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Pathophysiology of human ventilatory control

JA Dempsey[1] and **CA Smith**[1]

[1]John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin – Madison, Madison WI

Abstract

We review the substantial progress recently made in understanding the underlying mechanisms controlling breathing and the applicability of these findings to selected human diseases. Emphasis is placed on the sites of central respiratory rhythm and pattern generation as well as newly described functions of the carotid chemoreceptors and the integrative nature of the central chemoreceptors and the interaction between peripheral and central chemoreception. Recent findings supporting critical contributions from cortical central command and muscle afferent feedback to exercise hyperpnea are also reviewed. These basic principles and the evidence supporting chemoreceptor and ventilatory control system plasticity during and following constant and intermittent hypoxemia and stagnant hypoxia are applied: a) to the pathogenesis, consequences and treatment of obstructive sleep apnea; and b) to exercise hyperpnea and its control and limitations with aging, COPD and CHF.

In healthy humans ventilation is tightly controlled by a system which 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 a breath. 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 central medullary rhythm/pattern generator and integrator, extensive sensory inputs to the central integrator and finally the precise synchronous distribution of motor output to respiratory musculature of the upper airway as well as the chest and abdominal walls. Our understanding of how this is all accomplished with such high precision and efficiency in the healthy human has made significant strides over the past two decades. In this brief review we summarize a few of these accomplishments in the basic science of ventilatory control and how these findings have impacted our understanding and treatment of selected clinical problems.

Central rhythm/integration

The advent of the *in vitro* neonatal rodent brainstem preparation has allowed for precise identification of specific medullary sites for separate but coupled rhythm generation or “oscillators”. These neurons reside in the pre-Bötzinger complex for inspiration and in the parafacial respiratory group (pFRG) for (active) expiration [41]. Of the several models proposed for producing respiratory rhythm the most promising appears to be a hybrid model which combines emergent properties of networks of synaptic connections and intrinsic

Corresponding Author: Jerome A. Dempsey, Ph.D., University of Wisconsin-Madison, 1300 University Ave., Room 4245 MSC, Madison, WI 53706-1532, Tel: 608-263-1732, Fax: 608-263-2582, jdempsey@wisc.edu.

membrane properties of individual neurons together with independent pacemaker– type neurons [118, 119]. In order for the underlying respiratory rhythm to generate a physiologic breathing pattern requires a highly complex coordinated process wherein the premotor and motor respiratory neuronal activities influence the timing and amplitude of a broad array of respiratory muscles including those controlling upper airway resistance as well as the respiratory pump. Research into how abnormalities or mutations of the medullary neuronal networks responsible for rhythm and pattern generation may impact human disease is in its infancy, although abnormal breathing patterns often with CO_2 retention in waking and especially in sleep have been documented in neurodegenerative diseases such as Parkinson's, ALS post-polio syndrome with bulbar involvement and multiple system atrophy and linked to deficits in neurons in the pre-Bötzinger complex, pontine raphe and adjacent areas [2, 99, 114]. Furthermore the pre-Bötzinger complex has been identified as a major site of action mediating the markedly depressive effects of opiate agonists on respiratory rhythm and the reversal of this depressive affect via μ–opioid antagonists [75, 85].

Chemoreception

This past decade has provided the most significant advances in understanding peripheral and central chemoreceptor function since Nobel laureate Heymans discovery of carotid chemoreceptor function in the 1930s [57] and Mitchell and Loeschke's identification of medullary chemosensitive areas in the 1960s [84]. A summary of key developments most relevant to human pathophysiology are as follows.

Carotid body chemoreception

(see Fig 1). We now know that hypoxia triggers sensory input from the carotid body by inhibiting O_2 sensitive potassium channels in the glomus cells of the carotid body acting through several mechanisms, including release of gaseous transmitters (NO, CO, H_2S), AMP activated protein kinases and/or reactive oxygen species [102, 108]. Basic knowledge of these mechanisms will prove invaluable in the pursuit of pharmacological approaches to inhibiting or stimulating carotid chemoreceptor function in some chronic diseases (also see "Plasticity" section below). It is also now clear that carotid bodies are polymodal receptors responsive to several circulating stimuli beyond just O_2, CO_2 and H+ such as K+, norepinephrine, temperature, osmolarity as well as glucose and insulin. Further, reductions in carotid body blood flow (in addition to changes in PaO_2) also provide powerful carotid body stimulation and remodeling over time [30, 74]. On the effector end, in addition to ventilation, the carotid bodies are now well established as key mediators of sympathetic vasoconstrictor outflow and this mediation occurs through medullary pathways that operate independently of the respiratory rhythm generating network [51].

Peripheral/central chemoreceptor interdependence and central chemoreceptors as a site of convergence

Several hydrogen ion sensitive sites in the medulla and midbrain have been identified that stimulate breathing [52, 88]. However the parafacial retrotrapezoid nucleus (pFRG/RTN) characterized by glutamatergic interneurons that strongly express Phox2b are likely to be the

major site of central CO_2 chemoresponsiveness. Phox2b has also been identified as a key gene participating in early embryonic development of the autonomic nervous system [122]. Moreover, a Phox2b mutation has been identified as a predisposing genotype underlying congenital central hypoventilation syndrome (CCHS), wherein severe hypoventilation and apnea routinely attend administration of sedatives and anesthetics or with sleep onset [136]. The RTN chemo sensors also appear to serve as important sites of integration of several stimuli, as these neurons are significantly modulated by inputs from vagally mediated pulmonary stretch receptors and from the hypothalamus[122]. Recent evidence (using c–FOS immunoreactivity) also shows these RTN Phox2b neurons to be activated by acute exercise in the rodent [9] – indirectly suggesting potential participation of the RTN chemosensitive neurons in the "central command" stimulus to exercise hyperpnea (also see Exercise Hyperpnea section below).

The Phox2b neurons are part of an uninterrupted chain of neurons in a circuit that includes the carotid bodies and their afferents as well as the nucleus of the tractus solitarius projections to the RTN [122]. The functional consequences of this linkage are that stimulation of the peripheral chemoreceptors enhances the slope of the central CO_2 ventilatory response; and conversely, inhibition of the carotid bodies reduces the slope of the central CO_2 response [13][1] (see Fig 2:A). Accordingly, when carotid bodies are bilaterally denervated (CBX) in several species – including humans – not only is the hypoxic ventilatory response eliminated (as expected) but in addition the central hyperoxic CO_2 response is also markedly depressed [19, 113]. These findings are clearly inconsistent with the common presumption that hyperoxic CO_2 rebreathe tests selectively test central chemoresponsiveness, *per se*. [31, 109]. Even during normoxic i.e. air breathing conditions, denervation of the carotid bodies or inhibition of the isolated, perfused intact carotid bodies [13, 43] results in substantial hypoventilation and CO_2 retention on the order of +5 to 13 mmHg $PaCO_2$ which persists for days and often weeks following CBX. We believe this substantial contribution of the carotid body to eupneic breathing represents not only a contribution of tonic activity from the carotid bodies to medullary rhythm generating neurons but also the powerful interactive effects of chemoreceptor input on RTN CO_2 responsive neurons. The central projections of the carotid chemoreceptors to the hypothalamus and specifically to the paraventricular nucleus (PVN) may also be of significance as shown by the depressed sympathetic and phrenic nerve responses to acute carotid body stimulation achieved by blocking or lesioning neurons in these regions [110].

