}CO_2/\dot{V}_A \cdot K$, where resting $\dot{V}CO_2 = 250$ mL/min. Each example shown is from an experimental study in sleeping humans or canines in which the apneic threshold and the slope of the CO_2 response below eupnea were measured during NREM sleep using a mechanical ventilator in the assist-control mode to gradually raise tidal volume and transiently lower partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) until apnea occurred. The top panel shows effects of changing "plant" gain—low plant gain means low sensitivity of arterial PCO_2 ($PaCO_2$) response to changes in $\dot{V}_A$ ($\Delta PaCO_2/\Delta\dot{V}_A$) and the opposite is true of high plant gain. In these examples, we have changed plant gain by itself with steady-state hyper- or hypoventilation along the iso-metabolic hyperbola. The red filled-in areas indicate the magnitude of increase in alveolar ventilation needed to transiently reduce $PaCO_2$ sufficiently to reach the apneic threshold. For example, under control conditions in NREM sleep (eupneic $PaCO_2$ ~45 mm Hg, denoted by X), a transient ventilatory overshoot of ~1 L/min is required to reduce $PaCO_2$ ~5 mm Hg to the apneic threshold of 40 mm Hg. With steady-state hyperventilation (e.g., oral acetazolamide; $PaCO_2$, 30 mm Hg), the required transient ventilatory overshoot to achieve apnea ($PaCO_2$, 23 mm Hg) is approximately twice that of control; conversely, with steady-state hypoventilation (e.g., metabolic alkalosis, COPD, opiate use; $PaCO_2$ ~55 mm Hg), the required ventilatory overshoot to achieve apnea ($PaCO_2$ ~51 mm Hg) is about one-third that of control. Not illustrated here are: (1) the effects of transient arousal from sleep, which will increase the magnitude of the ventilatory overshoot above eupnea; (2) reductions in cerebral vasculature CO_2 responsivity as often occurs in congestive heart failure (CHF) which will increase the ventilatory response to transient changes in $PaCO_2$ by allowing changes in brain extracellular fluid PCO_2 to more closely reflect those in $PaCO_2$[210]; and (3) the dynamic effects of lung volume on plant gain. For example, at low lung volumes, plant gain is raised; thus, the CO_2 washout from the alveoli will occur more quickly and will require smaller transient increments in ventilation to reach the apneic threshold.[211] The lower panel shows effects of changing "controller" gain or chemoreceptor sensitivity to $PaCO_2$ ($\Delta\dot{V}_A/\Delta PaCO_2$) above eupnea (which affects the magnitude of the transient ventilatory overshoot) and below eupnea (which affects the CO_2 "reserve" or difference in $PaCO_2$ between eupneic breathing and the apneic threshold). Here the slope of the ventilatory response to CO_2 above and below eupnea represents the controller gain for each condition studied. Note the increased CO_2 response slopes above and below eupnea in CHF and with healthy subjects in hypoxic environments and the reduced CO_2 sensitivity in hyperoxia which is further reduced with carotid body denervation (CBX). K, constant 0.863; PCO_2, partial pressure of CO_2; $\dot{V}_A$, alveolar ventilation; $\dot{V}CO_2$, CO_2 production rate; $\dot{V}_E$, minute ventilation. (Modified from Dempsey.[103])

