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Clinical consequences of altered chemoreflex control

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Abstract

Control of ventilation dictates various breathing patterns. The respiratory control system consists of a central pattern generator and several feedback mechanisms that act to maintain ventilation at optimal levels. The concept of loop gain has been employed to describe its stability and variability. Synthesizing all interactions under a general model that could account for every behavior has been challenging. Recent insight into the importance of these feedback systems may unveil therapeutic strategies for common ventilatory disturbances. In this review we will address the major mechanisms that have been proposed as mediators of some of the breathing patterns in health and disease that have raised controversies and discussion on ventilatory control over the years.

Keywords

Exercise hyperpnea; High altitude; Sleep apnea; Loop gain; Cheyne–Stokes; Oxygen induced hypercapnia; Lung

1. Introduction

Ventilation is a rhythmic act that maintains the oxygen (O₂) and carbon dioxide (CO₂) in the arterial blood and tissues within levels required for survival. The automatic process of breathing originates from the respiratory circuits in the pons and medulla: the dorsal respiratory group within the caudal third of the nucleus of the tractus solitarius (cNTS), the ventral respiratory column (VRC), and the pontine respiratory group (Alheid and McCrimmon, 2008). The cNTS is the principal site of sensory input from pulmonary and airway afferents and from peripheral chemoreceptors and contains mainly inspiratory neurons. Respiratory rhythm generation occurs mainly in the rostral VRC and the activity of caudal VRC modulates the amplitude of respiratory motor output. In the caudal VRC, the ventral respiratory group (VRG) is subdivided into rostral and caudal VRG based on the prominence of inspiratory and expiratory neurons respectively. The rostral VRC contains the

Botzinger and preBotzinger complex, the retrotrapezoid nucleus (RTN), and the parafacial respiratory group. The preBotzinger complex is considered essential for inspiratory rhythm generation (Alheid and McCrimmon, 2008; Ramirez, 2011). The existence of a separate expiratory rhythm generator has been proposed in the region of the RTN/parafacial group (Janczewski and Feldman, 2006). RTN neurons serve as central chemoreceptors and the RTN appears to play a role in the integration of central and peripheral chemoreceptor afferents. The pontine respiratory group contains neurons of the parabrachial complex and the Kolliker–Fuse nucleus with projections to the VRC and areas of the NTS (Alheid and McCrimmon, 2008). The pneumotaxic center in the upper pons inhibits inspiration and damage in this area results in large tidal volumes and bradypnea (Roca and Malhotra, 2010). The central controller provides the major source of input to spinal motoneurons activating the respiratory muscles.

The respiratory center is modulated by chemoreceptors, cells responsive to the chemistry of the fluid around them. Central chemoreception is mediated by the simultaneous effects of CO₂ via proxy of changes in hydrogen ion (H⁺) concentration on multiple types of acid sensitive neurons, as well as glia and vascular cells (Guyenet et al., 2010). It is still unclear if chemoreception relies on a few cells or is widely distributed throughout the brain. The combination of sites that determine chemoreception could vary by arousal state, age and gender (Nattie and Forster, 2010). Several acid-sensitive ion channels on a given neuron may be involved. The RTN contains the most thoroughly characterized group of chemoreceptor cells although the molecular mechanism of their activation is still unknown. Their CO₂ sensitivity seems to rely on three mechanisms: a cell autonomous sensitivity to acid, a paracrine effect mediated by surrounding glial cells and inputs from peripheral chemoreceptors and possibly other central acid sensitive neurons. Other potential chemoreceptor sites include the serotonergic neurons of the raphe, the noradrenergic neurons of the locus coeruleus, NTS neurons and orexinergic neurons (Guyenet et al., 2010, 2012). The peripheral chemoreceptors are located in the carotid bodies at the bifurcation of the common carotid arteries and the aortic bodies near the arch of the aorta (mainly relevant in nonhuman species). They are sensitive to partial arterial oxygen pressure (PaO₂) and to a lesser extent to arterial carbon dioxide partial pressure (PaCO₂) and pH changes. The response of the peripheral chemoreceptors to PaCO₂ is more rapid than that of the central ones. The interactions between central and peripheral chemoreceptors are still debated, but a hyperadditive model has been proposed whereby the gain on the former chemoreceptors can amplify the gain on the latter ones, and vice versa (Smith et al., 2010). Stimulation of the peripheral chemoreceptors during acute hypoxia is accompanied by sympathoexcitation initiated at the carotid bodies. Repeated intermittent hypoxia increases chemosensitivity and sympathetic activity during acute hypoxia (Lusina et al., 2006). The observed linkage between the sympathetic and hypoxic ventilatory response can be secondary to a common central control region or separate control centers modulated to a similar degree, but the causal pathways are still being defined. The rise in ventilation in response to increases in PaCO₂ is approximately linear, but the sensitivity to changes in PaO₂ is very nonlinear; the response to hypoxia is more vigorous at lower levels of PaO₂. Moreover, the effects of hypercapnic and hypoxic stimuli are typically multiplicative; that is, the combined response can exceed the sum of each stimulus given separately.

