



# Pathophysiology of human ventilatory control

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**ABSTRACT** We review the substantial recent progress 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, the integrative nature of the central chemoreceptors, and the interaction between peripheral and central chemoreception. Recent findings that support critical contributions from cortical central command and muscle afferent feedback to exercise hyperpnoea are also reviewed. These basic principles, and the evidence supporting chemoreceptor and ventilatory control system plasticity during and following constant and intermittent hypoxaemia and stagnant hypoxia, are applied to: 1) the pathogenesis, consequences and treatment of obstructive sleep apnoea; and 2) exercise hyperpnoea and its control and limitations with ageing, chronic obstructive pulmonary disease and congestive heart failure.



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We review control of breathing in humans and how new findings lead to novel treatments in sleep apnoea, CHF and COPD <http://ow.ly/wej7A>

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### Brief summary of key points

Key feedback mechanisms originating in sensitised chemoreceptors and locomotor muscles contribute importantly to abnormal ventilatory control during exercise and sleep in chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and obstructive sleep apnoea (OSA). Reducing the excessive hypersensitivity of these reflex receptors and their central projections may play major roles in the treatment of exercise hyperventilation, dyspnoea, sleep apnoea and autonomic imbalance.

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 minimising the work and metabolic cost of each breath. Breathing must remain a largely involuntary act of which we are unaware. 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 the respiratory musculature of the upper airway as well as the chest and abdominal walls. Our understanding of how all this is accomplished with such high precision and efficiency in the healthy human has made significant progress in the past two decades. In this brief review, we summarise 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 for (active) expiration [1]. Of the several models proposed for producing respiratory rhythm, the most promising appears to be a hybrid model that combines the emergent properties of networks of synaptic connections and intrinsic membrane properties of individual neurons together with independent pacemaker-type neurons [2, 3]. In order for the underlying respiratory rhythm to generate a physiological breathing pattern, a highly complex coordinated process is required, wherein the pre-motor 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. However, abnormal breathing patterns, often with CO<sub>2</sub> retention in waking and especially in sleep, have been documented in neurodegenerative diseases such as Parkinson’s disease, amyotrophic lateral sclerosis, post-polio syndrome with bulbar involvement and multiple system atrophy, all of which have been linked to deficits in neurons in the pre-Bötzinger complex, pontine raphe and adjacent areas [4–6]. 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 effect *via*  $\mu$ -opioid antagonists [7, 8].

### Chemoreception

The past decade has provided the most significant advances in understanding peripheral and central chemoreceptor function since the discovery of carotid chemoreceptor function in the 1930s by the Nobel laureate Heymans [9] and Mitchell and Loeschke’s identification of medullary chemosensitive areas in the 1960s [10]. Here we provide a summary of the key developments most relevant to human pathophysiology.

#### Carotid body chemoreception

We now know that hypoxia triggers sensory input from the carotid body by inhibiting oxygen-sensitive potassium channels in the glomus cells of the carotid body *via* several mechanisms, including release of gaseous transmitters (NO, CO, H<sub>2</sub>S), AMP-activated protein kinases and/or reactive oxygen species [11, 12] (fig. 1). 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 discussed in the section on Plasticity). It is now clear that carotid bodies are polymodal receptors responsive to several circulating stimuli beyond just O<sub>2</sub>, CO<sub>2</sub> and H<sup>+</sup>, such as K<sup>+</sup>, noradrenaline, temperature and osmolarity as well as glucose and insulin. Further, reductions in carotid body blood flow (in addition to changes in arterial oxygen tension) also provide powerful carotid body stimulation and remodelling over time [13, 14]. On the effector side, 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 [15].