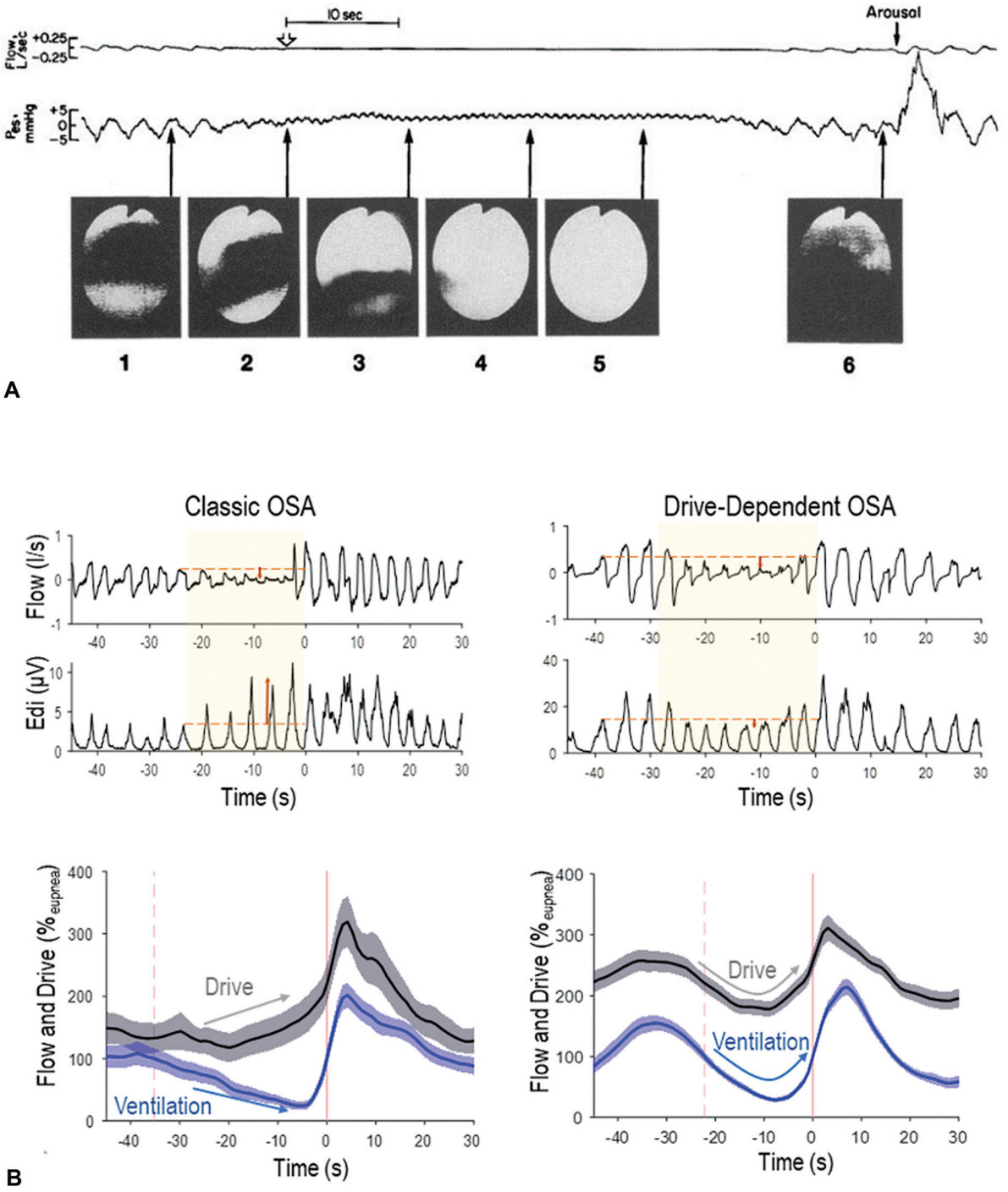

Fig. 6 (**A**) Effects of a spontaneous central apnea on upper airway patency during NREM sleep. Fiberoptic nasopharyngoscopy was used to determine airway dimensions at the level of the velopharynx or oropharynx. Initiation of central apnea occurred at the inverted open arrow with the cessation of both cyclical airflow and esophageal pressure. Complete airway occlusion occurred after ~15–20 seconds of airflow cessation and before an inspiratory effort occurred. Apnea continued and the airway remained closed for another ~35 seconds until inspiratory efforts began and then the airway opened completely with a ventilatory overshoot upon arousal from sleep.[113] (Reproduced with permission from Badr et al.[113]) (**B**) Illustrative examples of classic and drive-dependent obstructive sleep apnea (OSA). The patient with classic OSA (left) experiences a fall in flow to complete obstruction. Diaphragm EMG activity (E_{di}) is unchanged as ventilation falls leading to the obstruction and then rises in response to a falling O_2 saturation over the later stages of the apnea. In contrast, the patient with drive-dependent OSA (right) exhibits a characteristic fall in E_{di} during individual events, as seen in raw EMG signals (top) and in ensemble averaged data (below). Note that the drive-dependent patient shows a fall in drive that is in synchrony with the event-related loss in flow, ending in airway obstruction. Toward apnea termination, E_{di} rises in response to developing hypoxemia. At apnea termination, flow and E_{di} rise together, often augmented via transient arousals. (Modified from Gell et al.[117])

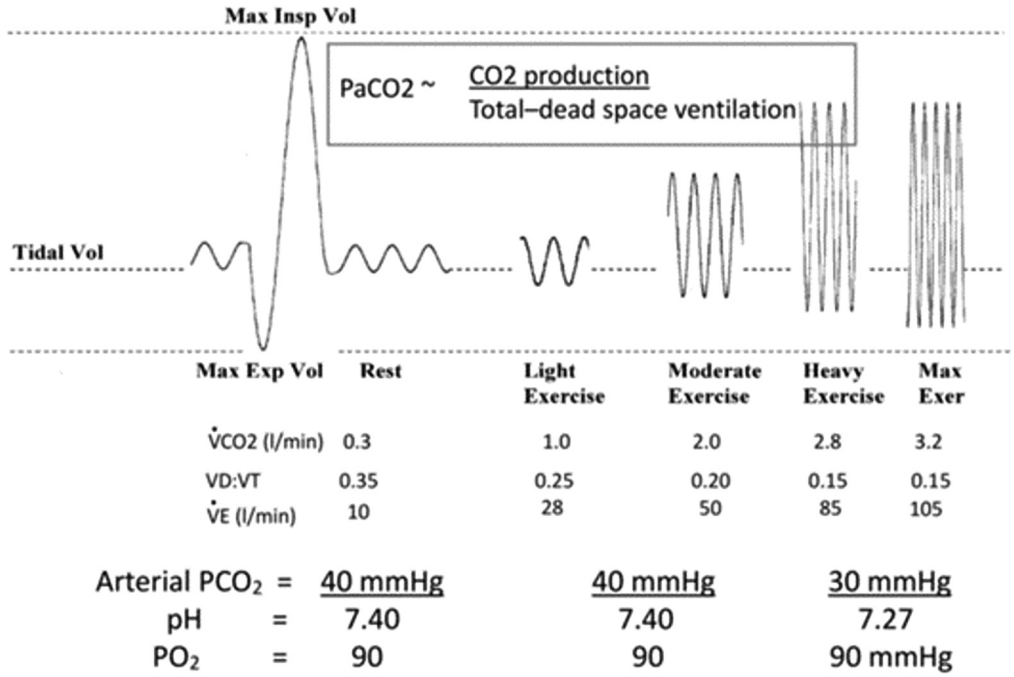

Fig. 7 Description of typical ventilatory and arterial blood–gas responses to steady-state, incremental exercise in untrained young healthy adults (maximal oxygen consumption [$\dot{V}O_{2max}$] ~35–50 mL/kg/min; aged 20–35 years). Note: (1) the incremental rise in tidal volume (V_T) and then breathing frequency (f_b) with inspiratory time (T_i) remaining slightly less than expiratory time (T_e), and the reduction in end-expiratory lung volume; (2) the fall in the dead-space to tidal volume ratio (V_D/V_T) and ratio of minute ventilation to carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$), which maintains the ratio of alveolar ventilation to carbon dioxide production ($\dot{V}_A/\dot{V}CO_2$) and partial pressure of carbon dioxide ($PaCO_2$) near resting values throughout moderate intensity exercise; and (3) the hyperventilatory response to heavy and maximum exercise intensities coincident with the onset of metabolic acidosis. (Reproduced with permission from Dempsey et al.[118])

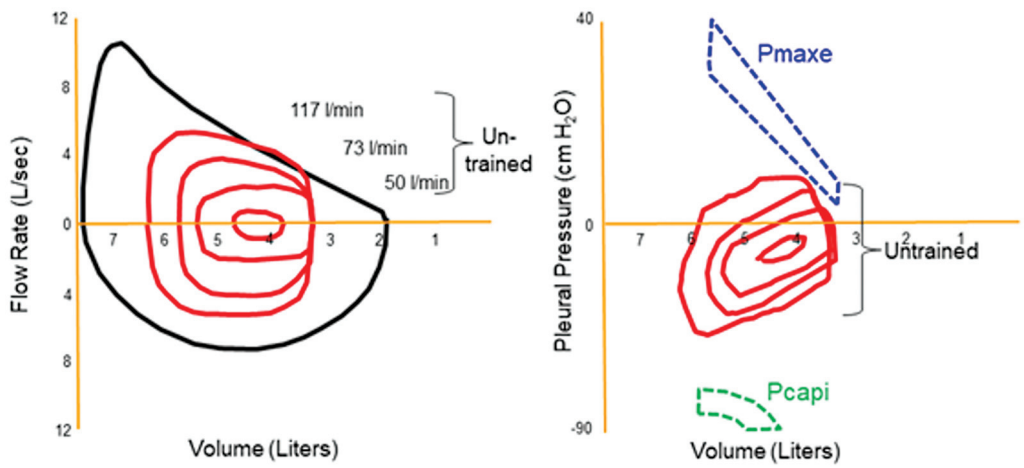

Fig. 8 Mean values for tidal flow-volume and esophageal (pleural) pressure-volume loops during incremental steady-state exercise in untrained young adult males. The maximum voluntary flow-volume loop (shown in black) was determined following exercise. The maximum effective pleural pressure on expiration (P_{maxe}) indicates a range of pressures at which further increases in pressure via expiratory muscle effort elicits dynamic airway compression and no further increase in flow rate. P_{capi} indicates maximum range of dynamic pressures capable of generation by the inspiratory muscles across the various lung volumes and flow rates experienced during exercise. Note that in these untrained individuals ($\dot{V}O_{2max}$ <50 mL/kg/min), (1) the maximum available flow-volume loop significantly exceeds the demand during maximal exercise; (2) the tidal expiratory pressures remain <P_{maxe}; (3) the maximum inspiratory muscle pressures developed during tidal breathing remain <50% of the maximum dynamic pressure available at the flow rates and lung volumes achieved during exercise; and (4) $\dot{V}_E$ averaged 50, 73, and 117 L/min at mild, moderate, and maximum exercise intensities. (Reproduced with permission from Dempsey et al.[118])