So we can no longer view either the peripheral or central carotid chemoreceptors as "stand-alone" receptors responding only to changes in their immediate environment (see Fig. 2:B). Further, the carotid bodies are not just reflex O_2 sensors – rather they appear to provide a nonspecific tonic afferent input that sensitizes – through multiple CNS pathways – respiratory pattern generating medullary neurons.

[1]Other views using other preparations with isolated carotid and/or brainstem perfusions also show an interdependence between the chemoreceptors but opinions vary as to whether this interdependence is hypo- or hyperadditive in its effect on ventilation and central respiratory drive [32, 125, 143].

Plasticity/after effects of sustained chemoreceptor activation

Substantial evidence has accumulated to demonstrate that the ventilatory control system is highly plastic in response to chemoreceptor stimuli. For example, with hypoxia-induced chemoreceptor stimulation three types of post stimulus after-effects and plasticity have been observed. First, an acute short-term potentiation (STP) occurs as manifested in a slowly declining hyperpnea persistent over several seconds following withdrawal of carotid body simulation [38] – a centrally mediated output that provides a stabilizing effect to breathing pattern following transient ventilatory overshoots – especially in sleep [8]. Secondly, a time–dependent hyperventilation and increased sympathetic nerve activity occurs over hours and days in the face of sustained hypoxic exposure which is mediated primarily by increasing carotid sinus nerve output from the carotid body– a chemosensitization which begins within a few hours of hypoxic exposure [90] and which coincides with increased protein expression and multiplication of O_2 sensory glomus cells of the carotid body [133]. Thirdly, upon reversal of the sustained hypoxic stimulus via acute normoxia or even hyperoxia, hyperventilation and the increased sympathetic nerve activity continue, declining only very slowly over several days [27, 53].

In order to explain the persistent hyperventilation and excessive sympathoexcitation following removal of the hypoxic stimulus requires some type of ongoing “central” stimulating effect resulting from the prolonged chemoreceptor input. Accordingly, central sensitization of phrenic nerve activity in response to augmented carotid sinus nerve input has also been shown to occur during prolonged hypoxic exposure [33] and this might be explained, at least in part, by sensitization of central chemoreceptors by heightened carotid body input (see Fig. 2). In addition, acute CNS hypoxia, *per se*, especially in the presence of normal tonic input from the carotid chemoreceptors causes a tachypneic hyperventilation and increased sympathetic nerve activity in unanesthetized canines and goats [18, 29, 40] – an effect which likely reflects the balance struck between hypoxic-induced inhibition vs. excitation of different groups of medullary and hypothalamic neurons [89]. Sensitivity of the CNS hypoxic sensitive neurons appears to be enhanced after a few days of hypoxic exposure [92].

Plasticity/after-effects of intermittent hypoxia (IH)

Following even very brief periods of intermittent hypoxia interspersed with normoxia, hyperventilation and increased sympathetic activity are sustained over an hour or more i.e. so called long term facilitation [83]. Several mechanisms appear to contribute to the sustained activity following removal of the chemoreceptor stimulus. First, with brief intermittent hypoxia, carotid sinus nerve activity stayed elevated upon return to normoxia; no morphologic changes at the level of the carotid body were apparent. Increased reactive oxygen species and inflammatory cytokines have been implicated in the sustained carotid body sensitization [104]. Increased carotid body AT1 receptors have also been shown to result from prolonged intermittent hypoxia and in animal models of CHF [80]. In turn, the carotid body sensitization in CHF models has been attributed to reduced cardiac output and reduced carotid chemoreceptor blood flow (i.e. “stagnant” hypoxia) [30]. Secondly, central adaptive responses also occur following intermittent hypoxia as seen in the persistent elevation of tonic hyperactivity of neurons of the level of the paraventricular nucleus (PVN)

[115] and the RVLM [116]. This after– effect phenomena in the CNS likely contributes significantly to the daytime elevation of sympathetic activity and the hypertension observed during the daytime in patients with OSA and nocturnal intermittent hypoxia [28].

Given these recent understandings of the mechanisms underlying these types of enhanced chemosensitivity and their after-effects on ventilation and sympathetic activity further studies have used pharmacologic means to attenuate this plasticity. Thus, anti-inflammatory medications [64], blockade of increased ROS [107] prevention of up-regulation of angiotensin receptors [42] will all attenuate IH or low blood flow effects on chemosensitivity. Further, increasing cardiac output via habitual physical training will also attenuate the increased chemoreceptor sensitivity in CHF animal models [77]. These approaches all offer as yet untried treatments for chemo-hypersensitivity and its sequelae attending OSA and autonomic imbalances in humans.

Finally, the aftereffects or long-term facilitation of both phrenic and hypoglossal nerve activity elicited by even a few sessions of intermittent hypoxia (for example 5 minutes of normoxia followed by 5 minutes of hypoxia for three days/week for 10 weeks) elicited increased serotonin, immunoreactive BDNF and endothelial growth factor at the level of the phrenic motor neurons) [20]. This type of moderate, brief IH also upregulated growth and trophic factors in non-respiratory motor neurons, suggesting that this type of adaptation to IH represents a general feature of motor systems [20]. It is important to note that this moderate, short-lived type of IH – unlike the persistent cyclical and long-lived nature of the IH attending severe sleep apnea – probably has little if any persistent daytime effects on chemosensitivity or negative consequences for the cardiovascular system. Accordingly, some investigators are recommending IH in promoting synaptic plasticity and spontaneous ventilation following selected types of spinal cord injury [126].

Exercise hyperpnea in health and disease

In healthy humans of all ages the ventilatory response to exercise of up to some 10 to 20 fold greater than resting levels is achieved with remarkable precision and efficiency in terms of both CO_2, O_2 and pH regulation of arterial blood and economy of effort on the part of the respiratory muscles. The key primary drivers of this hyperpnea which is so tightly and mysteriously linked to respiratory CO_2 exchange has been narrowed to a central command, feedforward stimulus with parallel recruitment of both locomotor and respiratory muscles and a feedback stimulus involving thinly myelinated afferents from contracting locomotor muscles [44]. Only recently however have new insights been gained into these mechanisms in humans, with implications for the regulation of exercise hyperpnea in health, COPD and CHF.

Central command

Several lines of evidence in the past decade have demonstrated the importance of feedforward central command to exercise hyperpnea in the human as originally hypothesized by Krogh and Lindhard one century ago [73], based upon their observation of anticipatory hyperventilation prior to exercise and the immediate increase in ventilation at exercise onset. First, hyperventilation and cardiovascular responses were shown to occur in

the hypnotized human at rest in response to “suggested exercise” [129, 142]. This observation extended older ones which showed that the increased drive to recruit motor units of locomotor muscles during exercise – as triggered by either weakening of the rhythmically contracting muscles via partial curarization [46] or epidural lidocaine [5, 59] or inhibiting central motor command via tendon vibration [49] – was accompanied by increased heart rate and ventilatory responses to a given level of exercise.