Secondary modulators also affect ventilation: voluntary control from the cerebral cortex through the corticospinal and corticobulbar tracts, the limbic system and hypothalamus can affect breathing (Evans, 2010; Evans et al., 1999; Kc and Dick, 2010; Nattie and Li, 2012; Shea, 1996). Receptors in the lung include stretch, irritant and J receptors and bronchial C-fibers (Kubin et al., 2006). Finally nose and upper airway receptors, joint and muscle proprioceptors, arterial baroreceptors, pain and temperature can all influence the pattern of breathing (Roca and Malhotra, 2010). During wakefulness a tonic input from various brainstem centers is present (so-called wakefulness stimulus) and is suppressed during sleep (Bulow, 1963; Fink, 1961). Chemosensitivity is also diminished during sleep (McKay and Morrell, 2010; Roca and Malhotra, 2010). Both the hypercapnic and hypoxic ventilatory responses are blunted in stages 2 and 3/4 compared to wakefulness and further decreased in REM sleep (Douglas et al., 1982a,b; Stephenson et al., 2000).

Control of breathing encompasses a wealth of mechanisms that dictate the behavior of the respiratory system at rest, under physiological challenges, and in disease. In this review we highlight several examples of interesting breathing patterns/findings in health and disease that have raised controversies and discussion over recent years (Table 1).

1.1. The concept of loop gain

Several ventilatory control disorders manifest as oscillatory fluctuations in ventilation. The propensity for ventilation to oscillate can be encapsulated by the engineering concept of loop gain, which describes the overall stability of the feedback system controlling ventilation. To employ this concept, we consider the ventilatory control system as characterized by three main components: (a) the ‘controller gain’, which is the response as a change in ventilation per change in unit PaCO_2 or PaO_2 ; (b) the ‘plant gain’, which can be expressed as the change in PaCO_2 or PaO_2 per unit change in ventilation; (c) the circulation delay between the lungs and the peripheral and central chemoreceptors (Cherniack and Longobardo, 2006) (Fig. 1). If we consider a disturbance to the system, i.e. a transient hyperventilation, this disturbance will lower PaCO_2 (depending on the plant gain), and after a delay, the controller will respond to the disturbance with a corrective action (depending on controller gain). Whether oscillations will develop or not, depends on the ratio of the magnitude of the corrective action to the magnitude of the disturbance; this ratio is called “loop gain” (LG) (Khoo et al., 1982).

LG is the product of controller gain and plant gain and determines the stability of the control system. In an inherently stable system, LG is less than 1, i.e. the response to the initial perturbation is smaller in magnitude than the initial insult and the effect of a transient disturbance is eventually suppressed. If LG is greater than 1, the feedback loop will magnify the initial insult and an oscillation will continually grow in amplitude until periodic central apnea (cessation of breathing effort) or ‘periodic breathing’ is observed. An important subtlety is that oscillations will grow or decay at a frequency called the natural frequency (~1 cycle/min in heart failure; ~3 cycles/min in adults at high altitude) that depends on the circulatory delay: thus, LG is examined at this frequency to reflect the propensity to oscillate (Khoo et al., 1982). It is at this natural frequency that the system responds to a sinusoidal disturbance with a response precisely “in phase” with the disturbance, positively reinforcing

it to produce periodic breathing if LG is >1 ; if LG is <1 then transient disturbances are damped away and the system is considered to be stable. This mathematical approach to respiratory control has provided important insight to respiratory instability as exemplified later in this review (Edwards et al., 2013).

2. Cheyne–Stokes respiration in heart failure

Perhaps the most common expression of ventilatory control system instability is Cheyne–Stokes breathing (CSB), characterized by cyclic crescendo–decrescendo changes in ventilation with recurrent periods of central apnea or hypopnea. CSB is seen in approximately a third of patients with congestive heart failure (CHF) and left ventricular systolic dysfunction (Wang et al., 2007). CSB is characterized by a longer cycle duration compared to other forms of periodic breathing due to a longer lung to peripheral chemoreceptor circulation time (Hall et al., 1996). Surprisingly, given the deleterious effect of delay on control instability, there is little direct evidence of a lower cardiac output or greater circulatory delay in those with CSB versus matched CHF patients without CSB. However, raising cardiac output with exercise, pharmacological intervention, or cardiac resynchronization do appear to reduce ventilatory oscillations in CHF (Murphy et al., 2011; Sinha et al., 2004; Stanchina et al., 2007).