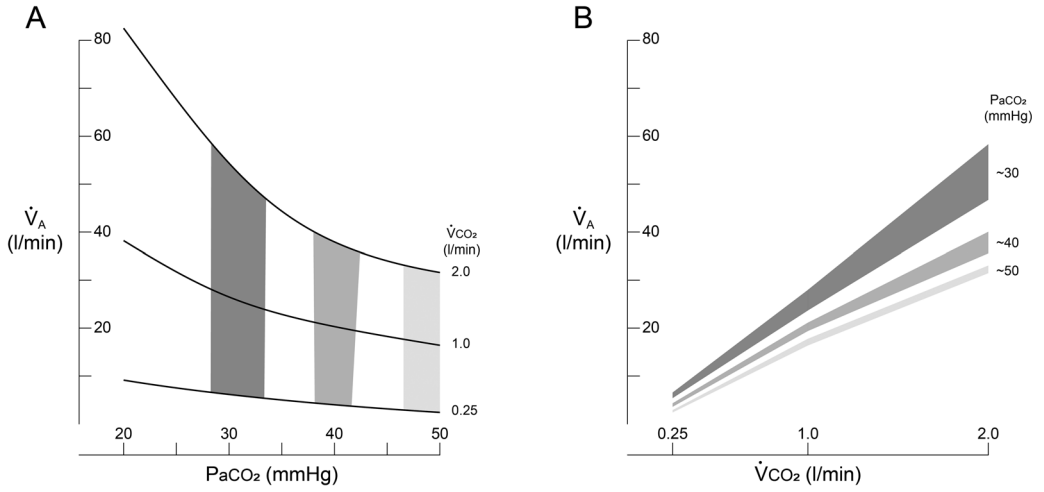

Fig. 9 The eucapnic ventilatory response to exercise is maintained when the resting $PaCO_2$ set-point is altered, by changing the gain of the ventilatory response to increasing $\dot{V}CO_2$. (**A**) The red X denotes the resting $PaCO_2$ (40 mm Hg) at resting $\dot{V}CO_2$ of 0.25 L/min in control and after steady-state hyperventilation secondary to metabolic acidosis or progesterone administration ($PaCO_2$, 30 mm Hg) and hypoventilation via metabolic alkalosis or carotid chemoreceptor denervation ($PaCO_2$, 50 mm Hg). Note (**A**) that during exercise at 2.0 L/min $\dot{V}CO_2$, $\dot{V}_A$ increases: (1) 40 L/min from rest to maintain $PaCO_2$ at its normal resting level of 40 mm Hg; (2) 50 L/min when resting $PaCO_2$ was 30 mm Hg; and (3) 30 L/min when resting $PaCO_2$ was 50 mm Hg. (**B**) The change in $\dot{V}_A$:$\dot{V}CO_2$ slope required to maintain eucapnia at the three resting set points for $PaCO_2$. These experimental results are an example of the strong, precise link of $\dot{V}_A$ to $\dot{V}CO_2$ which prevails in the face of a changing resting $PaCO_2$ and independently of any change in CO_2 chemosensitivity.[36,125]

dependent on the $PaCO_2$ set-point.[124] As shown in ►**Fig. 9**, a low resting $PaCO_2$ brings about a greater change in $\dot{V}_A$ *versus* a high resting $PaCO_2$ for any given $\dot{V}CO_2$ to maintain isocapnia during exercise.[125] These alterations in the slope of $\Delta\dot{V}_A/\Delta\dot{V}CO_2$ with changes in the resting $PaCO_2$ were not attributable to changes in the $\Delta\dot{V}_E/\Delta PaCO_2$ response and occurred even in the absence of carotid chemoreceptors.

It is widely held that the primary exercise stimulus during steady-state conditions is feedforward with respect to $PaCO_2$ regulation. This notion is based on evidence that (1) people with central congenital hypoventilation syndrome (dysfunctional central chemoreceptors) exhibit normal ventilatory responses to steady-state exercise compared with healthy controls[126] and (2) CB denervated humans and ponies exhibit blunted but not significantly impaired ventilatory responses, indicating that CB chemoreceptors "fine-tune" breathing only.[127,128] For the purposes of this review, we shall focus on two feedforward stimuli supported as obligatory to exercise hyperpnea. Further information can be found on this issue in a comprehensive review by Forster et al.[119]

Central Neurogenic

Commonly referred to as "central command," central neurogenic stimuli originate from suprapontine structures, both cortical and subcortical.[129,130] Demonstration of parallel increases in heart rate, blood pressure, and phrenic nerve activity during electrical stimulation of the hypothalamic locomotor region of paralyzed cats provided unequivocal evidence of a central neurogenic component to respiratory control.[131,132] Clever approaches to the study of central command in the genesis of exercise hyperpnea in humans stem from observations of hyperventilation during imagined exercise at rest under hypnosis.[133–135] When brain blood flow was estimated using positron emission tomography, activation of several cortical sites including the dorsolateral prefrontal cortex, supplemental motor area, and sensorimotor areas were markedly increased.[133] The cerebellum also shows increased activation and has been hypothesized to play a major role in respiratory modulation, memory, and learning.[134]

The periaqueductal gray matter region of the midbrain is believed to be an integration center of central neurogenic stimuli due to its functional connectivity to higher brain centers and the brainstem.[136–138] Electrodes implanted in the periaqueductal gray matter of patients who had undergone neurosurgery for pain or movement disorders showed increased activity during mild exercise coincident with small increases in ventilation and heart rate.[139] While there is a large body of evidence supporting central neurogenic stimuli as obligatory to exercise hyperpnea, counter evidence exists from studies in anaesthetized animals and in healthy humans during sinusoidal exercise,[140–142] discussed later.

Peripheral Neurogenic

Peripheral neurogenic stimuli originate from peripheral sensory receptors, not including receptors sensitive to changes in $PaCO_2$ that constitute feedback control. Electrical stimulation of S6-L1 elicits tetanic contractions of hind-limb muscles in anesthetized cats, which reflexly increases heart rate, blood pressure, and ventilation[143] by C-fiber activation.[144] In humans, intrathecal fentanyl (μ-opioid receptor agonist) injections to the lumbar cord partially blocks sensory inputs and blunts the exercise ventilatory response,[145] implying that group III/IV muscle afferents are obligatory to exercise hyperpnea. Alternatively, an argument is made that ventilation is coupled to $\dot{V}CO_2$.[140]

When exercise workload is altered in a sinusoidal fashion, the change in $\dot{V}_E$ and $\dot{V}CO_2$ during each sinusoid is attenuated as the duration of each sinusoid decreases. Because central command and presumably muscle afferent feedback are coalesced with exercise workload, the dissociation between workload and $\dot{V}_E/\dot{V}CO_2$ suggests that CO_2 flow to the lungs ($\dot{Q}.C\bar{v}CO_2$) is a primary, required stimulus to exercise hyperpnea.