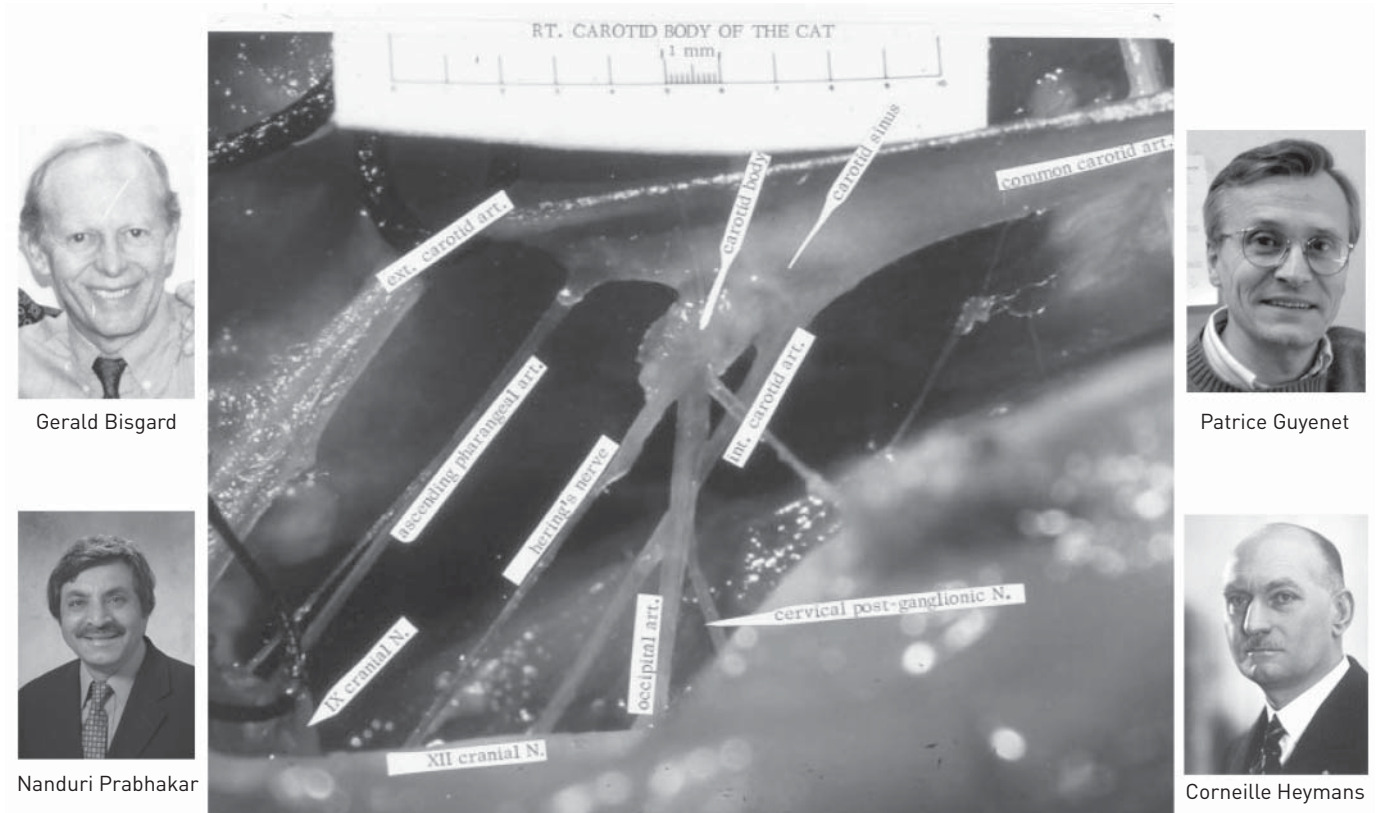


FIGURE 1 Carotid chemoreceptor in the cat. The heart is to the right and brain to the left, with the carotid chemoreceptor located at the bifurcation of the common carotid artery, <15 s circulation time from the lung. Note that the human carotid body is about 2–7 mm in diameter, and is innervated by the carotid sinus nerve (labelled here as Hering's nerve), and vagal and sympathetic nerves of the superior cervical ganglion. The perfusion of the carotid chemoreceptor is the largest of any organ in the body, *i.e.*  $\sim 2000 \text{ mL}\cdot\text{min}^{-1}$  per 100 g tissue. N: nerve; ext.: external; int.: internal; art.: artery. Photographs show Nobel laureate Corneille Heymans (1892–1968), who first described the function of the carotid chemoreceptor in the 1930s; Patrice Guyenet, who recently defined the neural pathways involved in peripheral/central chemoreceptor interdependence; and Gerald Bisgard and Nanduri Prabhakar, who have both made important contributions over the past two decades to our understanding of carotid chemoreceptor  $\text{O}_2$  sensing mechanisms and especially its plasticity. The photograph of the carotid chemoreceptor is reproduced courtesy of Edward H. Vidruk (University of Wisconsin–Madison, Madison, WI, USA).

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

Several  $\text{H}^+$  sensitive sites in the medulla and midbrain have been identified that stimulate breathing [16, 17]. However, the parafacial retrotrapezoid nucleus (RTN), which is characterised by glutamatergic interneurons that strongly express *Phox2b*, is likely to be the major site of central  $\text{CO}_2$  chemoresponsiveness. *Phox2b* has also been identified as a key gene product participating in early embryonic development of the autonomic nervous system [18]. Moreover, a *Phox2b* mutation has been identified as a predisposing genotype underlying congenital central hypoventilation syndrome, in which severe hypoventilation and apnoea routinely attend administration of sedatives and anaesthetics or occur with sleep onset [19]. The RTN chemosensors also appear to serve as important sites for integration of several stimuli, as these neurons are significantly modulated by inputs from carotid chemoreceptors, vagally mediated pulmonary stretch receptors and the hypothalamus [18]. Recent evidence (using c-FOS immunoreactivity) has shown these RTN *Phox2b* neurons are also activated by acute exercise in the rodent [20], indirectly suggesting potential participation of RTN chemosensitive neurons in the “central command” stimulus to exercise hyperpnoea (also discussed in the section on Exercise hyperpnoea in health and disease).

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 [18]. The functional consequences of this linkage are that stimulation of the peripheral chemoreceptors enhances the slope of the central  $\text{CO}_2$  ventilatory response; conversely, inhibition of the carotid bodies reduces the slope of the central  $\text{CO}_2$  response (fig. 2a and b) [21]. Other studies using different experimental preparations with isolated carotid and/or brainstem perfusions also show interdependence between the chemoreceptors, but opinions vary as to whether this interdependence is hypo- or hyperadditive in its effect on ventilation

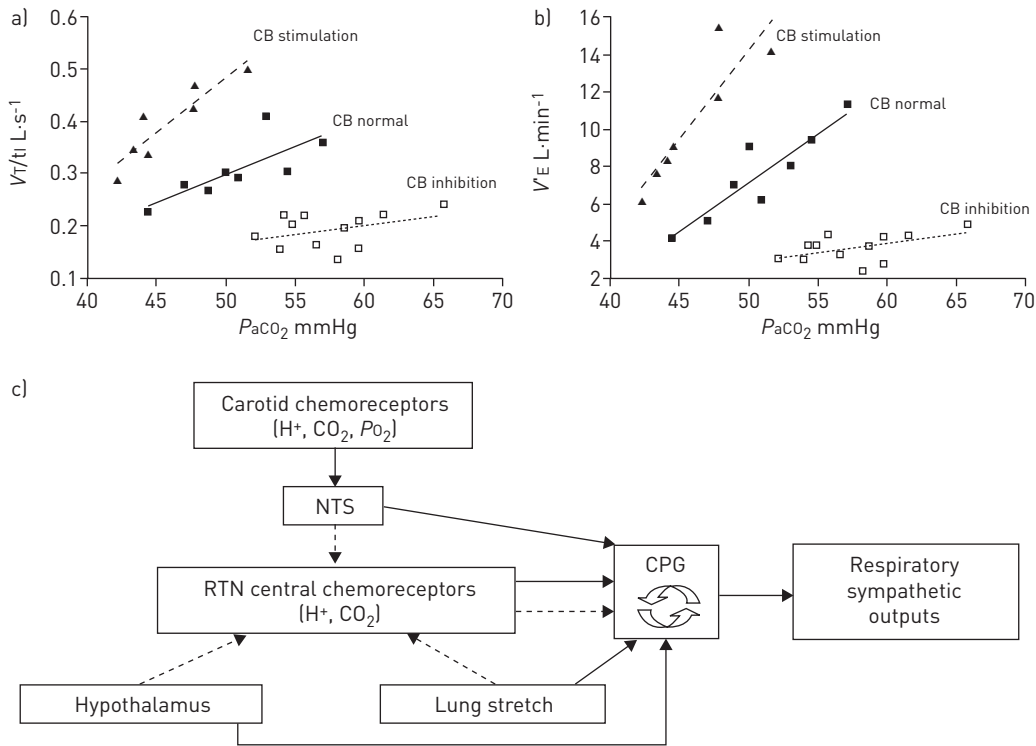


FIGURE 2 Hyperadditive effects of carotid chemoreceptor input on central CO<sub>2</sub> response. In a canine, the carotid chemoreceptor is denervated on one side. The remaining carotid chemoreceptor is vascularly isolated from the systemic and cerebral circulation and perfused extracorporeally. The central chemoreceptor response to CO<sub>2</sub>, by itself, is determined by steady-state inhalation of CO<sub>2</sub>-enriched air. Animals were studied during quiet wakefulness. Note that, when the isolated carotid body (CB) is inhibited (CB CO<sub>2</sub> tension (PCO<sub>2</sub>)=20 Torr and CB oxygen tension (PO<sub>2</sub>)=500 Torr), the central CO<sub>2</sub> response slope was reduced to about one-fifth of normal, and when the isolated CB was stimulated (CB PO<sub>2</sub>=40 Torr, CB PCO<sub>2</sub>=40 Torr) the central CO<sub>2</sub> response slope increased two-fold on average. a) The effects on the tidal volume (VT)/inspiratory time (ti) response slope indicate changes in the neural “drive” to breathe and reflect coincident changes in the rate of rise of the diaphragm electromyogram. b) Effects of CB inhibition/stimulation on the minute ventilation (VE) response slope reflect changes in both respiratory frequency and VT. PaCO<sub>2</sub>: arterial CO<sub>2</sub> tension. Reproduced from [21] with permission from the publisher. c) Schematic of central/peripheral chemoreceptor interdependence. Both the traditional concept supporting only separate chemoreceptor functions (solid lines) and the newer concept of interdependent chemoreceptor function (dashed lines) are shown. NTS: nucleus tractus solitarius; RTN: retrotrapezoid nucleus; CPG: central pattern generator. See panels a), b) and the main text for explanation and references to original research supporting this schematic.