Where in the CNS does the central command originate? Animal studies using electrical or pharmacological simulation of subthalamic and mesencephalic locomotor regions have triggered cardiovascular and ventilatory responses in parallel with locomotion – even in the absence of muscle contraction (i.e. fictive locomotion) [39]. In addition, these regions were shown to be activated in intact exercising animals [65]. However, recent human studies clearly point to the motor cortex and midbrain as key sites of central command. First, electrical or magnetic transcranial stimulation [47], deep brain stimulation [50] and stimulation of the primary cortex [103] all elicited diaphragmatic contractions. Secondly, PET imaging in the “suggested” exercise paradigm mentioned above revealed increased blood flow to the motor control regions of the cortex and cerebellum [128, 141]. Most recently, the use of deep brain stimulating electrodes with recording of field potentials in human neurosurgical patients has been used to specifically identify the periaqueductal gray (PAG) and the subthalamic nucleus (STN) has major sites of central command of cardiorespiratory responses to stress [10, 11, 128]. The PAG receives inputs from prefrontal cortex, hypothalamus and nociceptive pathways and has outputs to the brainstem medullary cardiorespiratory control areas. Simulation of muscle afferent inputs in humans also elicited excitation of PAG neuronal activity [11]. Paterson et al. [100] propose that the PAG area is a key ”command center” of functional connectivity to higher centers and to the STN as well as receiving sensory input from the periphery. These findings have also promoted the concept that the essential nature of the control system for exercise hyperpnea resides in the central command centers. However, as summarized below this regulation also appears to require feedback.

Muscle afferent feedback

When studied in isolation using direct stimulation of muscle, substantial evidence exists for thinly myelinated afferents – responding to the mechanical distortion of muscle contraction and/or metabolite accumulation. Their sensory pathway ascends via the dorsal horn of the spinal cord to the nucleus of the solitary tract, to cardiorespiratory neurons of the ventral lateral medulla – having a major effect on the cardiorespiratory response to muscle contraction. What is in doubt is whether these afferents play a significant role in exercise hyperpnea in the normally exercising human i.e. when central command and other mechanisms sensitive to respiratory CO_2 exchange are also operative. A straight forward approach to determining whether this feedback mechanism is ”essential” to the normal hyperpnea is to block it during steady-state, rhythmic exercise i.e. when all potential competing stimuli are present. This has been accomplished several times in humans with epidural lidocaine injection – all with negative evidence i.e. showing no effect or even an increase in the ventilatory or heart rate response to exercise in the presence of epidural blockade with only a small reduction in blood pressure response [5, 44, 60]. However, this

approach has been shown to also block efferents as well as afferents causing limb muscle weakness. Thus, as with the curare experiments (see above) this intervention would likely elicit a compensatory response from central command to recruit more motor units in order to maintain force output with corresponding increases in cardiorespiratory responses. Another approach to block these afferents but without affecting the efferent pathway is to take advantage of their sensitivity to μ-opioids [58]. Accordingly, we used intrathecal administration of Fentanyl at the lumbar level as a partial blockade of muscle afferents and demonstrated that this drug did not influence leg strength, nor did it have cardioventilatory effects at rest breathing room air or CO_2 or during arm exercise [3]. However, this blockade did cause substantial hypoventilation and CO_2 retention as well as significant reductions in blood pressure and heart rate in healthy subjects during rhythmic leg cycling exercise (see Fig. 3:A). Similar cardiorespiratory effects of fentanyl were also observed in constant load and time trial cycling exercise [4, 6]. We caution that these data do not mean that feedback chemoreception – secondary to sustained CO_2 retention of 4–8 mmHg $PaCO_2$ observed with afferent blockade – is ineffective. To the contrary, when the ventilatory equivalent of the heightened chemoreceptor activity secondary to the Fentanyl-induced CO_2 retention was accounted for it was estimated that the total effect of the Fentanyl block approached 40 to 50% of the total hyperpnea during mild and moderate steady state exercise [26].

It is especially surprising that muscle afferent blockade affected the cardioventilatory responses even under conditions of mild to moderate exercise intensities where O_2 supply to contracting muscle met O_2 demand. Such findings are consistent with newer concepts which point to muscle “metaboreceptor” activation in response to venous distention [54] – a mechanism which is especially appealing because the proposed stimulus i.e. increased muscle blood flow, is a major determinant of respiratory CO_2 exchange and by regulating breathing is participating in its own control. Finally we need to emphasize that we cannot distinguish whether this substantial contribution of muscle afferents to the cardiorespiratory response found with opioid agonist infusion is secondary to the blockade of the supraspinal pathway from the dorsal horn via the NTS to the medullary rhythm generator neurons and/or whether we have interfered with the interactive effects of ascending afferents on the integrative function of the cortical “central command” centers (see section above). What seems clear from the blockade data (see Fig 3) is that the concept of a purely central, adaptive feedforward control of the cardioventilatory response to exercise is not tenable. Rather, muscle afferent feedback provides critical information deciding both the cardiorespiratory as well as locomotor muscle effort [4, 6, 25].

Healthy aging

The major change affecting exercise hyperpnea and its limitations with healthy aging are the marked reductions in lung elastic recoil leading to airway narrowing/closure at high lung volumes, a reduced maximum expiratory flow : volume loop, maldistribution of ventilation and increased dead space ventilation [70, 71, 81]. These changes have no discernable effect on resting eupneic ventilation or arterial PCO_2 but during exercise there are two major consequences. First, expiratory flow limitation occurs at a level of hyperpnea which would not elicit these limitations in the younger adult and this in turn will cause hyperinflation, increased work of breathing and dyspnea. Secondly, even though the Vd/V_T is increased

with age $PaCO_2$ is maintained near resting normocapnic levels throughout moderate exercise intensities because the elderly subject increases total $\dot{V}E$ (and $\dot{V}E/\dot{V}CO_2$) above that in the young, so as to maintain $\dot{V}_A/\dot{V}CO_2$ comparable to that in the young adult (see Fig. 4). We do not know exactly how respiratory CO_2 exchange is sensed to promote this precise regulation of alveolar ventilation relative to $\dot{V}CO_2$, however these types of evidence confirm the importance of this humoral mechanism at least as a “fine tuner” of the hyperpneic response [26, 140]. On the other hand this augmented (total) ventilatory response combined with the age-diminished max flow : volume envelope results in a greater work of breathing in the exercising elder [81].

COPD

represents an extreme example of a highly compliant lung and a compromised expiratory flow : volume loop which precipitates expiratory flow limitation with only modest increases in flow rate above resting levels. The ensuing progressive hyperinflation with mild to moderate exercise intensities appears as the major contributor to dyspnea and to exercise limitation [94]. Three approaches to reducing the expiratory flow limitation have resulted in improved exercise performance and decreased limb fatigue. First, inhalation of low density He : O_2 expands the maximum flow : volume envelope in most patients thereby reducing the expiratory flow limitation during exercise and also reducing the rate of development of limb fatigue during exercise [7]. Secondly, supplemental inspired O_2 reduced chemoreceptor drive and exercise $\dot{V}E$ and improved exercise performance [94]. Thirdly, intrathecal fentanyl was used (see Fig. 5) to reduce muscle afferent input in COPD patients resulting in reduced breathing frequency, which in turn reduced $\dot{V}d$ and total ventilation (but not alveolar ventilation), flow limitation and hyperinflation [45]. So, as in health (see Fig. 3) muscle afferent input in exercising COPD patients contributes significantly to exercise hyperpnea but with a negative – rather than positive – influence on excise performance [26]. Given the markedly diminished aerobic capacity and reduced fatigue resistance [7] of limb locomotor muscles in the sedentary COPD patient [78, 131], specific resistance training of the legs [111] might result in a reduced muscle metaboreflex, and therefore less tachypnea and hyperpneic response to exercise.