In support of this notion, Phillipson et al[41] found that CO_2 loading or scrubbing from the venous circulation of sheep led to proportional changes in $\dot{V}_A$, such that $PaCO_2$ was maintained isocapnic during steady-state exercise. This impressive demonstration is not without limitations, such as the small range of $\dot{V}CO_2$ changes studied. Furthermore, only $C\bar{v}CO_2$ was altered, whereas during exercise $C\bar{v}CO_2$ changes very little, as the major increase in CO_2 flow is determined by an increase in venous return. A further difficulty is the absence of a mixed-venous CO_2 sensor in humans with sufficient gain to explain the substantial hyperpnea associated with exercise. The "vascular distention" hypothesis posits that $\dot{V}CO_2$ is not sensed through $C\bar{v}CO_2$, but via increased $\dot{Q}$, and simultaneous activation of group III/IV muscle afferents.[146,147]

Another plausible theory in support for CO_2 flow as obligatory to exercise hyperpnea was suggested by Yamamoto and Edwards, who also used extracorporeal perfusion in anesthetized rats to demonstrate proportional increases in $\dot{V}_A$ with the rate of femoral vein CO_2 loading, with no appreciable changes in the mean $PaCO_2$.[42] The authors concluded that "temporal fluctuations in the arterial PCO_2 can be sufficient information to signal for the required ventilation." Indeed, breath-to-breath oscillations in arterial pH can be detected at rest and during exercise in humans[148] and the slope of these oscillations increases during exercise in some but not all studies.[148,149] So arterial PCO_2/pH oscillations are amplified during exercise in the presence of constant mean arterial blood–gas values, but no evidence yet exists that any resultant sensitization of chemoreceptor gain will be sufficient to explain a significant fraction of the 10- to 12-fold increases in $\dot{V}_E$ above resting levels required during even moderate exercise.

In summary, the ventilatory response to steady-state mild to moderate intensity exercise is an excellent example of integrated systems symmorphosis. The tight coupling between $\dot{V}_A$ and $\dot{V}CO_2$ ensures arterial blood–gas and acid–base homeostasis, while the mechanics of breathing minimize respiratory muscle work and $\dot{V}O_2$. Exercise hyperpnea remains a phenomenon; however, strong evidence supports central and peripheral neurogenic stimuli, including stimuli linked to CO_2 flow to the lung, as obligatory to its control.

During heavy exercise in health, hyperventilation ensues in part due to chemoreceptor activation caused by metabolic acidosis, increased body temperature, and other humoral stimuli[150] (see ►**Fig. 7**). That locomotor muscle fatigue also contributes to this hyperventilatory response is suggested by the hyperventilation elicited during exercise in the face of partial neuromuscular blockade. This effect is likely due to the enhanced descending central motor drive required to maintain muscle force output in a fatiguing muscle.[151,152] Tonic and phasic activity of accessory inspiratory muscles increases[153] as respiratory muscle $\dot{V}O_2$ approaches 10% of whole-body maximum $\dot{V}O_2$.[154] Should exercise be of sufficient intensity and duration, accumulation of fatigue-inducing metabolites in the respiratory muscles will occur,[155,156] which elicits cardiovascular and hemodynamic adjustments known as the respiratory muscle metaboreflex.[157]

Exercise Hyperpnea: Pathophysiology

In the young healthy adult, the exercise ventilatory response is near perfect in terms of precision in the matching of $\dot{V}_A$ to $\dot{V}CO_2$ and in mechanical efficiency (i.e., work of breathing/respiratory muscle $\dot{V}O_2$; ►**Figs. 7**–**9**). The defining departures from this response with healthy aging or with chronic cardiorespiratory diseases include an imprecision in arterial blood–gas regulation, inefficient breathing mechanics, excessive drives to breathe, and heightened sensations of exertional dyspnea.

Healthy Aging

Normal aging beyond the second decade results in a reduction in the lung and airway's maximal available *capacity* for flow and volume (due primarily to a reduction in lung elastic recoil) together with an increased ventilatory *demand* (►**Fig. 10A**). High pulmonary capillary pressures at any given $\dot{Q}$ (due to an age-dependent reduction in pulmonary vascular compliance), together with a loss of alveolar capillary surface area, results in a rise in $\dot{V}_A/\dot{Q}$ nonuniformity and elevated V_D/V_T at rest and during exercise.[158,159] What are the consequences of this inefficient gas exchange to the healthy, exercising 70-year-old? On the one hand, remarkably, the high V_D/V_T is compensated as total $\dot{V}_E$ is elevated at any given $\dot{V}CO_2$ to maintain $\dot{V}_A$:$\dot{V}CO_2$ proportionality, nearly identical to that achieved in the 30-year-old with much lower V_D/V_T. How might the controller "determine" the fraction of the blood not properly exposed to gas exchanging alveoli and therefore gauge the extent of the V_D? Perhaps in the presence of a high V_D, the lower rate of CO_2 unloading from the pulmonary capillaries to the alveoli may lead to amplified intra- and inter-breath oscillations in $PaCO_2$ which in turn would sensitize chemoreceptor gain (see section "Exercise Hyperpnea"). Alternatively, plasticity in ventilatory control that "somehow" senses a gradually increasing V_D over time may occur with aging (see "Plasticity" section below). Note that concomitant age-associated changes in CO_2 chemosensitivity do not explain this adaptive increase in VE:VCO2 allowing the precise regulation of $\dot{V}_A$:$\dot{V}CO_2$ in the face of a rising V_D/V_T.