and central respiratory drive [22–24]. 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<sub>2</sub> response is also markedly depressed [25, 26]. These findings are clearly inconsistent with the common presumption that hyperoxic CO<sub>2</sub> rebreathing tests selectively test central chemoresponsiveness, *per se* [27, 28]. Even during normoxic, *i.e.* air, breathing conditions, denervation of the carotid bodies or inhibition of the isolated, perfused intact carotid bodies [29, 30] results in substantial 25–35% reductions in alveolar ventilation (V<sub>A</sub>) and CO<sub>2</sub> retention in the order of +5–13 mmHg of arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>) that persists for days and often weeks following CBX. We believe this substantial contribution of the carotid body to eupnoeic breathing represents not only a contribution of tonic activity from the carotid bodies to medullary rhythm generating neurons but also the powerful interdependent effects of chemoreceptor input on RTN CO<sub>2</sub>-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 [31].

We can no longer view either the peripheral or central carotid chemoreceptors as “stand-alone” receptors responding only to changes in their immediate environment (fig. 2c). Further, the carotid bodies are not just reflex O<sub>2</sub> sensors; rather they appear to provide a nonspecific tonic afferent input that sensitises respiratory pattern generating medullary neurons through multiple central nervous system (CNS) pathways.

### ***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/or plasticity have been observed. First, an acute short-term potentiation occurs as manifested in a slowly declining hyperpnoea persistent for several seconds following withdrawal of carotid body stimulation [32], a centrally mediated output that provides a stabilising effect on breathing pattern following transient ventilatory overshoots, especially in sleep [33]. Secondly, a time-dependent hyperventilation and increased sympathetic nerve activity occurs over hours and days in the face of sustained hypoxic exposure. This is mediated primarily by increasing carotid sinus nerve output from the carotid body, a chemosensitisation that begins within a few hours of hypoxic exposure [34], and which coincides with increased protein expression and proliferation of O<sub>2</sub> sensory glomus cells of the carotid body [35]. 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 [36, 37].

In order to explain the persistent hyperventilation and excessive sympathoexcitation following removal of the hypoxic stimulus, some type of ongoing “central” stimulating effect resulting from the prolonged chemoreceptor input is required. Accordingly, central sensitisation of phrenic nerve activity in response to augmented carotid sinus nerve input has also been shown to occur during prolonged hypoxic exposure [38] and this might be explained, at least in part, by sensitisation of central chemoreceptors by heightened carotid body input (fig. 2). In addition, acute CNS hypoxia, *per se*, especially in the presence of normal tonic input from intact (but isolated) carotid chemoreceptors, causes a tachypnoeic hyperventilation and increased sympathetic nerve activity in unanaesthetised canines and goats [39–41]. This effect probably reflects the balance struck between hypoxia-induced inhibition *versus* excitation of different groups of medullary and hypothalamic neurons [42]. Sensitivity of these CNS hypoxia-sensitive neurons appears to be enhanced after a few days of hypoxic exposure [43].

### ***Plasticity/after-effects of intermittent hypoxia***

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 [44]. Several mechanisms appear to contribute to the sustained activity following removal of the chemoreceptor stimulus. First, with brief intermittent hypoxia carotid sinus nerve activity remained elevated upon return to normoxia; no morphological changes at the level of the carotid body were apparent. Increased reactive oxygen species and inflammatory cytokines have been implicated in sustained carotid body sensitisation [45]. Increased numbers of carotid body AT1 receptors have also been shown to result from prolonged intermittent hypoxia and to occur in animal models of CHF [46]. In turn, the carotid body sensitisation in CHF models has been attributed to reduced cardiac output and reduced carotid chemoreceptor blood flow (*i.e.* “stagnant” hypoxia) [13]. Secondly, central adaptive responses also occur following intermittent hypoxia as seen in the persistent elevation of tonic hyperactivity of neurons at the level of the PVN [47] and the rostral ventrolateral medulla [48]. This after-effect phenomenon in the CNS probably contributes significantly to the daytime elevation of sympathetic activity and the hypertension observed during the daytime in patients with OSA and nocturnal intermittent hypoxaemia [49].

Given these recent insights into the mechanisms underlying these types of enhanced chemosensitivity and their after-effects on ventilation and sympathetic activity, further studies have used pharmacological means to attenuate this plasticity. Thus, anti-inflammatory medications [50], blockade of increased reactive oxygen species [51] and prevention of upregulation of angiotensin receptors [52] will all attenuate intermittent hypoxia or low blood flow effects on chemosensitivity. Furthermore, increasing cardiac output *via* habitual physical training will also attenuate increased chemoreceptor sensitivity in CHF animal models [53]. These approaches all offer as yet untried treatments for chemo-hypersensitivity and its sequelae associated with OSA and autonomic imbalances in humans.

Finally, the after-effects or long-term facilitation of both phrenic and hypoglossal nerve activity elicited by even a few sessions of intermittent hypoxia (for example, eight 2-min intervals of 8% inspiratory oxygen fraction daily for 10 days) resulted in increased serotonin, immunoreactive brain-derived neurotrophic factor and endothelial growth factor at the level of the phrenic motor neurons [54, 55]. This type of moderate, brief intermittent hypoxia also upregulated growth and trophic factors in nonrespiratory motor neurons, suggesting that this type of adaptation to intermittent hypoxia represents a general feature of motor systems [54, 55]. It is important to note that this moderate, short-lived type of intermittent hypoxia, unlike the persistent cyclical and long-lived nature of the intermittent hypoxia associated with severe sleep apnoea, probably has little, if any, persistent daytime effects on chemosensitivity or negative consequences for the cardiovascular system. Accordingly, some investigators are recommending intermittent hypoxia for promoting synaptic plasticity and spontaneous ventilation following selected types of spinal cord injury [56].