Congestive Heart Failure

patients commonly respond to exercise with a tachypneic hyperventilation and even occasionally cyclic periodic breathing – the severity of which is prognostic of morbidity and mortality in CHF patients [72, 95]. Deadspace ventilation and $\dot{V}E/\dot{V}CO_2$ are high owing primarily to the increased breathing frequency but so is $\dot{V}_A/\dot{V}CO_2$ – thus arterial hypocapnia is common [144]. There are several potential reasons for the hyperventilatory response. First, carotid chemoreceptors are substantially hypersensitized in CHF, owing to the chronic ”stagnant hypoxia” at the level of carotid body created by the low cardiac output, low blood flow and reduced shear stress [30]. This chemo-hypersensitization will also increase control system loop gain (see Sleep Apnea section below) and contribute to the periodic breathing [24]. Secondly, muscle mechanoreceptors are also hypersensitized in CHF in combination with a depressed muscle metaboreceptor sensitivity [106, 120]. Accordingly, intrathecal fentanyl-induced blockade of muscle afferents in human CHF patients resulted in substantial hypoventilation and CO_2 retention over a wide range of

exercise intensities as compared to age matched controls [98]. Thirdly, high pulmonary vascular pressures are common in CHF, especially during exercise and in the presence of pulmonary edema this would precipitate pulmonary C fiber stimulation and a tachypneic ventilatory response and would also be expected to contribute to an unstable, periodic breathing [95, 96].

These hyperventilatory responses as well as the underlying hypersensitivity of muscle afferents and chemoreceptors in CHF contribute importantly to exercise performance limitation – primarily because of the augmented intrathoracic pressures and increased work of breathing as well as high sympathetic vasoconstrictor outflow effects on limb perfusion. Thus, when pressure support mechanical ventilation was used to reduce respiratory muscle work in CHF patients, ratings of limb discomfort were reduced and exercise performance improved [93]. Further, pressure support elicited substantial increases in limb muscle blood flow and muscle oxygenation [15, 97, 97] in both CHF patients and an animal model [82] due to both an increase in stroke volume and cardiac output in combination with a greater local vasodilation of locomotor muscle vasculature[2]. Similarly, transient inhibition of hypersensitized carotid chemoreceptors in CHF animal models also reduced locomotor muscle vascular resistance and increased limb blood flow both at rest and during exercise [121].

Chronic exercise training [132] as well as specific respiratory muscle training [16, 66] in CHF animal models and in human patients reduces the hypersensitivity of the carotid chemoreceptors, limb muscle mechanoreceptors and the respiratory muscle metaboreflex. These “desensitizing” effects on multiple feedback regulators result in a reduced work of breathing and reduced sympathetic vasoconstriction, thereby improving O_2 transport to contracting locomotor muscle and exercise performance.

Obstructive sleep apnea (OSA) and the ventilatory control system

Significant amounts of sleep apnea and sleep disordered breathing exist in the general population with obesity, male gender, age, and craniofacial structure as major risk factors [28]. Severe cases (> 20–30 apneas/hypopneas (AHI)/HbO_2 desaturations per hour) commonly leading to high chemosensitivity, elevated sympathetic vasoconstrictor activity, and endothelial dysfunction – all eliciting both nocturnal and daytime systemic and often pulmonary hypertension [28]. A form of daytime hypoventilation and CO_2 retention in the obese is also tightly linked – perhaps via chemoreceptor “resetting” – to carryover effects from nocturnal hypoventilation and CO_2 retention and is often effectively eliminated via the use of nasal positive pressure ventilation to correct the nocturnal hypoventilation [105]. In many CHF patients and sojourners to high altitude the ventilatory control system and enhanced chemosensitivity clearly play a major role in the pathogenesis of “central” or mixed (obstructive plus central) type of repetitive apneas (see ref [68] for review). But what role might these control mechanisms play in the more prevalent condition of cyclical

[2]This dual effect i.e. increased CO and limb vascular conductance during pressure support was attributed to: a) a mechanical effect of a reduced intrathoracic pressure on the left ventricle in the highly afterload-dependent CHF patient an effect which is in the opposite direction to the decreased exercise stroke volume observed with positive pressure support in health [55, 82]; and b) a reduced reflex feedback effect from respiratory muscle metaboreceptors.

obstructive sleep apnea? Certainly the popular view that OSA is a problem of an anatomically compromised upper airway has merit – but accumulating evidence now recognizes that repetitive airway obstructions in sleep are also often a function of other important characteristics of the ventilatory control system [29, 36, 147].

Anatomical : functional links in OSA

First, we know that central respiratory motor output recruits, first the hypoglossal, then (msec later), the phrenic motor neurons serving the upper airway dilators and respiratory pump musculature, respectively [56, 61]. Secondly, the fundamental effects of the loss of "wakefulness" includes both the withdrawal of tonic input to the upper airway dilator muscles thereby increasing airway compliance and collapsibility plus an unmasking of a critical dependence of ventilatory control and its stability on chemoreceptor and mechanoreceptor feedback. Thirdly, in subjects with moderately collapsible airways there is a tight link between CO_2–induced central ventilatory instability and airway calibre. So, inducing central output instability by administering brief hypoxic episodes in snoring subjects with mildly collapsible airways precipitated airway closure at the nadir of the oscillating drive [62, 134]; conversely, preventing oscillations in central respiratory motor output via preventing transient hypocapnia also prevented airway obstructions – at least in those subjects with a relatively high chemosensitivity and sensitive apneic threshold [145, 145]. Finally, the passive collapsibility of the upper airway – by itself – in sleeping humans accounts for only a relatively small portion of the variability in apnea : hypopnea index in OSA [63, 146]. Some recent studies of substantial numbers of OSA patients with moderate to severe OSA reveal that more than 80% have a highly collapsible airway – but 30–50% also showed key characteristics of instability including high control system "loop gain", sensitive arousal thresholds and/or sluggish responsiveness of upper airway dilator muscles to chemoreceptor stimuli [36, 37, 138, 145]. These characteristics are sometimes inherent to the patient, but are also acquired and intensified via the repeated intermittent hypoxemia, transient arousals and obstructions[3].

OSA pathogenesis

In Fig. 6:A we suggest two overlapping scenarios for the pathogenesis of cyclical OSA, based on the influences of airway collapsibility, neurochemical influences over pharyngeal dilators and respiratory pump musculature and on sleep stage stability. In Fig. 6:B right, a patient with a highly collapsible airway often experiences complete airway collapse when the compensatory tonic input to the upper airways are removed with sleep onset. On the left side of Fig. 5:B a patient with a high chemosensitivity plus a mildly collapsible airway is likely to experience airway obstruction during sleep at the nadir of the oscillating central respiratory motor output. In either case, whether the obstruction is repeated and becomes cyclical will depend upon how the patient's respiratory control system responds to the

[3]The tendency toward ventilatory instability depends upon "loop gain", an engineering term defining the gain of the negative feedback loop which regulates how ventilation responds to transient disturbances in breathing and the accompanying disruption of arterial blood gases. Chemosensitive gain is defined by the slope of the ventilatory response to hypercapnia and hypocapnia i.e. $\Delta \dot{V}E/\Delta PaCO_2$. Plant gain is determined by the magnitude of the reduction in $PaCO_2$ resulting from a given change in ventilation, ($\Delta PaCO_2/\Delta \dot{V}E$) i.e. the efficiency with which CO_2 is eliminated. These concepts and their effects on ventilatory stability and the apneic threshold may be more readily appreciated when presented in graphical form (see ref [24] and [139]).

obstruction as outlined in Fig. 6:A. The key ingredients to regaining respiratory stability are the ability to recruit airway muscles dilators and to effectively open the airway to restore airflow prior to arousal, because the transient arousal accentuates the ventilatory overshoot and hypocapnia leading to subsequent hypopneas, apneas and obstructions. Accordingly, how the chemoreceptor control system and the airway dilator musculature responds to accumulating CO_2 and HbO_2 desaturation during the apnea as well as the sensitivity of a patient's arousal threshold and the effectiveness of dilator muscle recruitment will determine whether initial obstructive events are followed by stable breathing, slowly evolving hypopneas with occasional arousals or repetitive obstructions (94).