At any given exercise $\dot{V}CO_2$, the added ventilatory response combined with the reduced flow-volume capacity with age would appear to enhance the possibility of expiratory flow limitation leading to hyperinflation during exercise. This scenario appears unlikely in non-smoking, sedentary aging individuals whose lungs age coincidentally with reductions in cardiovascular and muscle metabolic capacities which dictate a reduction in maximum $\dot{V}O_2$ (~10%/decade) and, therefore, a similar decline in the maximal demand for ventilation and

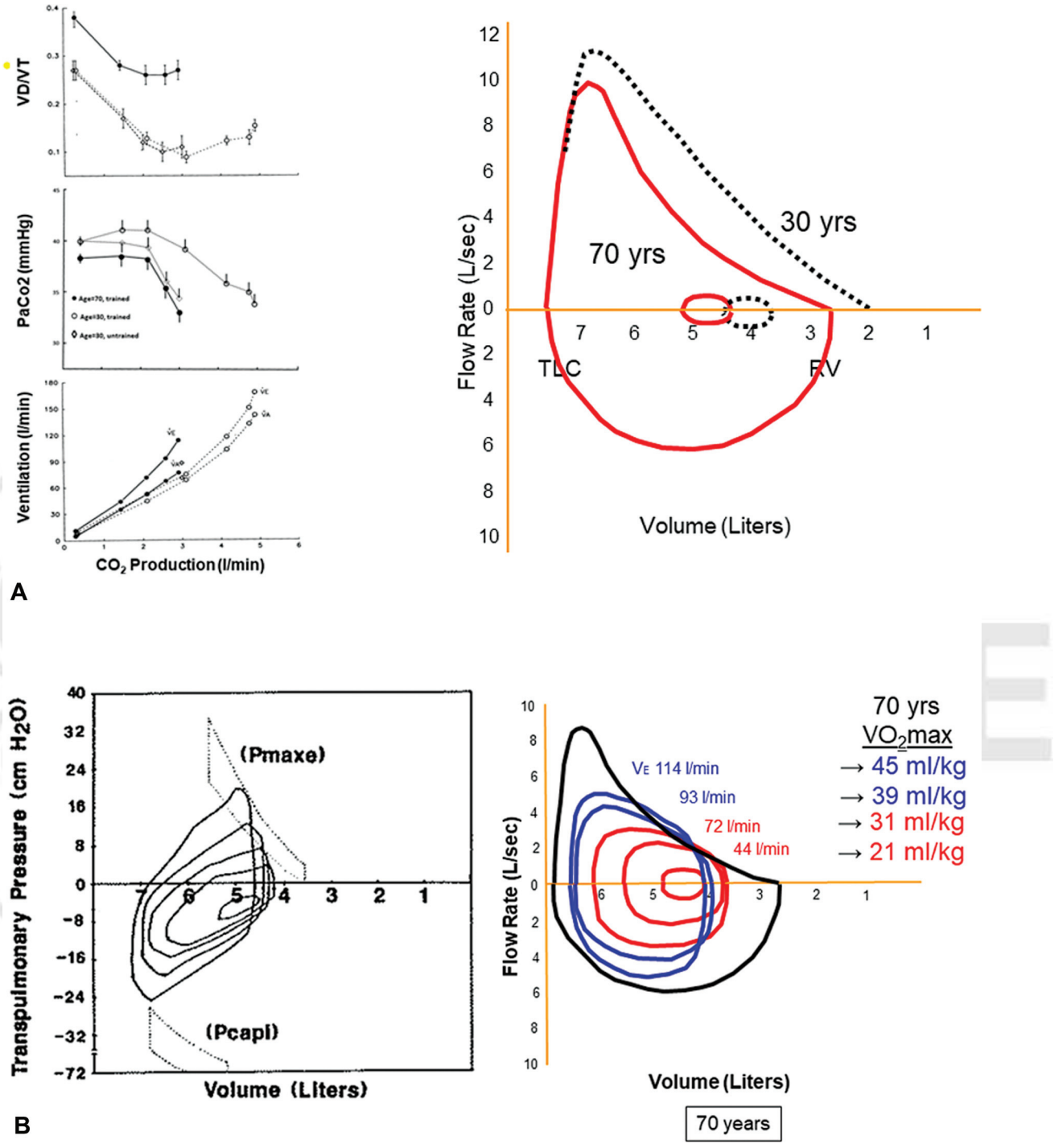

Fig. 10 (**A**) Decreased capacity for maximum flow-volume *vs*. increased ventilatory demand during exercise with healthy aging. The right-hand plot shows the reduced maximum flow-volume loop typical of a healthy, fit, 70-year-old *vs*. a 30-year-old male. The three left plots depict the plasticity in exercise hyperpnea which occurs with healthy aging. Note the higher dead-space to tidal volume ratio (V_D/V_T) at rest and throughout exercise in older *vs*. younger subjects, reflecting age-induced loss of lung elastic recoil and $\dot{V}_A/Q$ nonuniformity. Despite the higher V_D/V_T, alveolar ventilation to CO_2 production ($\dot{V}_A/\dot{V}CO_2$) and arterial CO_2 tension ($PaCO_2$) at rest and throughout exercise were essentially the same in young (untrained and trained) and older (trained) subjects, because minute ventilation to CO_2 production ($\dot{V}_E/\dot{V}CO_2$) was increased in the elderly to precisely compensate for their elevated V_D/V_T. (Modified from Johnson et al.[158]) (**B**) Effect of fitness level on expiratory flow limitation in healthy 70-year-old subjects. The maximum flow-volume loop (shown in black) is that from a healthy, active fit 70-year-old. The minute ventilation ($\dot{V}_E$) and tidal flow-volume loops are those achieved at four levels of maximum O_2 consumption ($\dot{V}O_{2max}$) of 21–31 mL/kg/min representative of sedentary untrained 70-year-olds (in red) and of 39–45 mL/mL/min in highly fit endurance-trained 70-year-old runners (in blue). Note that the maximum ventilatory demand is insufficient to induce flow limitation and hyperinflation in the sedentary 70-year-old but is sufficient in the highly trained 70-year-old. Also note the corresponding pressure-volume loops in the left diagram. Contrast these figures with the flow- and pressure-volume loops attained in young untrained subjects in ►**Fig. 8**, who are at similar $\dot{V}O_{2max}$ and $\dot{V}_E$ as are the trained 70-year-olds but have substantially greater capacities for maximum flow and volume.

pulmonary gas exchange. Accordingly, as shown in ►**Fig. 10B**, the ventilatory demands required at a maximum $\dot{V}O_2$ of 23 to 30 mL/kg/min in the sedentary 70-year-old are not sufficient to elicit flow limitation and excessive respiratory muscle work. However, the highly trained 70-year-old might differ because the age-dependent reductions in maximum $\dot{V}O_2$ (demand) can be markedly attenuated through a habitually active lifestyle. Another determining factor here is that some (but not all) longitudinal aging data show a 15 to 20% less aging-induced decline in forced expiratory volume and forced vital capacity in high *versus* low habitually active individuals.[160–162] Such a positive effect of lifelong activity on lung function would be somewhat protective in moderately fit older individuals, but in many highly trained endurance athletes, significant flow limitation with dynamic hyperinflation, high work of breathing, and severe dyspnea occurs at maximum levels of $\dot{V}O_2$ and $\dot{V}_E$ comparable to those experienced in the sedentary 30-year-old (►**Fig. 10B**). A significant portion of these highly trained older individuals also experience exercise-induced hypoxemia at maximum $\dot{V}O_2$ levels between 40 and 55 mL/kg/min.