## Exercise hyperpnoea in health and disease

In healthy humans of all ages, the ventilatory response to exercise of up to 10–20-fold greater than resting levels is achieved with remarkable precision and efficiency in terms of CO<sub>2</sub>, O<sub>2</sub> and pH regulation of arterial blood and economy of effort on the part of the respiratory muscles. The key primary drivers of this near-isocapnic hyperpnoea, which is so tightly and mysteriously linked to respiratory CO<sub>2</sub> exchange, has been narrowed to a central command, feed-forward stimulus with parallel recruitment of both locomotor and respiratory muscles and a feedback stimulus involving thinly myelinated afferents from contracting locomotor muscles [57]. There is strong evidence linking ventilation to increases and decreases in CO<sub>2</sub> flow to the lung (perfusion (Q') × content of CO<sub>2</sub> in mixed venous blood) as achieved *via* diet-induced changes in the respiratory exchange ratio and sinusoidal work rates in humans or *via* experimental manipulation of venous return to the lung in animal models; for a summary see [57–59]. Although the exact nature of this stimulus and its site(s) of action (presumably in the lung or pulmonary vasculature) remain unknown, we believe the evidence points strongly to an important modulatory role for CO<sub>2</sub> flow during exercise (see the Healthy ageing section) and especially under resting conditions. For example, note the marked similarity in resting values of arterial (and alveolar) CO<sub>2</sub> tension among and within healthy humans of markedly different body mass and tissue CO<sub>2</sub> production, which is only achievable *via* regulation of V<sub>A</sub> in precise proportion to CO<sub>2</sub> production (V<sub>CO<sub>2</sub></sub>) ( $P_{aCO_2} = V'_{CO_2} / V'_A \cdot K$ , where K=863). Attempts have been made to implicate the carotid chemoreceptors in this presumed V<sub>CO<sub>2</sub></sub> effect during exercise; however, several denervation studies have shown that chemoreceptors are not required for the isocapnic hyperpnoea normally achieved in moderate intensity steady-state exercise [57]. However, it is only recently that new insights have been gained into these mechanisms in humans, with implications for the regulation of exercise hyperpnoea in health, COPD and CHF.

### Central command

In the past decade, several lines of evidence have demonstrated the importance of feed-forward central command to exercise hyperpnoea in humans, as originally hypothesised by KROGH and LINDHARD [60] over a century ago, based on 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 hypnotised human at rest in response to “suggested exercise” [61, 62]. 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 curarisation [63] or epidural lidocaine [64, 65], or inhibiting central motor command *via* tendon vibration [66], 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 stimulation 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) [67]. In addition, these regions were shown to be activated in intact exercising animals [68]. However, recent human studies clearly point to the motor cortex and midbrain as key sites of central command. First, electrical or magnetic transcranial stimulation [69], deep brain stimulation [70] and stimulation of the primary cortex [71] all elicited diaphragmatic contractions. Secondly, positron emission tomography imaging in the “suggested” exercise paradigm mentioned above revealed increased blood flow to the motor control regions of the cortex and cerebellum [72, 73]. 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 grey (PAG) and the subthalamic nucleus (STN) as major sites of central command of cardiorespiratory responses to stress [72, 74, 75]. The PAG receives inputs from prefrontal cortex, hypothalamus and nociceptive pathways, and has outputs to the brainstem medullary cardiorespiratory control areas. Stimulation of muscle afferent inputs in humans also elicited excitation of PAG neuronal activity [75]. PATERSON [76] propose that the PAG area is a key “command centre” of functional connectivity to higher centres 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 hyperpnoea resides in the central command centres. However, as summarised, below this regulation also appears to require feedback.

### Muscle afferent feedback

When studied in isolation using direct stimulation of muscle in resting humans, substantial evidence exists for thinly myelinated afferents, responding to the mechanical distortions of muscle contraction and/or metabolite accumulation, in the regulation of exercise hyperpnoea. Their sensory pathway ascends *via* the dorsal horn of the spinal cord to the nucleus of the solitary tract, and to cardiorespiratory neurons of the ventral lateral medulla. What is in doubt is whether these afferents play a significant obligatory role in

exercise hyperpnoea in the normally exercising human, *i.e.* when central command and other mechanisms sensitive to respiratory CO<sub>2</sub> exchange are also operative. A straightforward approach to determining whether this feedback mechanism is “essential” to the normal hyperpnoea 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 and provided negative evidence in all cases, *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 [57, 64, 77]. However, this approach has been shown to block efferents as well as afferents, causing limb muscle weakness. Thus, as with the curare experiments [63], as mentioned above, this intervention would probably 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 blocking these afferents, but without affecting the efferent pathway, is to take advantage of their sensitivity to  $\mu$ -opioids [78]. 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 while breathing room air or CO<sub>2</sub> or during rhythmic arm exercise [79]. However, this blockade did cause substantial hypoventilation and CO<sub>2</sub> retention as well as significant reductions in blood pressure and heart rate in healthy subjects during rhythmic leg cycling exercise (fig. 3). Similar cardiorespiratory effects of fentanyl were also observed in constant load and time trial cycling exercise [80, 81]. We caution that these data do not mean that feedback chemoreception, secondary to the sustained CO<sub>2</sub> retention of 4–8 mmHg PaCO<sub>2</sub> observed with afferent blockade, is ineffective. On the contrary, when the ventilatory equivalent of the heightened chemoreceptor activity secondary to the fentanyl-induced CO<sub>2</sub> retention was accounted for, it was estimated that the total effect of the fentanyl block approached 40–50% of the total hyperpnoea during mild and moderate steady-state exercise [58].

It is especially surprising that muscle afferent blockade affected cardioventilatory responses even under conditions of mild-to-moderate exercise intensity where O<sub>2</sub> supply to contracting muscle met O<sub>2</sub> demand. Such findings are consistent with newer concepts which point to muscle “metaboreceptor” activation in response to venous distention [82], a mechanism which is especially appealing because the proposed stimulus to venous distention, *i.e.* increased muscle blood flow, is a major determinant of respiratory CO<sub>2</sub> exchange and by regulating breathing is participating in its own control. Finally, we need to emphasise 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 nucleus tractus solitarius 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” centres (see earlier). What seems clear from the blockade data (fig. 3) is that the concept of a purely central, adaptive feed-forward control of the cardioventilatory response to exercise is not tenable. Rather, muscle afferent feedback provides critical information deciding both cardiorespiratory responses as well as locomotor muscle effort or so-called “central fatigue” [80, 81, 83].

### Healthy ageing

The major change affecting exercise hyperpnoea and its limitations with healthy ageing 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 [84–86]. These changes have no discernable effect on resting eupnoeic ventilation or PaCO<sub>2</sub> but during exercise there are two major consequences. First, expiratory flow limitation occurs at a level of hyperpnoea that would not elicit these limitations in the younger adult and this in turn will cause hyperinflation, increased work of breathing and dyspnoea. Secondly, even though the dead space volume ( $V_D$ )/tidal volume ( $V_T$ ) ratio is increased with age, PaCO<sub>2</sub> is maintained near resting normocapnic levels throughout moderate exercise intensities because the elderly subject increases total minute ventilation ( $V'_E$ ) (and  $V'_E/V'_{CO_2}$ ) above that in the young, so as to maintain a  $V'_A/V'_{CO_2}$  ratio comparable to that in the young adult (fig. 4). As discussed earlier, we do not know exactly how respiratory CO<sub>2</sub> exchange is sensed to promote this precise regulation of  $V'_A$  relative to  $V'_{CO_2}$ , however, these types of evidence confirm the importance of this humoral mechanism at least as a “fine tuner” of the hyperpnoeic response [58, 59]. By contrast, this augmented (total) ventilatory response combined with the age-diminished maximum flow–volume envelope results in flow limitation and a greater work of breathing at any given  $V'_E$  in the exercising elder [86].