In general, the pathogenesis of CSB is considered the result of a hypersensitive ventilatory chemoreflex response to CO_2 in the background of a predisposing increase in circulatory delay. Patients with CSB consistently exhibit increased ventilatory responses to CO_2 compared to those without heart failure (Francis et al., 2000; Javaheri, 2000; Solin et al., 2000; Topor et al., 2001; Xie et al., 2002). The hyperventilation and reduced CO_2 levels in wakefulness in patients with CSB versus those without (Hanly et al., 1993; Naughton et al., 1993) and reduced CO_2 reserve (proximity to apneic threshold), are consistent with increased chemosensitivity given that these three factors are mathematically coupled (Manisty et al., 2006). Consistent with the key role of ventilatory control instability, CSB commonly occurs during non-rapid eye movement sleep, when ventilation is predominantly under metabolic control (Yumino and Bradley, 2008), but less commonly in REM when chemosensitivity is depressed. Yet the cause of the elevated chemosensitivity in CSB is not yet established. A clue may lie with the greater pulmonary congestion/edema in those with CSB compared to controls (greater nocturnal rostral fluid shift, lower PaO_2 and lower diffusing capacity for carbon monoxide) (Szollosi et al., 2008; Yumino et al., 2010). It is often suggested that pulmonary congestion activates pulmonary vagal afferent C fibers that stimulate central respiratory control centers (Yu et al., 1998). However, the role of vagal afferents in mediating increased chemosensitivity remains disputed given the observation of continued CSB despite lung transplantation (vagal denervation) in a case study (Solin et al., 1998). Alternatively, left atrial chamber stretch per se can raise ventilation independent of extravascular lung water (Lloyd, 1990), and also increases chemoreflex sensitivity (Chenuel et al., 2006). The high pulmonary capillary wedge pressure, elevated N-type pro B-type natriuretic peptide (NT-proBNP), and increased left ventricular end diastolic volume in patients with CSB are consistent with such a mechanism (Solin et al., 1999; Tkacova et al., 1997). Interestingly, however, a recent study in rabbits (Ding et al., 2011) demonstrated that reduced carotid arterial blood flow alone provides an increase in chemosensitivity (and

sympathoexcitation) regardless of whether or not it is caused by the induction of heart failure; thus it is quite possible that reduced flow per se promotes chemoreflex sensitization and CSB independent of congestion.

CSB may be further exacerbated by changes in ventilation that occur with arousal from sleep. Arousals typically occur at the peak of the ventilatory effort, and may act to promote instability by reinstating the waking drive to breathe and thereby provoking further overshoot (Trinder et al., 2000); likewise, an increase in upper airway resistance during sleep should also promote greater ventilatory undershoot (Jobin et al., 2012). Patients with heart failure and CSB also have less sensitive cerebral blood flow responses to arterial CO₂ levels; depressed cerebrovascular reactivity to CO₂ may also predispose to CSB by exposing the brain tissue to a greater change in tissue CO₂ and H⁺ for any given change in PaCO₂; this effect is expected to provide the central chemoreceptor with a greater oscillatory stimulus, promoting ventilatory oscillations and thus CSB (Xie et al., 2005).

CSB in patients with heart failure has clear adverse prognostic implications but it is uncertain if it is mechanistically linked to deterioration in cardiovascular function or is simply a reflection of it (Hanly and Zuberi-Khokhar, 1996; Naughton, 2012; Yumino and Bradley, 2008). The challenge arises because CSB is a known consequence of heart failure, so teasing out the extent to which it is also a contributing factor to the progression requires interventional studies. Interventions that target restoration of cardiac function in heart failure patients, e.g. medication optimization and heart transplantation, can lead to improvement of CSB. Thus, at present, the mainstay of therapy for CSB is treatment of the underlying cause, which in most cases requires optimizing heart failure medications. Directly treating CSB in patients with heart failure is associated with improved cardiac outcomes, but an improvement in survival has not been confirmed (Arzt and Bradley, 2006). The use of continuous positive airway pressure (CPAP) can provide improvements in cardiac function in HF patients with CSB (Arzt et al., 2007), but not in those with normal breathing patterns, or in those patients whose CSB is not eliminated with CPAP (non-responders) (Sin et al., 2000). Further, CPAP responders exhibit considerably improved survival compared to CPAP non-responders (Arzt et al., 2007) and untreated controls; yet there is also the possibility that CPAP responders have a survival advantage based on a less severe ventilatory control instability via a less severe cardiac condition. Indeed recent evidence suggests that CHF patients with the most unstable ventilatory control systems are the least likely to respond to CPAP therapy (Sands et al., 2011).

Anti-cyclic mask pressure based devices (e.g. adaptive servo ventilation ASV) are currently being studied. While we await hard outcome data from the ongoing clinical trials, we are limited to examining available data which suggest that important cardiac benefit might be conferred when CSB is abolished with effective therapy (Sharma et al., 2012).

3. High altitude illness and periodic breathing

Barometric pressure decreases with distance from the earth's surface and as a result partial pressure of inspired oxygen (P_IO₂) falls with increasing altitude. At the summit of Mount Everest (altitude 8848 m), the highest point on earth's surface, atmospheric pressure is only

253 mmHg and P_{iO_2} is 43 mmHg (West et al., 1983). At 8400 m, acclimatized climbers have a mean PaO_2 of just 24.6 mmHg and a mean $PaCO_2$ of 13.3 mmHg (Grocott et al., 2009); at this extreme, climbers are therefore breathing ~3-fold more vigorously than at sea level per unit of CO_2 produced. In the face of altitude-induced hypoxia, acute and long-term mechanisms are enacted to facilitate acclimatization, which when ineffective may contribute to severe altitude sickness.