Treatment implications

Given the critical contributions of a collapsible airway to all types of OSA it is not surprising that CPAP is a highly effective treatment. However, significant numbers of OSA patients are unable to tolerate CPAP or greatly under utilize it [135]. Three types of alternative treatments have shown promise in significantly reducing AHI in some OSA patients. These include the following:

- Use of supplemental O_2 to reduce chemoreceptor gain [139, 145] and acetazolamide [37, 67] or preventing hypocapnia via selective increments in F_ICO_2 – to reduce plant gain [145].
- Raising the arousal threshold using sedatives to prevent ventilatory overshoot by helping maintain sleep state during an obstructive apneic event until airway dilator muscle recruitment restores patency prior to arousal [12, 14, 35].
- Reducing airway collapsibility via recruitment of airway muscle dilators using small increments in $PaCO_2$ via a deadspace rebreathing system [145].
- Combining treatments to reduce loop gain or raise arousal threshold together with small reductions in airway collapsibility via moderate weight loss or mandibular advancement [17, 48, 127].

These new approaches have produced mixed results to date with the most consistent success in reducing obstructive AHI achieved when the treatment was tailored to an individual patient's specific deficiency; for example, lowering loop gain in the patient with high chemosensitivity or raising arousal threshold in those with high arousability. A challenge in using these approaches for treatment purposes is to simplify our ability to recognize specific risk factors in OSA populations so that therapy can be individualized and targeted [29, 36]. Recently, Wellman *et al.* [137] have proposed a promising screening tool using the routine clinical polysomnogram to characterize these risk factors in individual OSA patients. We also need to continue to explore new agents for reducing loop gain and arousability and especially for effective stimulation of upper airway muscle dilators without invoking confounding side effects on chemoreceptor gain or sleep state continuity or excessive sympathetic activation.

These principles of individualizing therapy for OSA by phenotyping patients have also been recently applied to an exciting, novel treatment for moderate to moderately severe OSA which utilizes hypoglossal nerve stimulation via implanted electrodes during inspiration

triggered by an implanted transducer which senses intrathoracic pressure [34, 123]. This therapy – recently receiving FDA approval in the USA – was shown to be safe and highly effective over six month periods in substantially reducing AHI in most of a selected group of CPAP intolerant OSA patients. Importantly, in keeping with the concept of tailoring treatments to individual characteristics, these patients were pre-screened to include only those with a site of upper airway collapse most likely to be prevented via forward movement of the tongue, achieved via hypoglossal nerve stimulation; and b) to exclude those with a significant prevalence of central and mixed apneas [123]. Based on current knowledge of the pathophysiology of OSA, we would predict that the patients included in this latter category would likely have high chemosensitivity and loop gain and might well benefit from a combined therapy of hypoglossal stimulation plus reduced chemoreflex gain via supplemental O_2 or a pharmacologic-induced blockade of hyperchemosensitivity.

Carotid body denervation as “treatment” for autonomic imbalances/OSA?

Throughout this review we have emphasized the important contributions of carotid chemoreceptors and their central projections and carotid body hypersensitivity to ventilatory control during exercise and sleep and to excessive sympathetic nerve activity in such diseases as chronic hypertension and heart failure and OSA. Does it follow that bilateral carotid body denervation (CBX) should be considered as a treatment to correct this autonomic imbalance in such diseases as drug-resistant hypertension or CHF or to prevent (some forms) of sleep apnea [91, 101]? There is support for carotid body denervation: a) some older studies of CBX in asthmatic humans showed significant sustained reductions in blood pressure [87]; b) in the rabbit model of CHF, CBX reduced renal sympathetic nerve activity and BP and prevented periodic breathing [79], and in rodent models of spontaneous hypertension CBX caused substantial reductions in systemic blood pressure [1]; c) CBX prevented the development of insulin resistance and hypertension induced via hypercaloric diets [112], substantially increased survival following myocardial infarction in rodents [22] and prevented hypertension induced by chronic intermittent hypoxemia in rats [76]; and d) using an irreversible pharmacologic inhibitor of the enzyme responsible for the gaseous transmitter H_2S in the carotid body in a rodent model of severe CHF, almost completely normalized the heightened carotid chemosensitivity as well as the accompanying breathing instability and sympathoexcitatory state [23]. On the other hand there are concerns, including: a) whether selective chemo-denervation can be achieved without including baroreceptor denervation [130]; b) to what extent will long term compensation for CBX normalize CO_2 chemosensitivity and eupneic ventilation in humans [19]; c) in the absence of carotid chemoreceptors will patients with airway disease, $\dot{V}_A/Q$ maldistribution and high Vd/V_T mount sufficient compensatory hyperpnea to prevent chronic hypercapnia and will patients who develop OSA with aging and/or weight gain experience apnea prolongation and more severe hypoxemia and its sequelae [29, 117]? Of course, following CBX, any sojourn to even moderately high altitudes will exacerbate the usual level of arterial hypoxemia. Alternatively, we need to determine if therapies which acutely inhibit carotid chemoreceptors or chronically reduce carotid chemoreceptor hypersensitivity (see above) present effective, safe and especially reversible alternatives and in what subpopulation of patients these approaches are likely to be effective. A strong case may also be made for the

well documented sympathoinhibitory effects of habitual exercise training – especially interval-type training – in CHF and hypertension [21, 69, 86, 124].

Summary

The major take home message of our brief review is that recent advances in our basic understanding of ventilatory control – especially those chemoreceptor and extra-chemoreceptor mechanisms controlling breathing and its plasticity during exercise and in sleep – have important implications for understanding the pathophysiology of breathing abnormalities and their consequences in such diseases as COPD, CHF and OSA. A major benefit to these newfound insights is that they are beginning to allow some innovative, meaningful inroads into treatment strategies.

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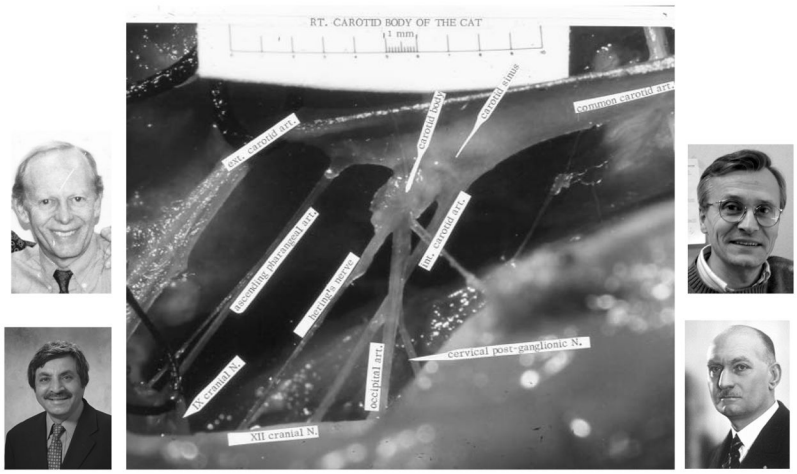


Figure 1.