### Chronic obstructive pulmonary disease

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 dyspnoea and to exercise limitation [87]. Three approaches to reducing the

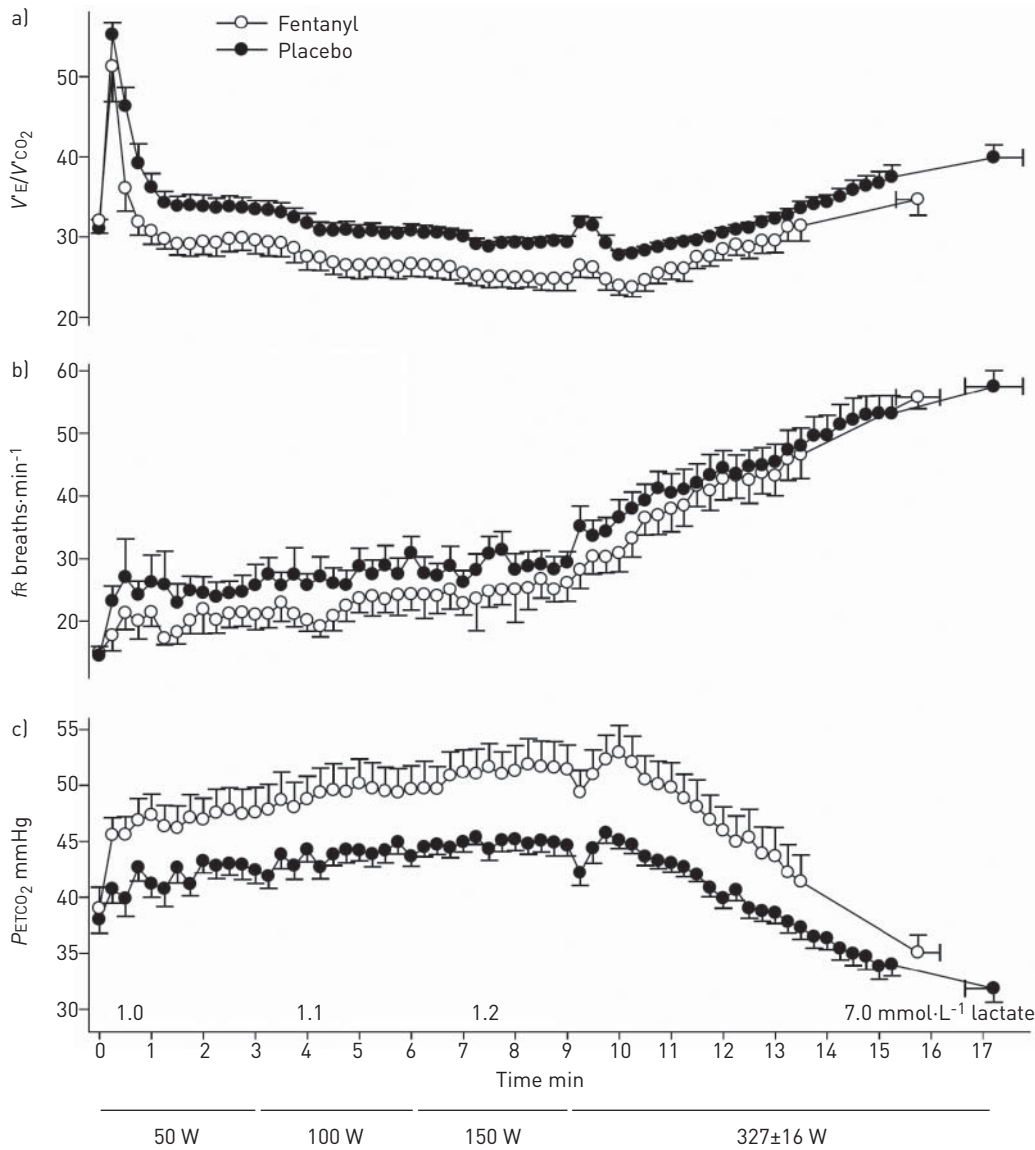


FIGURE 3 a) Reduced steady-state ventilation (minute ventilation ( $V'_E$ )/CO<sub>2</sub> production ( $V'_{CO_2}$ )) and b) respiratory frequency ( $f_R$ ), and c) the resultant CO<sub>2</sub> retention (end-tidal CO<sub>2</sub> tension ( $P_{ETCO_2}$ )), resulting from type III–IV muscle afferent blockade *via* intrathecal fentanyl in healthy humans during mild to heavy exercise intensities. Note the persistence of the hypoventilatory response over time in the presence of type III–IV limb muscle afferent blockade, especially during mild and moderate intensity exercise, despite the presence of increased CO<sub>2</sub>-induced chemoreceptor stimulation. Plasma lactate levels were within 0.5 mmol·L<sup>-1</sup> of resting values ( $0.9 \pm 0.1$  mmol·L<sup>-1</sup>) during 50–150 W exercise and rose to seven-fold greater than resting values during exercise at 325 W in both the placebo and fentanyl trials. Reproduced from [79] with permission from the publisher.

expiratory flow limitation have resulted in improved exercise performance and decreased limb fatigue. First, inhalation of low density He/O<sub>2</sub> mixtures expands the maximum flow–volume envelope in most patients thereby reducing the exercise-induced expiratory flow limitation during tidal breathing and also reducing the rate of development of limb fatigue during exercise [88]. Secondly, supplemental inspired O<sub>2</sub> reduced chemoreceptor drive and exercise  $V'_E$ , slowed the rate of development of limb muscle fatigue [88] and improved exercise performance [88, 89]. Thirdly, intrathecal fentanyl was used (fig. 5) to reduce muscle afferent input in COPD patients, resulting in reduced breathing frequency, which in turn reduced dead space minute ventilation and total ventilation (but not  $V'_A$ ), flow limitation and hyperinflation [90]. So, as in health (fig. 3), muscle afferent input in exercising COPD patients contributes significantly to exercise hyperpnoea but with a negative, rather than positive, influence on exercise performance [58]. Given the markedly diminished aerobic capacity and reduced fatigue resistance [88] of limb locomotor muscles in the