Acute ascent to high altitude (defined as >2500 m) lowers PaO_2 , which induces a rise in ventilation via the peripheral chemoreceptors. This hyperventilation also promotes hypocapnia and respiratory alkalosis, which limit the response to hypoxia. Ventilatory acclimatization follows within days to weeks of ascent and involves a progressive increase in ventilation and lowered $PaCO_2$ for any given altitude (i.e. any given PiO_2). These effects are not rapidly reversed, and the mechanisms involved are subject to current research. The most notable effect is the progressive ~2–3 fold rise in the sensitivity of the ventilatory response to hypoxia, in contrast to a minimal effect on the CO_2 response slope (Sato et al., 1994; White et al., 1987). Such hypoxic ventilatory sensitization is considered to result from both a progressively increased intrinsic chemosensitivity of the carotid bodies as well as augmented neural processing of chemoreceptor inputs (Bisgard, 2000; Dwinell and Powell, 1999). There is also a progressive left-shift of the CO_2 response (increase in ventilation) which may occur in part via renal bicarbonate excretion which acts to offset the acute respiratory alkalosis (Weil, 1986).

Not all sojourners overcome the physiological challenges of high altitude; many are susceptible to illnesses ranging from the mild symptoms of acute mountain sickness (AMS), to the severe life-threatening conditions of high altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE). The pathophysiology of these syndromes is not entirely understood. AMS manifests as headaches, sleep disturbances, gastrointestinal symptoms, but can develop into HACE manifesting as encephalopathy. Hypoxemia is considered the initial cause of each condition, particularly as treatment with oxygen has vital remedial effects. HACE likely results from hypoxemia-induced cerebral vasodilation and increased cerebral capillary pressures plus perhaps a chemically-induced increase in the permeability of cerebral endothelium (Hackett and Roach, 2001). In HAPE, hypoxia-induced pulmonary vasoconstriction raises pulmonary artery pressures and facilitates edema formation in some lung units. Yet it is the non-uniformity of pulmonary arteriolar vasoconstriction that is considered to be a key contributor to HAPE; heterogeneous vasoconstriction provides high pressures to the capillaries supplied by the least constricted arterioles (Duplain et al., 2000). The role of impaired sodium driven alveolar fluid clearance and inflammation has also been described (Basnyat and Murdoch, 2003).

There is considerable heterogeneity in the susceptibility to altitude illness. In part this susceptibility can be attributed to a less powerful ventilatory response to hypoxia and a greater prevailing hypoxic exposure as a consequence (Nespoulet et al., 2012). Indeed respiratory stimulants (acetazolamide, theophylline) considerably improve altitude-illnesses presumably ultimately acting via partial restoration of normoxia (Fischer et al., 2000; Leaf and Goldfarb, 2007). Further, a major mechanism underlying the known beneficial effects of gradual ascent may be the increased time for strengthening the hypoxic ventilatory response.

Despite the beneficial effects of a strong hypoxic ventilatory response on minimizing arterial hypoxemia, a major trade-off is the reduced stability of the ventilatory control system. Periodic breathing in the form of cyclic central apneas and hypopneas occurs in almost all individuals at a sufficiently high altitude. These respiratory disturbances promote cyclic arousal from sleep (Khoo et al., 1996; Reite et al., 1975) that may disrupt daytime functioning, although the consequences of altitude-induced sleep apnea have not been well established. The presence of periodic breathing at altitude is strongly associated with a robust hypoxic ventilatory response (Nespoulet et al., 2012; White et al., 1987) and thus—paradoxically—is seen frequently in the patients with higher oxygen levels i.e. those that are the least susceptible to AMS. Hence, future studies examining the potentially deleterious effects of altitude-induced periodic breathing (and associated cyclic hypoxemia) on sleepiness and daytime wellbeing that control for baseline oxygenation are lacking. Interestingly, oxygen, and oral acetazolamide and theophylline can all improve periodic breathing and arousal from sleep as well as resting oxygenation and AMS (Anholm et al., 1992; Khoo et al., 1996; Lahiri et al., 1983; Reite et al., 1975; Sutton et al., 1979; Fischer et al., 2000; Leaf and Goldfarb, 2007).

4. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a common disorder with serious neurocognitive and cardiovascular sequelae. The pathogenesis of this condition is thought to be highly variable across individuals with some having primarily an anatomical problem, whereas other afflicted individuals have dysfunction of upper airway dilator muscles and others have unstable ventilatory control. Some patients likely have combinations of abnormalities, which work together to predispose to OSA. OSA patients in general have anatomical compromise based on either fat deposition from obesity or via craniofacial structure. Through protective reflexes present during wakefulness, increased pharyngeal dilator muscle activity is present which maintains pharyngeal patency even in those with anatomical compromise. However, with the onset of sleep, and concomitant loss of protective reflexes, the pharyngeal airway is susceptible to collapse in the face of falling pharyngeal dilator muscle activation.