Chronic Obstructive Pulmonary Disease

COPD represents an extreme example of a highly compliant lung and a compromised maximum expiratory flow-volume curve which leads to expiratory flow limitation with only modest increases in flow rates above resting levels. The ensuing progressive hyperinflation with mild to moderate exercise appears as the major contributor to dyspnea and exercise limitation.[163] Use of multielectrode diaphragm EMG measurements in patients with COPD of varying disease severity by O'Donnell and coworkers revealed that during exercise, the inspiratory neural drive to breathe and dyspnea ratings are augmented at any given $\dot{V}_E$, culminating in exercise limitation[150] (►**Fig. 11A, B**). The excessive neural drive to breathe during exercise in COPD has multiple well-documented sources, including augmented sensitivities of carotid chemoreceptors and limb and respiratory muscle afferents, plus engagement of pulmonary C-fiber afferents secondary to elevated pulmonary arterial pressures.[58,164,165] In addition, the limb muscle fatigue induced by even mild exercise in COPD[166] would be expected to elevate compensatory central neurogenic inputs to augment the drive to breathe and dyspnea during exercise as more motor units are recruited to maintain force in the failing limb locomotor musculature.[151,152]

Several approaches to reducing the excessive drive to breathe in COPD have resulted in less dyspnea, improved exercise performance, and decreased limb fatigue. First, inhalation of low-density He/O_2 mixtures expands the maximum expiratory flow-volume envelope in most patients, thereby reducing expiratory flow limitation and reducing the

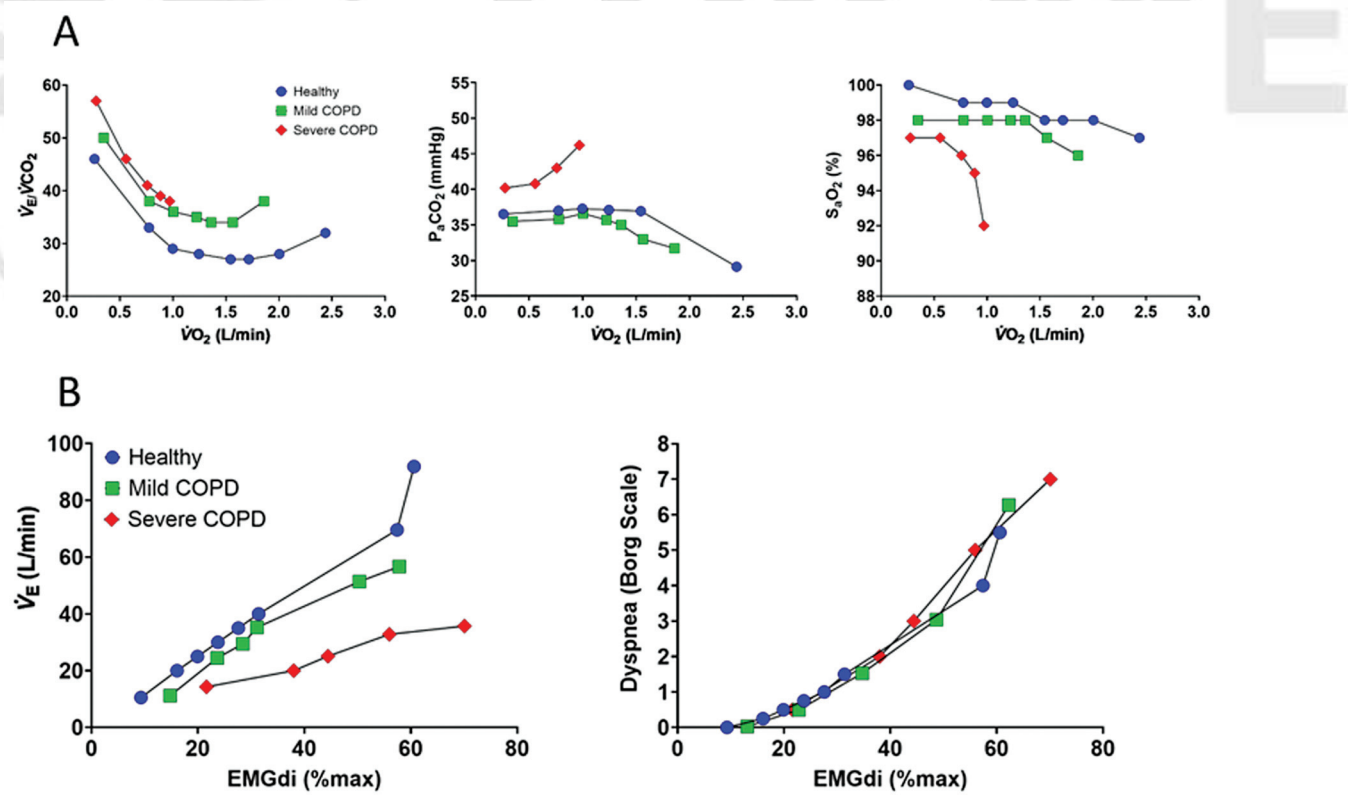

Fig. 11 (**A**) Elevated minute ventilation to CO_2 production ($\dot{V}_E/\dot{V}CO_2$) in mild and moderate chronic obstructive pulmonary disease (COPD) patients during exercise. Arterial CO_2 pressure ($PaCO_2$) is well controlled in most COPD patients, but CO_2 retention commonly occurs in more severe COPD patients as expiratory flow limitation and hyperinflation are exacerbated and the raised $\dot{V}_E/\dot{V}CO_2$ is insufficient to compensate for an elevated dead-space to tidal volume. (Modified from Dempsey et al.[150]) (**B**) Diaphragm EMG (EMGdi), a measure of neural inspiratory drive, is elevated along with dyspnea perception score for any given minute ventilation ($\dot{V}_E$) during exercise in mild and especially severe COPD. (Modified from Dempsey et al.[150]; Despite the differences in lung mechanics among the three groups, the fundamental relationship between the neural respiratory motor output [EMGdi] and dyspnea severity remains similar.)

rate of limb fatigue development during exercise.[166] In turn, the reduced limb fatigue likely results from a lowered work of breathing and attenuated respiratory muscle metaboreflex, thereby increasing blood flow availability to locomotor muscles.[167,168] Second, supplemental inspired O_2 reduced chemoreceptor drive and exercise $\dot{V}_E$, slowed the rate of development of limb muscle fatigue and improved exercise performance.[163,166] Third, inspiratory muscle training was shown to reduce diaphragm EMG activity and dyspneic sensations during exercise.[169] Fourth, intrathecal fentanyl was used to reduce muscle afferent input in COPD patients, resulting in reduced breathing frequency, which in turn reduced dead-space ventilation and total $\dot{V}_E$, flow limitation, hyperinflation, and dyspnea.[165] So, as in healthy individuals, muscle afferent input in exercising COPD patients contributes significantly to exercise hyperpnea, but with a negative, rather than positive influence on exercise performance.[170] Given the diminished aerobic capacity and reduced fatigue resistance of limb locomotor muscles in the sedentary COPD patient,[166,171] specific resistance training of the legs[172] would be expected to reduce stimulation of muscle metaboreflexes and, thus, prevent excessive drives to breathe that evoke tachypneic, hyperpneic, and dyspneic responses to exercise.