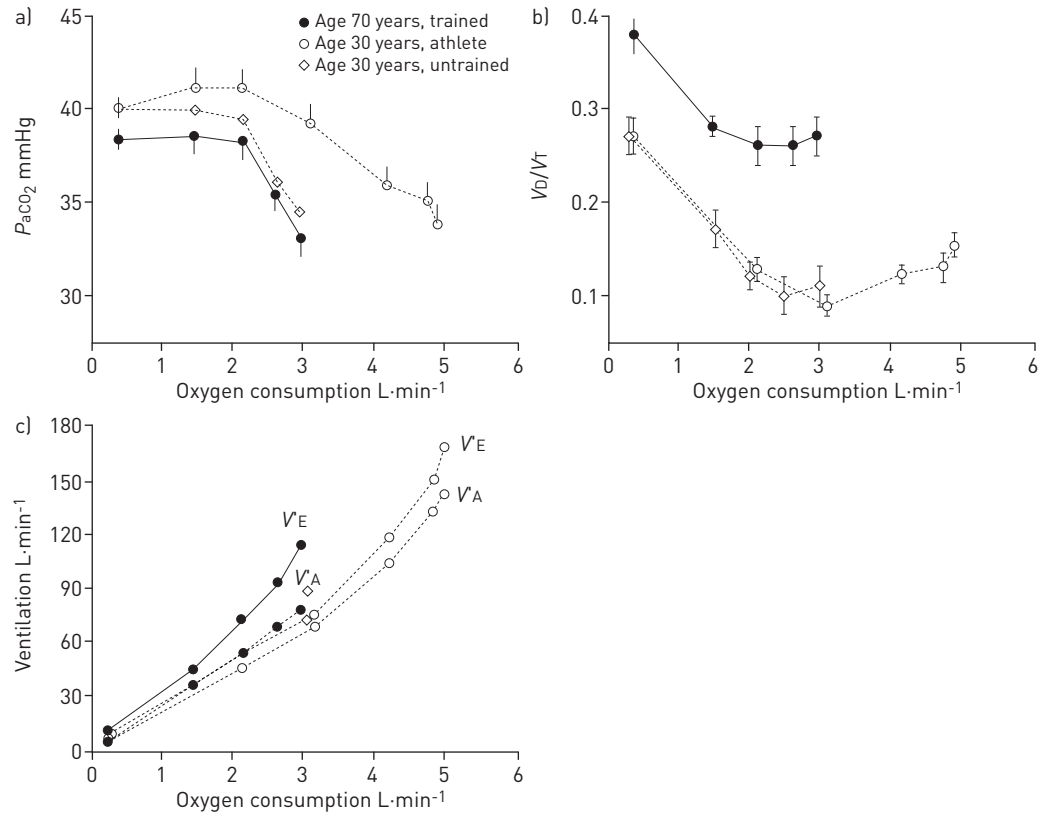


FIGURE 4 Steady-state ventilatory response to treadmill walking in young and elderly healthy subjects. a) Arterial CO<sub>2</sub> tension ( $P_{aCO_2}$ ) is determined by the relationship of alveolar ventilation ( $V'_A$ ) to CO<sub>2</sub> production ( $V'_{CO_2}$ ) so that  $P_{aCO_2} = (V'_{CO_2}/V'_E - V'_D) \times K$  where  $V'_E$  is total minute ventilation,  $V'_D$  is dead space minute ventilation and  $K$  is a constant [58]. b) Note in the elderly that their dead space ventilation (dead space volume ( $V_D$ )/tidal volume ( $V_T$ )) is greater than in younger subjects at rest and exercise. c) The older subjects adjust their total  $V'_E/V'_{CO_2}$  so it is higher than in the young during mild-to-moderate intensity exercise resulting in similar  $V'_A/V'_{CO_2}$  ratio and isocapnic hyperpnoea. Data from [85].

sedentary COPD patient [91, 92], specific resistance training of the legs [93] might result in reduced stimuli to muscle metaboreflexes and, therefore, less tachypnoea and hyperpnoeic response to exercise.

#### Congestive heart failure

CHF patients commonly respond to exercise with tachypnoeic hyperventilation and even occasionally oscillatory breathing over time, the severity of which is prognostic of morbidity and mortality in CHF

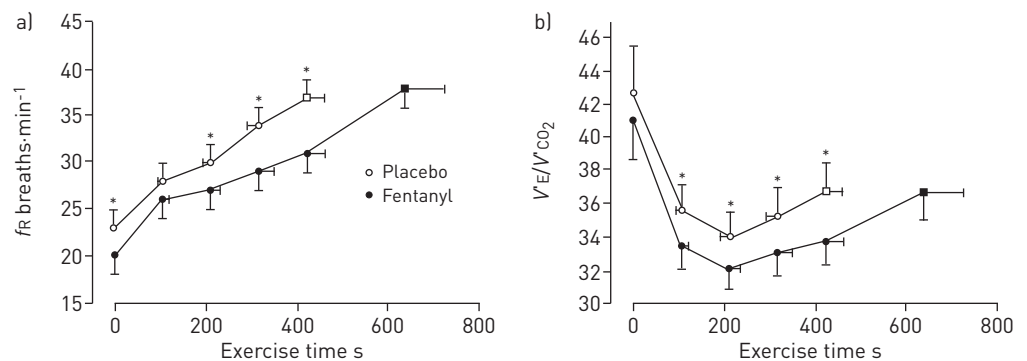


FIGURE 5 Effects of intrathecal fentanyl blockade on a) respiratory frequency ( $f_R$ ) and b) minute ventilation ( $V'_E$ )/CO<sub>2</sub> production ( $V'_{CO_2}$ ) ratio in chronic obstructive pulmonary disease patients cycling at 80 W (80% of maximum). Fentanyl block resulted in a reduced  $f_R$  and  $V'_E/V'_{CO_2}$  which persisted throughout the exercise. Dead space volume/tidal volume ratio during exercise was also reduced as  $f_R$  fell with fentanyl (data not shown). Dyspnoeic sensations were reduced and exercise time prolonged as  $V'_E$  and expiratory flow limitation were reduced with fentanyl blockade. \*:  $p < 0.05$  between conditions. Reproduced from [90] with permission from the publisher.

patients [94, 95]. Dead-space ventilation and  $V'_E/V'_{CO_2}$  are high, owing primarily to the increased breathing frequency, but so is  $V'_A/V'_{CO_2}$ ; thus, arterial hypocapnia is common [96]. There are several potential reasons for the hyperventilatory response. First, carotid chemoreceptors are substantially hypersensitised 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 [13]. This chemo-hypersensitisation will also increase control system loop gain (see the section on OSA) and contribute to the unstable, oscillatory ventilation sometimes observed during exercise [97]. Secondly, muscle mechanoreceptors are also hypersensitised in CHF in combination with a depressed muscle metaboreceptor sensitivity [98, 99]. 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 with age-matched controls [100]. Thirdly, high pulmonary vascular pressures are common in CHF, especially during exercise and in the presence of pulmonary oedema; this would precipitate pulmonary C fibre stimulation and a tachypnoeic ventilatory response and would also be expected to contribute to unstable, oscillatory ventilation [95, 101].

These hyperventilatory responses as well as the underlying hypersensitivity of muscle afferents and chemoreceptors in CHF contribute importantly to exercise performance limitation. This is primarily because of the augmented intrathoracic pressures and increased work of breathing and accompanying dyspnoea 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 [102]. Further, pressure support elicited substantial increases in limb muscle blood flow and muscle oxygenation [103, 104], in both CHF patients and an animal model [105], due to both an increase in stroke volume and cardiac output in combination with a greater local vasodilation of locomotor muscle vasculature. This dual effect, *i.e.* increased cardiac output and limb vascular conductance during exercise with pressure support, was attributed to: 1) a mechanical effect of 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 stroke volume observed with positive pressure support during exercise in health [105, 106]; and 2) a reduced reflex feedback effect from respiratory muscle metaboreceptors [105]. Similarly, transient inhibition of hypersensitised carotid chemoreceptors in CHF animal models also reduced locomotor muscle vascular resistance and increased limb blood flow both at rest and during exercise [107].