The role of ventilatory control instability in the pathogenesis of obstructive sleep apnea has only recently been appreciated. Individuals with high LG, as has been associated with OSA (Wellman et al., 2004, 2013; Younes et al., 2001), are prone to periodic breathing. The mechanism whereby high LG yields OSA is debated but likely involves fluctuations in output from the central pattern generator in the brainstem. The central pattern generator provides output to both the pump muscles (diaphragm) as well as the upper airway muscles via the hypoglossal motor nerve. When output to the upper airway muscles reaches a nadir, the upper airway is susceptible to narrowing; the subsequent difficulty reopening a narrowed airway in the face of progressively increased ventilatory drive and more-negative downstream pressures is likely to be one mechanism by which increased LG promotes obstructive apneas. In addition, a higher LG promotes a greater rise in ventilatory drive for even small reductions in airflow, thereby promoting arousal from sleep and posing a hindrance to achieving stable breathing (Edwards et al., 2012; Wellman et al., 2011). Thus, methods to stabilize ventilatory control (e.g. oxygen, acetazolamide, or new methods to promote isocapnia) are likely to improve OSA in selected individuals (Wellman et al., 2008;

Xie et al., 2013). On the other hand, some recent data suggest that unstable ventilatory control (high LG) may be an acquired abnormality in OSA, suggesting it is an effect rather than a cause of OSA (Loewen et al., 2009). Ongoing studies should help to resolve these issues, but high loop does likely predispose to the development of OSA and may represent a perpetuating factor once the disease is established. Ultimately treatment of OSA will likely be based on underlying cause such that individualized therapy can be provided based on the mechanism predisposing to OSA in a given individual.

5. Obesity hypoventilation syndrome

Obesity hypoventilation syndrome (OHS) is characterized by a combination of obesity (body mass index $> 30 \text{ kg/m}^2$) and arterial hypercapnia ($\text{PaCO}_2 > 45 \text{ mmHg}$) during wakefulness, not explained by other causes of alveolar hypoventilation (Malhotra and Hillman, 2008; Piper, 2011). Accurate epidemiologic data are limited but prevalence is reported to be up to 31% in hospitalized severely obese patients and incidence increases as obesity increases (Nowbar et al., 2004). The condition is largely under-recognized and very often patients are diagnosed with the syndrome after intensive care unit admission for acute hypercapnic respiratory failure (Carrillo et al., 2012; Pepin et al., 2012). Symptoms can be very similar to OSA with excessive daytime sleepiness, morning headaches, dyspnea and decreased objective attention/concentration (Mokhlesi, 2010; Nowbar et al., 2004). Up to 90% of patients with OHS have a combination of central hypoventilation and OSA (Rapoport et al., 1986).

It is unclear why some obese individuals maintain normal ventilation during wakefulness and sleep while others develop daytime hypercapnia (Piper and Grunstein, 2010). Obesity is associated with restrictive physiology with reduced respiratory system and lung compliance because of breathing at abnormally low lung volumes (Behazin et al., 2010; Pelosi et al., 1997). High pleural and intra-abdominal pressures reduce functional residual capacity, cause small airway closure and air trapping, lower expiratory flow rates and increase intrinsic positive end expiratory pressure. All of the above may be further exacerbated in the supine position and increase the work of breathing. Patients with OHS have lower vital capacity, total lung capacity and expiratory reserve volume compared to eucapnic obese patients (Kaw et al., 2009; Piper and Grunstein, 2011). Hypercapnic patients were found to have an abnormally high work of breathing both sitting and supine, awake and asleep, compared to eucapnic patients with OSA (Lee et al., 2009). Patients with OHS also have a more central fat distribution. Centrally distributed weight reduces lung volumes to a greater degree and is associated with poorer gas exchange than peripherally deposited weight (Lazarus et al., 1997; Resta et al., 2000; Zavorsky and Wilson, 2010).

Obesity is normally associated with increased respiratory drive which helps to maintain eucapnia (Steier et al., 2009). Patients with OHS, however, fail to exhibit this augmented drive and ventilatory responsiveness to hypoxia and hypercapnia (Piper and Grunstein, 2011; Sampson and Grassino, 1983; Zwillich et al., 1975). Hypoventilation worsens during sleep, at least in part due to upper airway obstruction (Malhotra and Hillman, 2008; Piper and Grunstein, 2011). The degree of daytime hypercapnia seems to be directly related to the degree of sleep disordered breathing and in many cases OHS responds to relief of upper