Congestive Heart Failure

CHF patients also show excessive neural drives to breathe and occasionally, even oscillatory, periodic breathing during exercise. The severity, efficiency, and stability of their tachypneic hyperventilatory response to exercise is prognostic of morbidity and mortality.[173,174] As with COPD, the major sources of excessive ventilatory drive in CHF during exercise include chemoreceptor sensitization (see "Chemoreceptors" section above), muscle mechanoreceptor sensitization, and pulmonary C-fiber stimulation secondary to high pulmonary capillary pressures and interstitial pulmonary edema.[164] Intrathecal fentanyl administration in CHF patients was especially effective in reducing hyperventilatory responses, thereby demonstrating a major contribution from hypersensitized locomotor muscle afferents to the hyperventilatory response to exercise.[175]

Respiratory Neuroplasticity

Breathing is a vital behavior that must exhibit plasticity—defined as a persistent change in the neural control system (morphology and/or function) based on experience.[176] Plasticity is a fundamental property of robust neural systems to defend homeostasis against threats from recurrent and/or enduring physiological challenges across the lifespan (e.g., exposure to high altitude/hypoxia, injury/disease, aging, weight gain/loss, and pregnancy). Plasticity may occur at any level of respiratory control, including CB chemoreceptors, brainstem central pattern generators, and/or spinal α-motor neurons.[177] Below, we briefly discuss three models of respiratory neuroplasticity: (1) long-term modulation of the exercise ventilatory response, (2) ventilatory acclimatization/de-acclimatization, and (3) respiratory long-term facilitation.

Long-Term Modulation of the Exercise Ventilatory Response

Long-term modulation of the exercise ventilatory response is an example of respiratory neuroplasticity akin to associative learning. Repeated hypercapnic exercise in goats and humans with external CO_2 loading via increased respiratory dead-space or inspired CO_2 elicits hyperventilation during subsequent exercise when the hypercapnic stimulus is removed.[178,179] It stands to reason that error signals detected by chemoreceptors (including the CB and RTN) initiate changes within the CNS that encode the relationship between $\dot{V}_A$ and $PaCO_2$ for a given $\dot{V}CO_2$, possibly from birth.[180–182] Localization of a respiratory memory to the CNS that is developed during periods of learning has not been identified, although we speculate that localization may occur within the cerebellum. It should also be acknowledged that several researchers have failed to replicate long-term modulation in humans,[183,184] likely due to methodological inconsistencies, such as the number of training trials.

Ventilatory Acclimatization/Deacclimatization

Sojourn to high altitude elicits time-dependent hyperventilation over several days, known as ventilatory acclimatization; upon return to normoxia, hyperventilation persists, known as ventilatory deacclimatization.[185,186] Two mechanisms underlying ventilatory acclimatization/deacclimatization are (1) carotid chemoreceptor sensitization and (2) central/peripheral chemoreceptor interdependence.

CB denervation prevents ventilatory acclimatization[187] and isolated CB hypoxia alone (without systemic hypoxemia) elicits similar time-dependent hyperventilation to hypoxemia as in the animal exposed to whole body hypoxia,[188] demonstrating an obligatory role of the CB in ventilatory acclimatization to chronic sustained hypoxia. In anesthetized goats, carotid sinus nerve activity progressively increases during the first few hours of hypoxic exposure, suggesting that the CB undergoes changes in O_2 sensitivity.[189] CB plasticity is believed to be caused by a combination of factors, including upregulation of neuromodulators (e.g., dopamine, angiotensin-II, endothelin-I) and increased protein expression and proliferation of CB glomus cells.[190,191] Recently, HIF-1α has also been identified as a major player in CB plasticity induced by chronic sustained hypoxia exposure.[192]

Ventilatory deacclimatization, on the other hand, may partially be explained by central sensitization of phrenic nerve activity in response to carotid sinus nerve stimulation.[193] The carotid sinus nerve innervates the CB and relays sensory information to the NTS where second-order neurons extend to the RTN of the ventral medulla.[18,194] These CO_2 sensitive neurons increase their activity in response to systemic hypoxia and show no response following CB denervation.[185] Thus, central chemoreceptors located in the RTN are modulated by CB chemoafferent input. The net effect of carotid chemoreceptor activation on central chemoreceptor gain is argued to be hyper additive based on the observation that the CO_2 chemoreflex was enhanced by isolated CB stimulation via hypoxia and blunted by CB inhibition via hyperoxic–hypocapnia[20] (►**Fig. 3**).