Chronic exercise training [108, 109] as well as specific respiratory muscle training [110, 111] in CHF animal models and in human patients reduces the hypersensitivity of the carotid chemoreceptors, limb muscle mechanoreceptors and the respiratory muscle metaboreflex. These “desensitising” effects on multiple feedback regulators result in a reduced work of breathing and reduced sympathetic vasoconstriction, thereby improving  $O_2$  transport to contracting locomotor muscles and exercise performance.

### OSA and the ventilatory control system

Significant amounts of sleep apnoea and sleep disordered breathing exist in the general population, with obesity, male sex, age and craniofacial structure as major risk factors [49]. Severe cases (apnoea–hypopnoea index (AHI)/oxyhaemoglobin ( $HbO_2$ ) desaturations  $>20$ – $30$  events· $h^{-1}$ ) commonly lead to high chemosensitivity, elevated sympathetic vasoconstrictor activity and endothelial dysfunction, all of which elicit both nocturnal and daytime systemic and often pulmonary hypertension [49]. A form of daytime hypoventilation and  $CO_2$  retention in the obese is also tightly linked, perhaps in part *via* chemoreceptor “resetting”, to carryover effects from nocturnal hypoventilation and  $CO_2$  retention during sleep and is often effectively eliminated *via* the use of nasal positive pressure ventilation to correct the nocturnal hypoventilation [112]. 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 apnoeas [113]. But what role might these control mechanisms play in the more prevalent condition of cyclical OSA? Certainly the popular view that OSA is a problem of an anatomically compromised upper airway has merit, but accumulating evidence now recognises that repetitive airway obstructions in sleep are also often a function of other important characteristics of the ventilatory control system [40, 114, 115].

### Anatomical/functional links in OSA

First, we know that central respiratory motor output recruits first the hypoglossal, then (milliseconds later) the phrenic motor neurons serving the upper airway dilators and respiratory pump musculature, respectively [116, 117]. Secondly, the fundamental effects of the loss of “wakefulness” include 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<sub>2</sub>-induced central ventilatory instability and airway calibre. Therefore, 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 [118, 119]; conversely, preventing oscillations in central respiratory motor output by preventing transient hypocapnia *via* dead space rebreathing, also prevented airway obstructions, at least in those subjects with a relatively high chemosensitivity and sensitive apnoeic threshold [120]. Finally, the passive collapsibility of the upper airway, by itself, in sleeping humans accounts for only a relatively small portion of the variability in AHI in OSA [121, 122]. Alternatively, 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 central instability including high control system “loop gain”, sensitive arousal thresholds and/or sluggish responsiveness of upper airway dilator muscles to chemoreceptor stimuli [114, 120, 123, 124]. These characteristics are sometimes inherent to the patient, but are also acquired and intensified *via* the repeated intermittent hypoxaemia, transient arousals and obstructions.

The tendency towards ventilatory instability depends on “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. In turn, loop gain is determined by both controller (chemosensitive) and plant gains. Chemosensor gain is defined by the slope of the ventilatory response to hypercapnia and hypocapnia, *i.e.*  $\Delta V'E/\Delta PaCO_2$ . Plant gain is determined by the magnitude of the reduction in  $PaCO_2$  resulting from a given change in ventilation ( $\Delta PaCO_2/\Delta V'E$ ), *i.e.* the efficiency with which CO<sub>2</sub> is eliminated. These concepts and their effects on ventilatory stability and the apnoeic threshold may be more readily appreciated when presented in graphical form (see references [97] and [125]).

#### **OSA pathogenesis**

In figure 6 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 on sleep stage stability. In one scenario, 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. In the other scenario, 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 obstruction as outlined in figures 6 and 7. The key ingredients to regaining respiratory stability are the ability to recruit airway muscle dilators and to open the airway effectively to restore airflow prior to arousal, because the transient arousal accentuates the ventilatory overshoot and hypocapnia leading to subsequent hypopnoeas, apnoeas and obstructions. Accordingly, how the chemoreceptor control system and the airway dilator musculature responds to accumulating CO<sub>2</sub> and HbO<sub>2</sub> desaturation during the apnoea 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 hypopnoeas with occasional arousals or repetitive obstructions [102].

#### **Treatment implications**

Given the critical contributions of a collapsible airway to all types of OSA it is not surprising that continuous positive airway pressure (CPAP) is a highly effective treatment. However, significant numbers of OSA patients are unable to tolerate CPAP or greatly underutilise it [126]. Three types of alternative treatments have shown promise in significantly reducing AHI in selected OSA patients. These include the following: use of supplemental O<sub>2</sub> to reduce chemoreceptor gain [120, 125] and administration of acetazolamide [123, 127] or preventing hypocapnia *via* selective increments in inspiratory CO<sub>2</sub> fraction to reduce plant gain [120]; raising the arousal threshold using sedatives to prevent ventilatory overshoot by helping maintain sleep state during an obstructive apnoeic event until airway dilator muscle recruitment restores patency prior to arousal [128–130]; reducing airway collapsibility *via* recruitment of airway muscle dilators using small increments in  $PaCO_2$  *via* a deadspace rebreathing system [120]. In addition, combining treatments to reduce loop gain or raise arousal threshold, together with small reductions in airway collapsibility *via* moderate weight loss or mandibular advancement has also been attempted [131–133].

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 simplifying our ability to recognise specific risk factors in OSA populations so that therapy can be individualised and

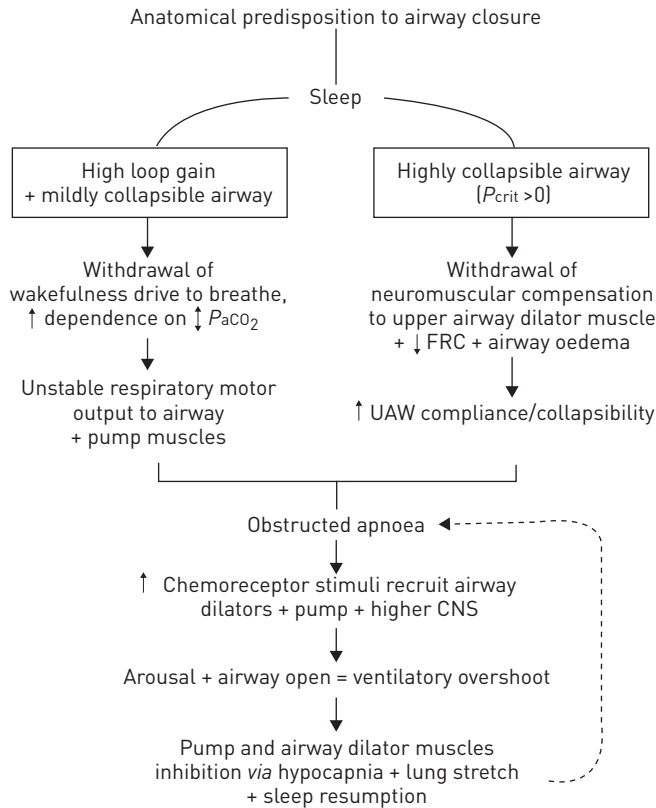


FIGURE 6 Schematic illustrating the interactive effects of airway anatomy with neurochemical control on the magnitude and stability of central respiratory motor output, airway muscle dilator recruitment, and arousability in the pathogenesis of cyclical obstructive sleep apnoea (OSA). Patients with an 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 during the obstructive apnoeic period on subsequent, post-apnoeic electroencephalogram arousal, ventilation and airway patency, *i.e.* all of which will dictate whether the apnoeic episodes will become cyclical. These control system characteristics include the chemoresponsiveness of both the upper airway and chest wall pump muscles, and of central nervous system (CNS) arousability to the rising chemoreceptor stimuli (also see the main text and fig. 7).  $P_{aCO_2}$ : arterial  $CO_2$  tension;  $P_{crit}$ : critical value of positive end-expiratory pressure; FRC: functional residual capacity; UAW: upper airway. Reproduced from [40] with permission from the publisher.