airway obstruction by CPAP (O'Donoghue et al., 2003; Piper and Grunstein, 2011). Only a minority (roughly 10%), however, of patients with OSA develop daytime hypercapnia. A model has been proposed where daytime hypercapnia can develop if sleep disordered breathing duration is sufficiently long or interapnea periods too short to restore ventilation and eucapnia (Berger et al., 2000). Berger and colleagues have suggested that gradual elevations in CO₂ occur over time since the ventilatory response to hypercapnia is insufficient compared to the rise in CO₂ which occurs during sleep. Daytime hypercapnia ensues with gradual increases in serum bicarbonate induced by nocturnal CO₂ retention. Patients with OHS also exhibit greater degrees of hypoxemia during sleep compared to eucapnic obese patients that could blunt hypoxic ventilatory drive or affect neurotransmitter synthesis (Jones et al., 1985; Piper and Grunstein, 2010, 2011; Zwillich et al., 1975). Leptin, a protein produced by adipocytes that acts on the hypothalamus to reduce appetite and increase energy intake, has been implicated in the impaired ventilatory response of OHS. Leptin deficient mice exhibit features similar to OHS with obesity, hypercapnia, impaired respiratory mechanics and blunted CO₂ response that can be reversed with leptin replacement (Tankersley et al., 1998). Interestingly serum leptin levels are increased in obese individuals and even higher in those with hypercapnia implying the development of resistance to the ventilatory stimulatory effects of leptin (Kalra, 2008; Phipps et al., 2002; Piper and Grunstein, 2010). Hyperleptinemia has been associated with a reduction in respiratory drive and hypercapnic response in obese individuals, irrespective of the amount of body fat (Campo et al., 2007).

The presence of OHS is associated with morbidity and mortality. Cardiac and metabolic complications such as hypertension, congestive heart failure, angina, cor pulmonale and insulin resistance are higher in OHS compared to eucapnic obesity (Berg et al., 2001; Priou et al., 2010). Compared to obese controls, OHS patients are more likely to be hospitalized, require more intensive care unit management, have longer lengths of stay and are more likely to be discharged to a long term facility (Berg et al., 2001; Nowbar et al., 2004). If left untreated, these patients have higher mortality compared to obese people without hypercapnia (Nowbar et al., 2004; Perez de Llano et al., 2005). Correction of hypercapnia during wakefulness can often be achieved with management of sleep disordered breathing with positive pressure ventilation. CPAP treatment alone can be sufficient in cases of OSA, but bilevel therapy may be required where there is a strong central hypoventilation component (Brown, 2013; Malhotra and Hillman, 2008). With noninvasive ventilation expiratory pressure is adjusted to eliminate obstructive events and prevent derecruitment of atelectatic lung and inspiratory pressure to control central hypoventilation. Continuous improvement can be observed after 3 months of CPAP therapy and in some cases bilevel can be converted to CPAP once hypercapnia is controlled (Piper and Sullivan, 1994; Piper et al., 2008). Weight loss achieved either through medical management or bariatric surgery is associated with improvements in respiratory mechanics and sleep disordered breathing, but its long term efficacy for OHS has not been extensively studied (Greenburg et al., 2009).

6. Oxygen induced hypercapnia

Severe chronic obstructive pulmonary disease (COPD) can be characterized by alveolar hypoventilation with hypercapnia secondary to ventilation/perfusion (V/Q) abnormalities

and increased work of breathing (Malhotra et al., 2001). Hypercapnia can appear or further worsen during acute exacerbations of the disease. Respiratory acidosis has been described in up to 20% of patients admitted with acute exacerbations of COPD and is predictive of subsequent intensive care unit use and mortality (Jeffrey et al., 1992; Plant et al., 2000). The role of high flow oxygen as an important cause of hypercapnia in the setting of acute exacerbations has been appreciated and debated for more than 50 years (Calverley, 2000; McNicol and Campbell, 1965). Although the existence of the phenomenon has been challenged, studies have shown that this mechanism is a factor in some patients who develop acute respiratory acidosis when given oxygen (Robinson et al., 2000). Clearly, in some cases, worsening hypercapnia can be related to progression of the underlying disease and perhaps unrelated to therapies provided. However, in a study of patients admitted with COPD exacerbation, acidosis resolved in a third of hyperoxic patients when oxygen concentration was reduced (Plant et al., 2000). It is unclear what distinguishes the retainers from the non retainers. Lower initial PaO_2 is the only described difference between those who develop worsening hypercapnia compared to those who do not, and hypoxemia is a better predictor of oxygen induced hypercapnia than the initial PaCO_2 (Bone et al., 1978; Robinson et al., 2000).

The mechanisms underlying CO_2 retention with oxygen treatment have been the subject of longstanding debate and relevant studies have produced variable results. A major limitation is that studies have been performed under varying conditions using widely different methodologies. Suppression of the hypoxic drive to breathe has traditionally been implicated. Aubier and colleagues found that uncontrolled oxygen administration led to an initial decrease in minute ventilation that soon recovered, however, and was only marginally lower than baseline. PaCO_2 continued to increase and the authors concluded that V/Q changes, an increase in the physiological dead space, were responsible for this response (Aubier et al., 1980). In a study of ventilated patients with advanced COPD, oxygen supplementation led to an increase in the CO_2 recruitment threshold, which is a measure of CO_2 responsiveness of the mechanically unloaded respiratory system and is independent of mechanical properties and respiratory muscle strength (Dunn et al., 1991). These data support a depression in central chemosensitivity to CO_2 during hyperoxia compared to normoxia. Robinson et al. (2000) separated a group of patients with COPD exacerbation into CO_2 retainers and non-retainers. Ventilation fell significantly with oxygen administration by about 20% in the retainers, whereas there was no change in the non-retainers. Both studies also confirmed the significant increase of alveolar dead space with hyperoxia (Dunn et al., 1991; Robinson et al., 2000). In theory, oxygen supplementation reduces hypoxic pulmonary vasoconstriction, which can increase perfusion to poorly ventilated lung units. Such diversion of blood flow can reduce perfusion of well ventilated lung units which contributes to ventilation without perfusion (i.e. dead space) (Malhotra et al., 2001). Hypercapnia might also cause some bronchodilation of well ventilated lung units further contributing to worsening deadspace (Robinson et al., 2000).