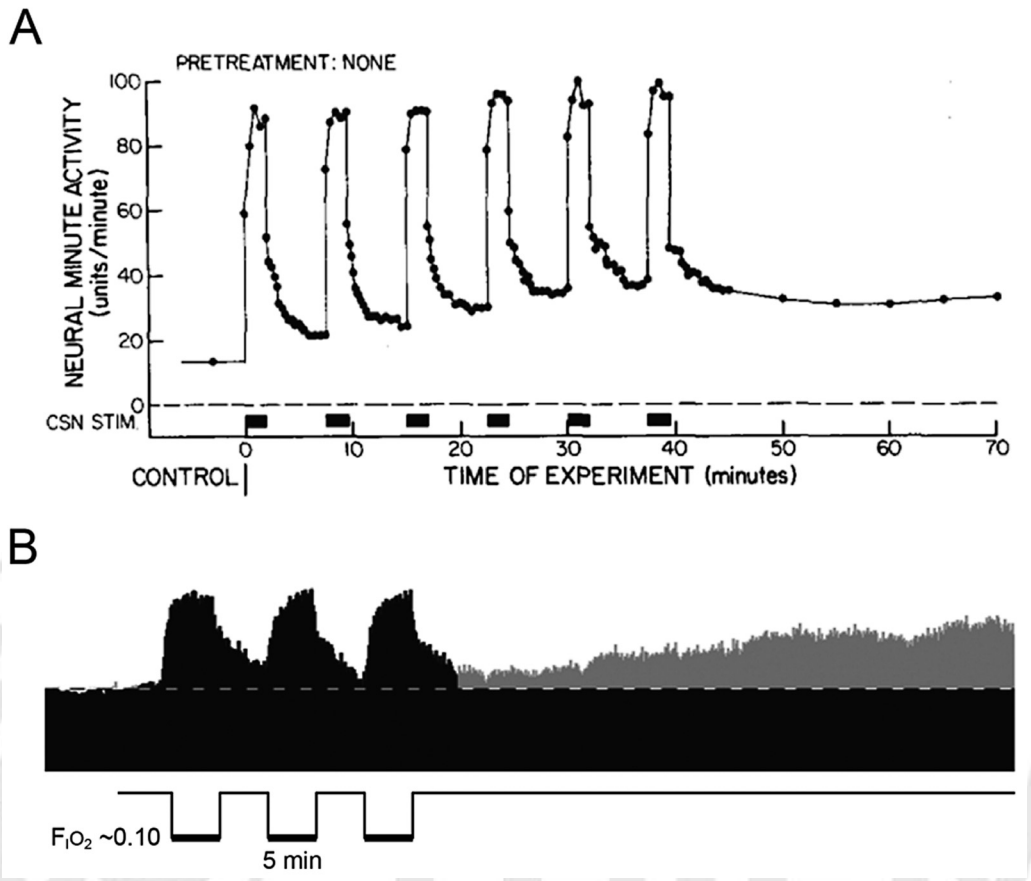

Fig. 12 (**A**) In a paralyzed, anesthetized or decerebrate cat, six 2-minute episodes of carotid sinus nerve (CSN) electrical stimulation were delivered (denoted by thick black bars) followed by 5-minute intervals. The increase in phrenic nerve activity that remained above baseline for ~5 minutes after each stimulation episode is known as phrenic "afterdischarge" or "short-term potentiation," whereas the persistent increase in integrated phrenic nerve activity that lasted up to 30 minutes after the final stimulation episode is a distinct mechanism of plasticity known as long-term facilitation. Modified from Millhorn et al.[186] (**B**) In anesthetized rats, three 5-minute episodes of acute intermittent hypoxia (AIH) were delivered with two 5-minute intervals. The inspired fraction of O_2 (FIO_2) is ~0.10 during episodes of hypoxia; normoxia (FIO_2 ~0.21), or hyperoxia (FIO_2 ~0.50) is often administered during intervals. Note the prolonged increase in raw phrenic nerve activity (shaded in gray), similar to that observed after CSN stimulation in the cat. Phrenic long-term facilitation is a pattern-sensitive, serotonin-dependent, and activity-independent form of spinal synaptic plasticity. (Modified from Devinney et al.[212])

Respiratory Long-Term Facilitation

First demonstrated in 1980 by Millhorn and colleagues,[186] repeated 2-minute episodes of electrical carotid sinus nerve stimulation in anesthetized cats elicited a prolonged increase in phrenic nerve activity that long outlasted the duration of its immediate effects. This form of respiratory motor plasticity, termed "phrenic long-term facilitation," can also be elicited by repeated brief exposures to hypoxia (i.e., acute intermittent hypoxia [AIH]), as shown in ►**Fig. 12**.[195] Moderate hypoxemia ($>$ 35 mm Hg PaO_2) stimulates CB chemoreceptors that activate brainstem raphe neurons to release the neurochemical serotonin. Serotonin binds to 5-HT_2 receptors on phrenic motor neurons which initiates an intracellular signaling cascade involving new protein (brain-derived neurotrophic factor) synthesis and protein kinase-Cθ activation.[196–199] Glutamatergic currents are potentiated through an undefined mechanism that strengthens synapses from pre-motor to α-motor neurons, possibly via NMDA receptor phosphorylation.[200] Consequently, phrenic, intercostal, hypoglossal, and other respiratory motor outputs are enhanced.[195]

Unlike chronic AIH associated with severe sleep apnea, which is known to elicit a plethora of cardiovascular maladaptations,[111] low doses of AIH may have therapeutic benefit.[201,202] While improvements in respiratory and non-respiratory motor function have been observed following therapeutic AIH in people with chronic spinal cord injury, the underlying mechanisms are poorly understood.[203,204] Poikilocapnic AIH does not appear to enhance corticospinal neurotransmission in respiratory nor limb muscles,[205–207] although this remains controversial.[208] Recent work shows that in healthy humans, AIH paired with concurrent hypercapnia (i.e., acute intermittent hypercapnic-hypoxia) enhances the amplitude diaphragmatic motor-evoked potentials induced by transcranial magnetic stimulation, without change in the amplitude of diaphragm potentials evoked by peripheral nerve stimulation.[209] Thus, a central neural mechanism of respiratory motor plasticity was identified. It is unclear if AIH is a viable therapeutic modality to harness respiratory neuroplasticity to restore or enhance breathing in humans.

Summary

We have examined a select few of the essential basic concepts and recent advances in our understanding of the control of breathing in health and disease:

- Quantifying the hyperbolic nature of $\dot{V}_A$:$\dot{V}CO_2$:$PaCO_2$ relationships revealed the importance of both the prevailing $PaCO_2$ and $\dot{V}CO_2$ (i.e., "plant gain") in determining the relative magnitude of homeostatic ventilatory demands.
- Breathing and sympathetic nerve activity are influenced in a feedback fashion via disturbances in O_2 and/or CO_2 acting at the level of the carotid chemoreceptors, at several sites within the CNS and through the interdependence of medullary CO_2 responsiveness on carotid chemoreceptor sensory input.
- Hypersensitization of carotid chemoreceptors plays a significant role in chronically elevated tonic levels of sympathetic outflow and systemic vasoconstriction observed in many chronic diseases, such as CHF, COPD, hypertension, and OSA. Quantifying these increased chemosensitivities as well as constraining the elevated tonic sympathetic activity remains a challenge.
- Descending central neurogenic stimuli from suprapontine structures and ascending neurogenic stimuli from peripheral receptors (e.g., group III/IV muscle afferents) have been identified as obligatory feedforward mediators of the near eucapnic and highly mechanically efficient exercise hyperpnea in health; however, the mechanism(s) underlying the primary, underlying stimulus to breathe (i.e., $\dot{V}CO_2$) remains elusive.
- In healthy aging, COPD and CHF, augmented neural drives to breathe during exercise have been linked to performance-limiting dyspneic sensations and have been identified as originating in hypersensitized chemoreceptors, muscle afferents, and the pulmonary vasculature. Elevated dead-space ventilation in these conditions is also mysteriously linked to an added compensatory drive to breathe.
- The loss of wakefulness drives to breathe during sleep increases susceptibility to pharyngeal collapse and ventilatory instability. Elevated controller and/or plant gains in the system controlling breathing promote centrally mediated ventilatory instability, often leading to airway obstruction (OSA) during decrements in inspiratory neural drive.
- Neuroplasticity in respiratory control is common throughout life with important therapeutic implications and may provide mechanistic explanations for respiratory long-term facilitation and ventilatory acclimatization to hypoxic exposures, and maybe even for exercise hyperpnea.

Conclusion

While substantial insight has been gleaned over the past 30 years into the mechanisms governing respiratory control, several fundamental questions remain which are acknowledged throughout this review. We conclude with a few of these: (1) how is $\dot{V}CO_2$ sensed and how is this information transmitted to respiratory control centers; (2) what is the signal that allows the central controller to determine the fraction of blood leaving the lung not adequately exposed to alveolar gas exchange and then provide an appropriate adjustment to the drive to breathe; and (3) how can we adapt respiratory stimuli and stabilizers to be used in the treatment of OSA? Finally, motivation for further progress may be readily found in the realization that we are still unable to account for a great majority of the drive to breathe during wakefulness, sleep, and exercise, i.e., most of living!

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Conflict of Interest
None declared.

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