Carotid chemoreceptor in the cat. Heart is to the right and brain to the left, with the carotid chemoreceptor located at the bifurcation of the common carotid artery. Note the sensory nerve from the chemoreceptor, designated here as Hering's nerve. Photos here are of Nobel laureate Corneille Heymans on the right who first described the function of the carotid chemoreceptor in the 1930s and on the left Gerald Bisgard (top) and Nanduri Prabhakar (bottom) who contributed importantly to our understanding of carotid chemoreceptor O_2 sensing mechanisms and its plasticity over the past two decades.

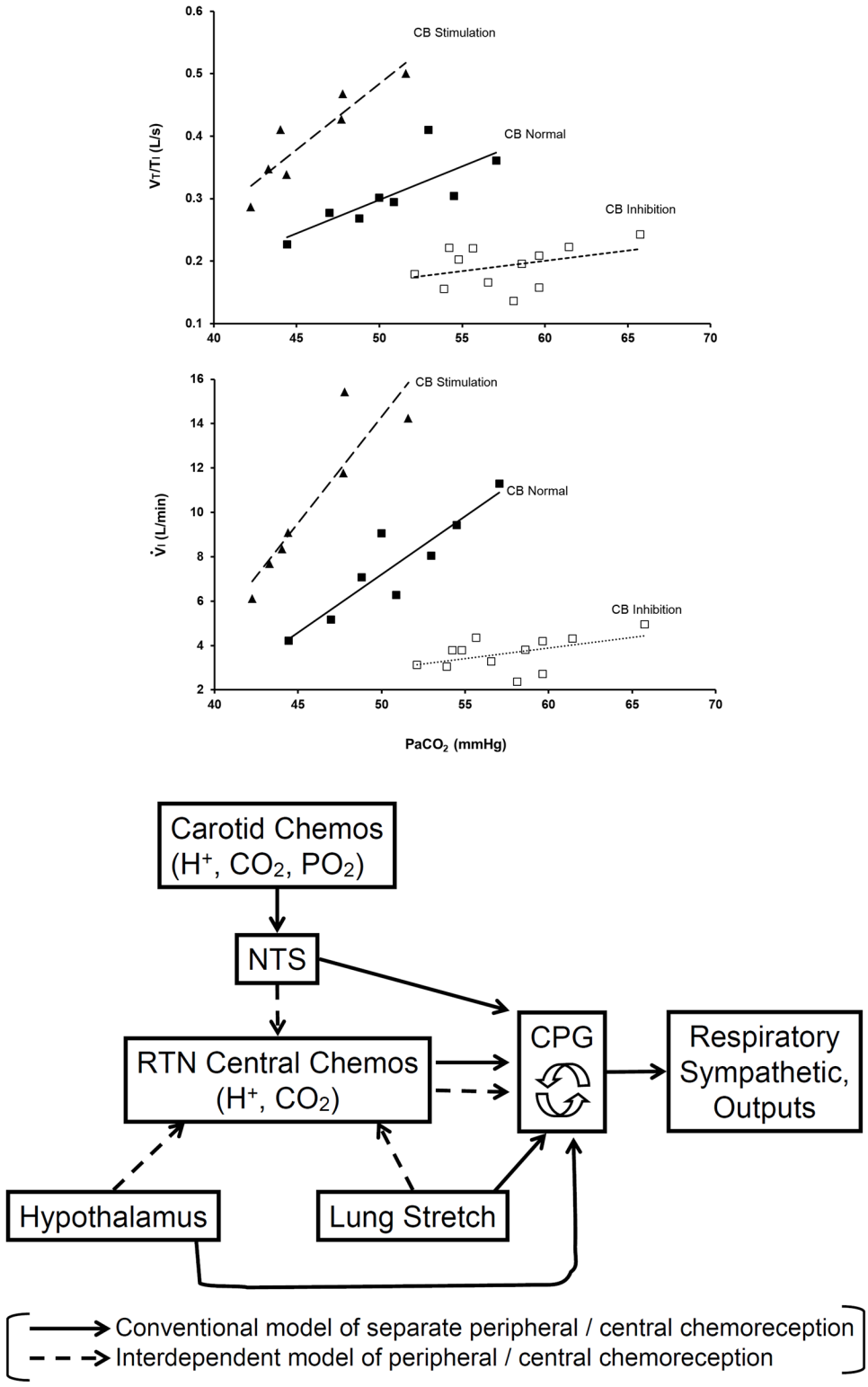


Figure 2.

A. Hyperadditive effects of carotid chemoreceptor input on central CO_2 response. In a canine, the carotid chemoreceptor is denervated on one side. The remaining carotid

chemoreceptor is vascularly isolated from the systemic and cerebral circulation and perfused extracorporeally. The central chemoreceptor response to CO_2, by itself, is determined by steady-state inhalation of CO_2-enriched air. Animals were studied during quiet wakefulness. Note that, when the isolated CB is inhibited (CB PCO_2 = 20 Torr and CB PO_2 = 500 Torr), the central CO_2 response was reduced to about one-fifth of normal, and when the isolated CB was stimulated (CB PO_2 = 40 Torr, CB PCO_2 = 40 Torr), the central CO_2 response increased an average of twofold. The effects on VT/Ti indicate changes in the "drive" to breathe. Effects on $\dot{V}E$ reflect changes in both f_b and VT. (From Blain et al. [13]).

Figure 2. B. Schematic of central-peripheral chemoreceptor interdependence. Shown is the traditional concept supporting only separate chemoreceptor functions (solid lines) and the newer concept of interdependent chemoreceptor function (dashed lines). NTS, nucleus tractus solitarius; RTN, retrotrapezoid nucleus; CPG, central pattern generator. See Fig. 2: A and text for explanation and references to original research.

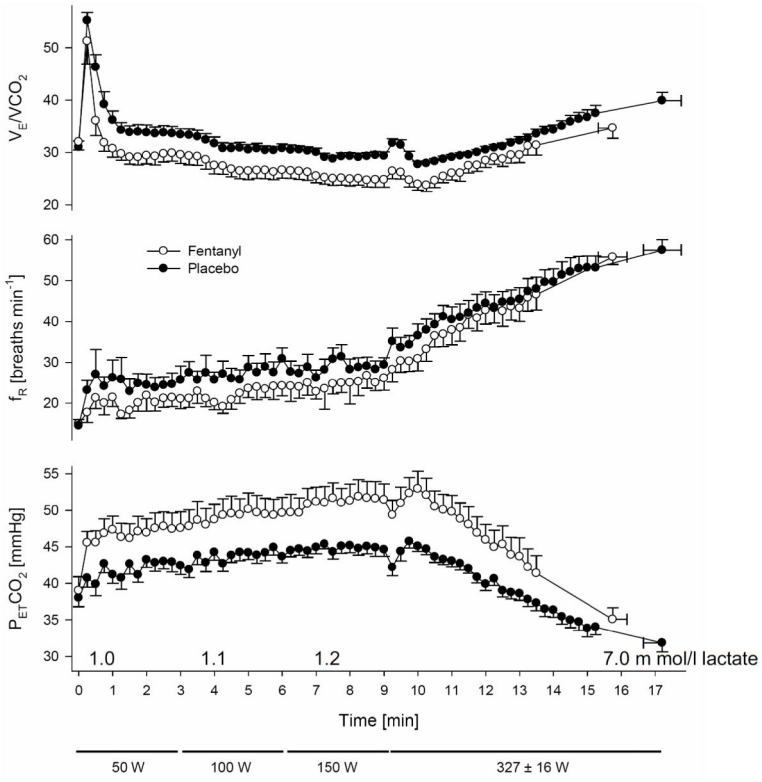


Figure 3.