The Haldane effect has been proposed as another mechanism relevant to oxygen induced hypercapnia. The affinity of hemoglobin for CO_2 is reduced with the binding of oxygen to hemoglobin. This rightward shift of the CO_2 dissociation curve increases PaCO_2 (Malhotra et al., 2001). Moreover patients with acute illness are often sleep deprived and exhausted at

presentation and oxygen may have anxiolytic and anti-dyspneic effects facilitating the onset of sleep, especially in patients with concomitant obstructive sleep apnea (Malhotra et al., 2001). Prior sleep deprivation also increases the subsequent arousal threshold. The loss of the wakefulness drive to breathe at sleep onset could therefore facilitate increases in PaCO_2 . Finally, the actual fractional oxygen concentration (FiO_2) delivered non-invasively depends on minute ventilation and inspiratory flow demand. That is, high inspiratory flow demand can lead to entrainment of room air during non-invasive oxygen delivery and reduce the actual FiO_2 being received by the patient. As such, falling minute ventilation can yield increases in actual non-invasively delivered FiO_2 leading to a vicious cycle of hypoventilation leading to worsening hyperoxia (Malhotra et al., 2001).

A proportion of patients with COPD exacerbation, especially those with more severe hypoxemia at baseline, can develop worsening respiratory acidosis with superfluous oxygen therapy through the interaction of the above mentioned mechanisms (Fig. 2). Since it is impossible to predict which patients are more vulnerable to CO_2 narcosis, judicious oxygen delivery to maintain oxygen saturation between 87 and 92% is advised (Calverley, 2000). The use of pulse oximetry may have reduced the incidence of severe oxygen-induced hypercapnia since supplemental oxygen can be titrated according to physiological need. However, occasional cases of profound hypercapnia are still likely to occur without careful attention to detail. Bi-level therapy in COPD exacerbations may help to limit progressive hypercapnic respiratory failure.

7. Exercise hyperpnea

Resting oxygen consumption and carbon dioxide output can rise 10-fold in a moderately fit subject during exercise. Nevertheless PaCO_2 does not increase and PaO_2 does not fall during exercise in health. This situation is achieved through exercise hyperpnea, a 'paradoxical' homeostatic increase of respiratory ventilation that is geared to metabolic demands instead of the normal chemoreflex mechanism (Poon et al., 2007). Control mechanisms underlying exercise hyperpnea have been the subject of research and debate for over 100 years.

The pattern of ventilatory response depends on the form and intensity of exercise. During moderate constant load exercise the first response at the onset is characterized by an abrupt increase in ventilation, followed by an exponential increase in ventilation, oxygen uptake and carbon dioxide elimination. The final response is characterized by a steady state. For the first few minutes of an incremental load exercise test, ventilation increases in proportion to metabolic rate and PaCO_2 remains close to resting levels but PaO_2 falls. Once work rate reaches a level that corresponds to 40–60% of maximum oxygen uptake, ventilation increases disproportionately to oxygen uptake, defining anaerobic threshold or first ventilatory threshold. A second non-linear increase is observed when the metabolic rate is equivalent to approximately 70–90% of maximum oxygen uptake, the second ventilatory threshold. At this point ventilation increases disproportionately to both oxygen uptake and carbon dioxide elimination, accompanied by a further increase in lactate (Mateika and Duffin, 1995).

Several feed-forward and feedback hypotheses have been proposed for the control of exercise hyperpnea involving central mechanisms, chemoreceptors and other receptors, supported by extensive and sometimes contradicting literature. The central command hypothesis postulates that a central command originating from the hypothalamus is capable of stimulating ventilation and exercise motion in parallel (Eldridge and Waldrop, 1991; Mateika and Duffin, 1995; Wasserman and Casaburi, 1986). Cortical projections directly to spinal respiratory motoneurons may also play a role. Short term potentiation, the ability of respiratory centers to sustain a hyperpnea despite the removal of the causal stimulus, has been implicated in phase II kinetics of exercise hyperpnea, but its importance remains unclear (Mateika and Duffin, 1995; Wasserman and Casaburi, 1986).