targeted [40, 114]. Recently, WELLMAN *et al.* [134] have proposed a promising screening tool using the routine clinical polysomnogram to characterise 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 individualising therapy for OSA by phenotyping patients have also been recently applied to an exciting, novel treatment for moderate-to-moderately severe OSA that utilises hypoglossal nerve stimulation during inspiration *via* implanted electrodes triggered by an implanted transducer which senses intrathoracic pressure [135, 136]. This therapy, which recently received Food and Drug Administration approval in the USA, was shown to be safe and highly effective over a 6 month period 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 prescreened to: 1) include only those with a site of upper airway collapse most likely to be prevented by forward movement of the tongue, achieved *via* hypoglossal nerve stimulation; and 2) to exclude those with a significant prevalence of central and mixed apnoeas [136]. Based on current knowledge of the pathophysiology of OSA, we would predict that the patients included in this latter category would probably have high chemosensitivity and loop gain. These patients might well benefit from a combined therapy of hypoglossal stimulation plus reduced chemoreflex gain, achieved *via* supplemental  $O_2$  or by means of an (as yet undiscovered) pharmacologically induced reversible blockade of hyperchemosensitivity.

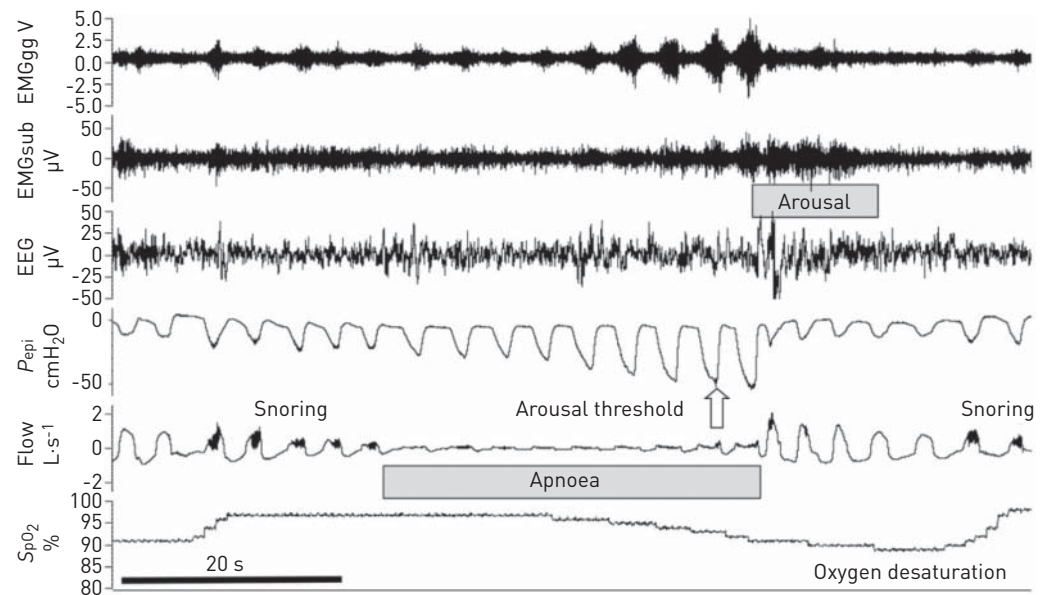


FIGURE 7 Polysomnographic tracing of an obstructed apnoeic event to illustrate the compensatory events occurring during and following the obstruction. The patient had an apnoea–hypopnoea index of 56 events·h<sup>-1</sup>. The cessation and resumption of flow defines the apnoeic event. Note the progressive increase in inspiratory effort ( $P_{epi}$ ) and airway dilator muscle electromyogram (EMG) during the apnoea, the transient arousal coincident with airway opening and ventilatory overshoot at apnoea 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 apnoea. Arousal is determined by the pharyngeal pressure achieved through respiratory pump muscle contractions during an airway obstruction at the point of EEG arousal. EMGgg: EMG of the genioglossus muscle (intramuscular); EMGsub: EMG of the submental muscle (surface); EEG: electroencephalogram (C3–A2);  $P_{epi}$ : pressure at the level of the epiglottis; Flow: airflow measured *via* nasal mask and pneumotachograph;  $SpO_2$ : arterial oxygen saturation measured *via* pulse oximetry at the finger. Reproduced from [114] with permission from the publisher.

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

Throughout this review, we have emphasised 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, heart failure and OSA. Does it follow that 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 apnoea [137, 138]? There is support for carotid body denervation: 1) some older studies of CBX in asthmatic humans showed significant sustained reductions in blood pressure [139]; 2) in the rabbit model of CHF, CBX reduced renal sympathetic nerve activity and blood pressure and prevented periodic breathing [140], and in rodent models of spontaneous hypertension, CBX caused substantial reductions in systemic blood pressure [141]; 3) in rodents CBX prevented the development of insulin resistance and hypertension induced *via* hypercaloric diets [142], substantially increased survival following myocardial infarction [143] and prevented hypertension induced by chronic intermittent hypoxaemia [144]; and d) using an irreversible pharmacological inhibitor of the enzyme responsible for the gaseous transmitter H<sub>2</sub>S in the carotid body in a rodent model of severe CHF almost completely normalised the heightened carotid chemosensitivity as well as the accompanying breathing instability and sympathoexcitatory state [145]. However, there are concerns, including: 1) whether selective chemo-denervation can be achieved without affecting baroreceptor sensory input or its sensitivity [146]; 2) to what extent will long-term compensation for CBX normalise markedly reduced CO<sub>2</sub> chemosensitivity and eupnoeic ventilation in humans [147]; 3) in the absence of carotid chemoreceptors, will patients with airway disease,  $V'A/Q'$  maldistribution and high  $VD/V_T$  mount sufficient compensatory hyperpnoea to prevent chronic hypercapnia [147]; and 4) will those denervated patients who develop OSA, with ageing and/or weight gain or upon achieving a post-menopausal state, experience apnoea prolongation and more severe hypoxaemia and its sequelae [40, 120]? Of course, following CBX, any sojourn to even moderately high altitudes will markedly exacerbate the usual level of

arterial hypoxaemia. Alternatively, we need to determine if therapies that acutely inhibit carotid chemoreceptors or chronically reduce carotid chemoreceptor hypersensitivity 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 chemoreceptor desensitising and sympathoinhibitory effects of habitual exercise training, especially interval-type training, in CHF and hypertension [148–151].

## 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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