Reduced steady-state ventilation ($\dot{V}E/\dot{V}CO_2$) and breathing frequency (fR), and the resultant CO_2 retention, resulting from type III–IV muscle afferent blockade via intrathecal fentanyl in healthy humans at mild to heavy exercise intensities. Fentanyl had no effect on mean SaO_2 except at the 327 W work rate where SaO_2 was 97.7% in placebo and 95% with fentanyl. Note the persistence of the hypoventilatory response in the presence of type III–IV afferent blockade – especially during mild and moderate intensity exercise – despite the presence of increased CO_2-induced chemoreceptor stimulation. Plasma lactate levels were within 0.5 mmol l^{-1} of resting values (0.9 ± 0.1 mmol l^{-1}) during 50–150 W exercise and rose to 7-fold > rest during exercise at 325 W in both the placebo and fentanyl trials. Data from Amann et al. [3].

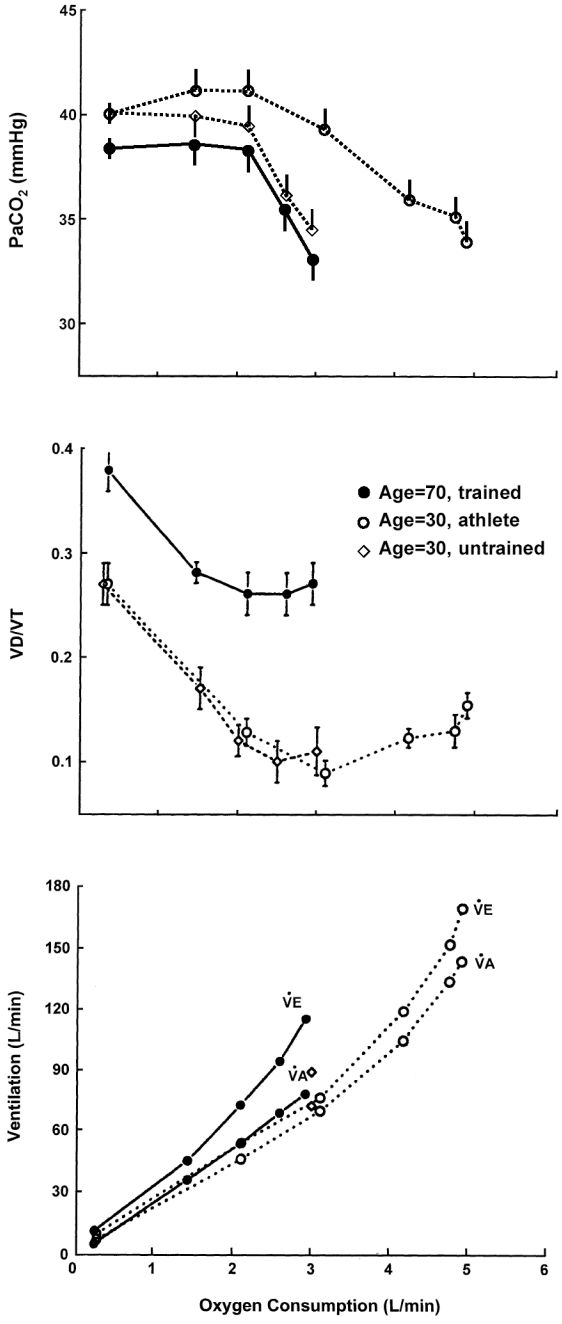


Figure 4.

Steady-state ventilatory response to treadmill walking in young and elderly healthy subjects. $PaCO_2$ is determined by the relationship of alveolar ventilation ($\dot{V}_A$) to CO_2 production ($\dot{V}CO_2$) so that: $PaCO_2 = \dot{V}CO_2/\dot{V}E - \dot{V}d \times k$ where $\dot{V}E$ is total minute ventilation, $\dot{V}d$ is dead space minute ventilation and k is a constant [26]. Note in the elderly that their dead space ventilation (Vd/VT) is greater than in younger subjects at rest and exercise. The older subjects adjust their total $\dot{V}E/\dot{V}CO_2$ higher than in the young during mild to moderate exercise intensities resulting in similar $\dot{V}_A/\dot{V}CO_2$ and isocapnic hyperpnea. Data from Johnson *et al.* [71].

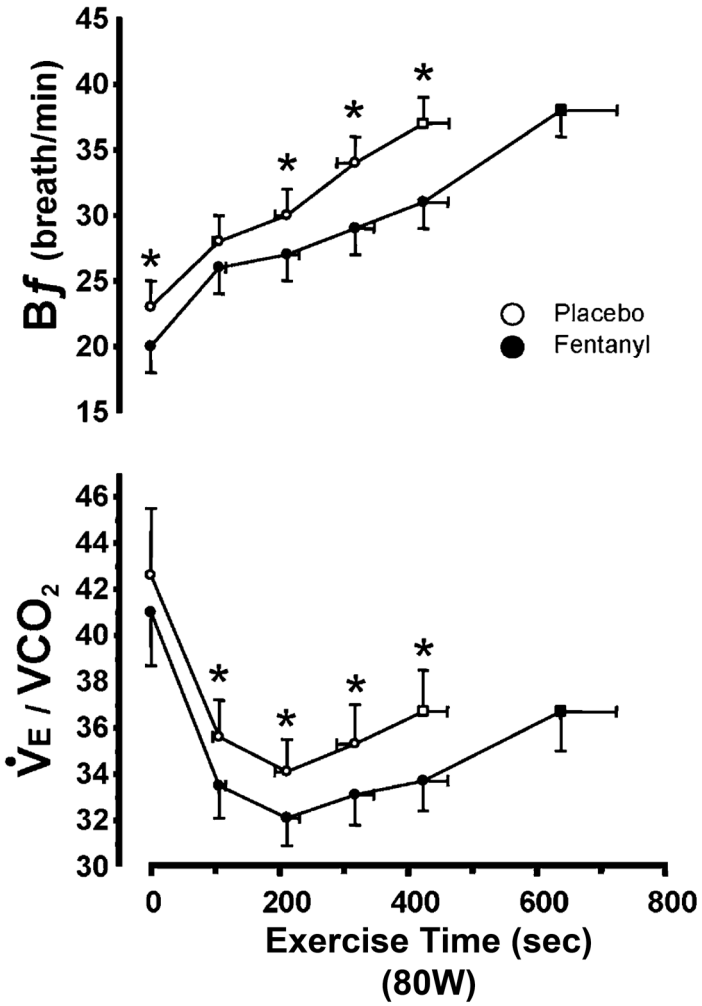
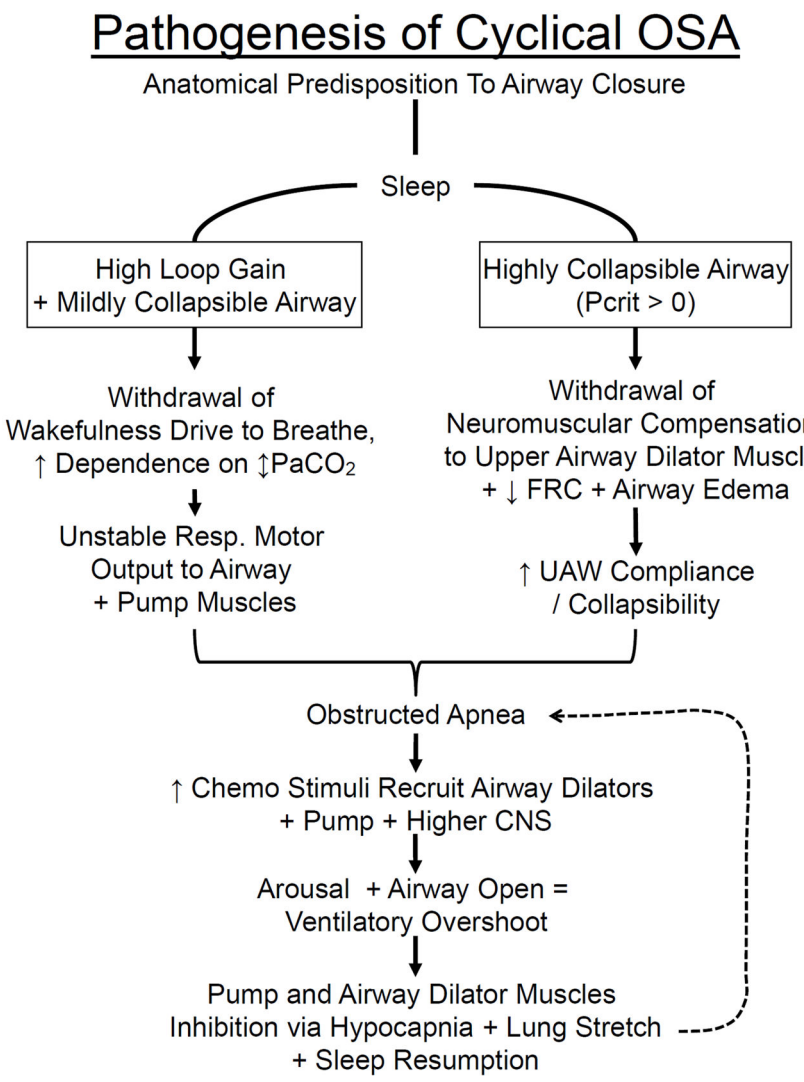