Changes in central chemoreceptor sensitivity or threshold during exercise are probably not responsible for changes in ventilation as shown in animal and human investigations. It has been suggested that the peripheral chemoreceptor response is enhanced during exercise and this enhancement must develop slowly as exercise continues. Stimulation of peripheral chemoreceptors by potassium likely has a minor role and may increase the sensitivity of peripheral chemoreceptors to other stimuli. Metabolic acidosis primarily due to lactic acid accumulation during heavy exercise may also contribute to the enhancement of peripheral chemosensitivity, although numerous studies have uncoupled lactate and ventilatory thresholds. Breath by breath oscillations in PaCO_2 and PaO_2 and arterial H^+ may elicit changes in carotid body discharge despite unchanging mean values through alterations in the phase relationship between respiratory rhythm and oscillations. Wasserman et al. (1975), however, demonstrated that the ventilation of carotid body resected and normal individuals was not significantly different during moderate exercise. Overall therefore the importance of the peripheral chemoreceptors is questionable.

The hypothesis that neural afferents from contracting muscles may elicit an increase in ventilation with exercise has been formulated as early as 1886 (Zuntz, 1886). Since then multiple studies support the contribution of group III and IV afferent neurons innervating contracting locomotor muscles to circulatory and ventilatory control. In a recent study Amann et al. (2010) showed that ventilation, heart rate and blood pressure were significantly reduced with partial blockade of sensory afferents from contracting muscles across a wide range of exercise intensities, even in the presence of apparently normal contributions from other major effectors of cardioventilatory response. Apart from mechanoreceptors, receptors sensitive to chemical stimuli, nociceptors and metaboreceptors, that comprise 35% and 55% of type III and IV fibers respectively, may also contribute, but studies regarding their role have given conflicting results (Mateika and Duffin, 1995). Finally, since alveolar gas tensions and respiratory exchange ratio do not change with transition from rest to exercise, ventilation must change in proportion to pulmonary blood flow. Several feedback and feed-forward mechanisms for ventilatory–circulatory coupling have been suggested, including a reflex mechanism originating in receptors in the right ventricular wall (Mateika and Duffin, 1995; Wasserman and Casaburi, 1986).

It is unlikely that a single mechanism dominates the respiratory response during exercise. The control system is probably capable of integrating multiple and potentially redundant feedback and feed-forward afferent and efferent signals in adapting the ventilatory pattern in

remarkable proportion to metabolic demands (Mateika and Duffin, 1995; Poon et al., 2007; Wasserman and Casaburi, 1986).

8. Conclusions

Despite years of investigations the control mechanisms responsible for generating respiratory responses observed during health, such as exercise hyperpnea, or disease, for example CHF, remain controversial. The application of mathematical models in an effort to quantify the behavior of the respiratory system has led to major advances in the understanding of control of ventilation. Improved research techniques in identifying underlying contributors to ventilatory patterns can lead to individual clinical assessment of ventilatory control and tailored treatment when appropriate (Edwards et al., 2012; Wellman et al., 2011, 2013).

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Disclosure statement

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Fig. 1.

Simplified schematic representation of loop gain in ventilatory control. The central and peripheral chemoreceptors interact through an additive model; that is, the combined effects of stimulation of both exceed the sum of each stimulus given separately (CO₂ = carbon dioxide; O₂ = oxygen; PaCO₂ = partial arterial pressure of carbon dioxide; PaO₂ = partial arterial pressure of oxygen).

Fig. 2. Mechanisms contributing to oxygen induced hypercapnia (CO_2 = carbon dioxide; FiO_2 = fractional concentration of inspired oxygen).

Table 1

Proposed mechanisms and treatment of breathing patterns associated with altered chemoreflex control.

Breathing pattern	Mechanism	Treatment
Cheyne–Stokes in heart failure	Increased chemosensitivity to CO ₂ , reduced proximity of PaCO ₂ to apneic threshold, circulatory delay	Heart failure medication optimization, PAP devices, heart transplantation
High altitude periodic breathing	Increased sensitivity to hypoxia, increased carotid body chemosensitivity, augmented neural input processing, left shift of the CO ₂ response	Gradual ascent, oxygen, acetazolamide
Obstructive sleep apnea	Compromised upper airway anatomy, upper airway muscle dysfunction, high loop gain	Weight loss, CPAP devices, oxygen, acetazolamide
Obesity hypoventilation syndrome	Reduced respiratory system compliance, increased work of breathing, high upper airway resistance, lower ventilatory drive, leptin resistance	Weight loss, bilevel or CPAP devices
Oxygen induced hypercapnia	Depression of central chemosensitivity to CO ₂ , increased physiological dead space, Haldane effect, sleep	Oxygen delivery titrated to an oxygen saturation of 87–92%; bi-level PAP
Exercise hyperpnea	Mechanoreceptors, nociceptors and metaboreceptors in exercising muscles, breath by breath oscillations in PaCO ₂ and PaO ₂ , central parallel stimulation of ventilation and exercise, ventilatory–circulatory coupling	

CO₂ = carbon dioxide; PaCO₂ = partial arterial pressure of carbon dioxide; PaO₂ = partial arterial pressure of oxygen; PAP = positive airway pressure.