Figure 5.

Effects of intrathecal fentanyl blockade on breathing frequency and $\dot{V}E/\dot{V}CO_2$ in COPD patients cycling at 80 W (80% of max). Fentanyl block resulted in a reduced fR and $\dot{V}E/\dot{V}CO_2$ which persisted throughout the exercise. Vd/VT during exercise was also reduced with fentanyl (not shown). Dyspnoeic sensations were reduced and exercise time prolonged as $\dot{V}E$ and expiratory flow limitation were reduced with fentanyl blockade. Data from Gagnon et al. [45].



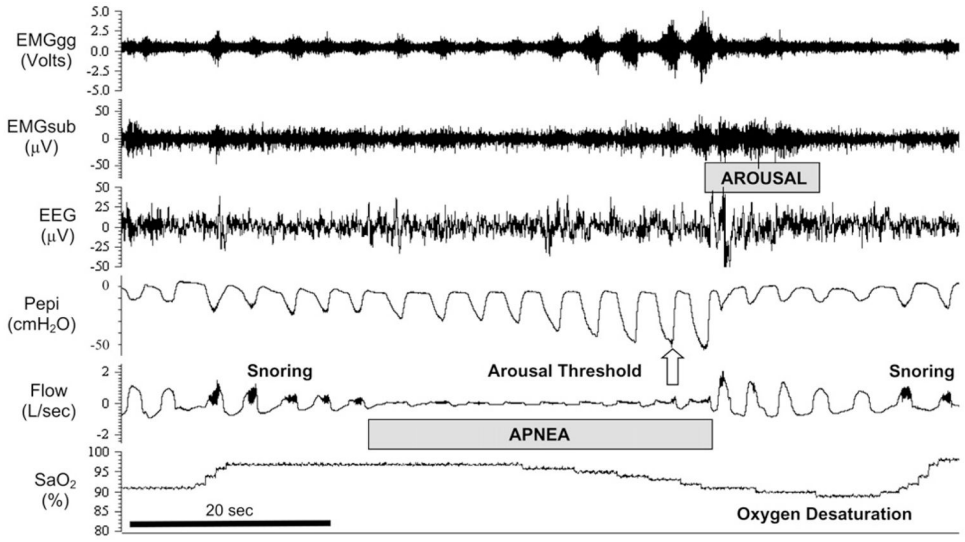


Figure 6.

A. Schematic illustrating the interactive effects of airway anatomy with neurochemical control on the magnitude and stability of central respiratory motor output, airway muscle dilator recruitment, and arousability in the pathogenesis of cyclical OSA. Patients with an anatomical predisposition to pharyngeal collapse may experience two types of overlapping scenarios leading to cyclical OSA in sleep. *Right*: progression initiated by an airway obstruction at sleep onset in a patient with a severely collapsible upper airway; *left*: progression to airway obstruction (at the nadir of the respiratory cycle) initiated by an unstable central respiratory motor output in a patient with elevated loop gain and a mildly collapsible airway. *Bottom*: factors that determine the consequences of airway obstruction and accumulating chemoreceptor stimuli on subsequent, postapneic ventilation, airway patency and EEG arousal. These control system characteristics include the responsiveness of both the upper airway and chest wall pump muscles and of central nervous system (CNS) arousability to the rising chemoreceptor stimuli (also see text and Fig. 5:A). UAW, upper airway; FRC, functional residual capacity. Used with permission from Dempsey et al. [29]. Figure 6. B. Polysomnographic tracing of an obstructed apneic event (between the dotted vertical lines in *A*) to illustrate the compensatory events occurring during and following the obstruction (apnea/hypopnea index = 56/hour). The cessation and resumption of flow defines the apneic event. Note the progressive increase in inspiratory effort (Pepi) and dilator muscle EMG (EMGgg) during the apnea, the transient arousal coincident with airway opening, and ventilatory overshoot at apnea termination. As the patient returns to sleep, note the gradual reduction in breathing frequency and flow rate, and increased pharyngeal pressure (signifying increased airway resistance) leading to the next obstruction. Evidence of snoring is shown on the flow tracing. Progressive increases in EMGgg activity occurred throughout the obstructive event, although in this instance they were not sufficient to restore flow, which occurred only upon arousal. Pharyngeal pressure serves as a measure of the inspiratory effort made against the obstructed airway, thereby reflecting the magnitude of central respiratory motor output in response to chemoreceptor stimuli accumulated during the obstructed apnea. Arousal threshold is determined by the pharyngeal pressure achieved through respiratory pump muscle contractions during an airway obstruction at the point of

EEG arousal. EMGgg, electromyogram of the genioglossus muscle (intramuscular); EMGsub, EMG of the submental muscle (surface); EEG, electroencephalogram (C3-A2); Pepi, pressure at the level of the epiglottis; Flow, airflow measured via nasal mask and pneumotachograph; SaO_2, arterial blood oxygen saturation measured via pulse oximetry at the finger. Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Eckert DJ and Malhotra A. 2008. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 5: 144–153.