Ventilatory neural drive in chronically hypercapnic patients with COPD: effects of sleep and nocturnal noninvasive ventilation

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A review outlining our current understanding of the ventilatory neural drive in sleep and chronic hypercapnic respiratory failure in COPD as well as the effect of noninvasive ventilation. Important gaps in the literature are highlighted. https://bit.ly/3AlABJR

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Abstract

Sleep brings major challenges for the control of ventilation in humans, particularly the regulation of arterial carbon dioxide pressure (P_{aCO_2}). In patients with COPD, chronic hypercapnia is associated with increased mortality. Therefore, nocturnal high-level noninvasive positive-pressure ventilation (NIV) is recommended with the intention to reduce P_{aCO_2} down to normocapnia. However, the long-term physiological consequences of P_{aCO_2} "correction" on the mechanics of breathing, gas exchange efficiency and resulting symptoms (*i.e.* dyspnoea) remain poorly understood. Investigating the influence of sleep on the neural drive to breathe and its translation to the mechanical act of breathing is of foremost relevance to create a solid rationale for the use of nocturnal NIV. In this review, we critically discuss the mechanisms by which sleep influences ventilatory neural drive and mechanical consequences in healthy subjects and hypercapnic patients with advanced COPD. We then discuss the available literature on the effects of nocturnal NIV on ventilatory neural drive and respiratory mechanics, highlighting open avenues for further investigation.

Introduction

Recent estimates indicate that COPD is the third leading cause of death globally [1]. The disease affects between 300 million and 400 million people worldwide [2, 3] and its prevalence is rising [1, 4]. As COPD progresses in severity, gas exchange and mechanical deficits become more pronounced, decreasing the ability of the respiratory system to remove carbon dioxide (CO_2). The resultant increase in arterial CO_2 partial pressure (P_{aCO_2}) eventually becomes persistent, resulting in the development of chronic hypercapnic respiratory failure [5].

The development of chronic hypercapnia in COPD signals advanced disease, carrying an increased risk of death [6]. This has triggered widespread interest in investigating treatment approaches aimed at normalising P_{aCO_2} in this patient subpopulation. Noninvasive ventilation (NIV) was initially explored as an approach for treating acute hypercapnia in COPD patients in a few centres in the 1960s [7], followed by more widespread use of the treatment of acute respiratory failure in patients with COPD in the 1990s [8]. More recently, the use of nocturnal NIV in COPD patients with chronic hypercapnic respiratory failure has gained renewed momentum owing to the positive documented effects of higher pressure support (difference between inspiratory and expiratory pressures) increasing minute ventilation and reducing P_{aCO_2} [9–14]. Accordingly, the European Respiratory Society (2019), the American Thoracic Society (2020) and the Canadian Thoracic Society (2021) published clinical practice guidelines recommending the use of nocturnal NIV in stable hypercapnic COPD patients [15–17].

Despite these clinical advances, our knowledge of the complex physiological mechanisms that interact to determine P_{aCO_2} in hypercapnic patients with COPD remains limited. This is particularly true during sleep, when the ventilatory neural drive is diminished [18]. Ventilatory neural drive refers to the efferent signalling from the medulla and motor cortex to the respiratory system which controls inspiratory muscle activity and can assist with understanding the physiological mechanisms behind respiratory disease states and symptoms [19]. Abnormalities in gas diffusion and the mechanics of ventilation which characterise COPD may worsen during sleep [20]. Shedding light on the influence of sleep on the ventilatory neural drive and its translation to the mechanical act of breathing is of foremost relevance to create a solid rationale for the use of nocturnal NIV in these patients. After a brief discussion of the mechanisms responsible for ventilatory neural drive in awake and asleep healthy subjects, we outline how sleep may influence ventilatory neural drive in hypercapnic patients with COPD. Based on this conceptual framework, we subsequently review the extant literature on the effects of nocturnal NIV on these outcomes, highlighting the open avenues for further investigation.

Ventilatory neural drive and mechanical output in healthy subjects: wakefulness and sleep

Ventilatory neural drive and mechanical output in awake healthy subjects

For diaphragm contraction to occur, efferent signals from the innervating phrenic nerve are required; they are the result of central rhythm generation modulated by integrated input from mechanoreceptors within the lungs and airways and chemoreceptors which respond to the partial pressure of dissolved gasses in the blood. In addition, inputs from cortical centres contribute to voluntary respiratory signalling and "wakefulness drive" to breathe [21, 22]. As described earlier, the total efferent signalling from the respiratory centres in the brain to the respiratory muscles is referred to as ventilatory neural drive, and it is often assessed through the surrogate measurement of diaphragmatic activation *via* diaphragmatic electromyography (EMG_{di}) [19, 23]. Understanding ventilatory neural drive is useful when studying respiratory diseases, providing information on the efficiency of the ventilatory pump, when used in conjunction with mechanical outputs such as volume and flow.

As the largest and most utilised inspiratory muscle, the diaphragm's electrical activity is frequently used to indirectly assess neural output, *i.e.* drive, from the brain's respiratory centres. EMG_{di}, measured using an oesophageal catheter placed to assess electrical activity within the crural diaphragm, is currently the predominant metric used to assess diaphragmatic activation [18, 24, 25]. The oesophageal catheter technique has been refined to involve multiple electrode pairs to reduce interfering EMG signals and several studies have verified its validity as a measure of diaphragmatic activation [23, 26, 27]. Measurement of diaphragmatic activation using EMG is especially important in patients with mechanical constraint, given that the inaccuracy of approximating ventilatory neural drive from respiratory output (using variables such as minute ventilation) is exacerbated in these patients, who often exhibit higher levels of disconnect between drive to breathe and ability of the respiratory muscles to respond, known as neuromechanical uncoupling [28, 29].

The respiratory pump includes additional muscles that help to facilitate inspiration, especially during more vigorous ventilation in response to increased mechanical loading. These include the external intercostal muscles, scalene muscles and sternocleidomastoid, which aid in elevating the ribcage during inspiration. In addition, inspiration is aided by muscles supporting the upper airway, including the genioglossus muscle, which moves anteriorly to facilitate airway dilation prior to inspiration [30]. External intercostal innervation originates in the respiratory centres of the medulla; however, external intercostal motor units typically fire with varying frequencies and at different points in time during inspiration when compared to the diaphragm [31]. The scalene muscles are typically active during resting breathing with electrical activity closely mirroring the patterns of the external intercostals during quiet breathing [32]. The sternocleidomastoid typically only becomes activated when lung volume reaches ∼65% of vital capacity [32, 33]. These additional respiratory muscles assume a more prominent role in quiet breathing in advanced respiratory disease [34], and studies have used techniques measuring parasternal surface electromyography (drive to the parasternal intercostal muscles) to assess the efficacy of various treatments used in COPD patient populations [35, 36]. However, recent evidence has demonstrated that this measurement of accessory muscle activity is poorly correlated with lung function in comparison to diaphragm EMG signals, largely due to the limitations in the surface electromyography technique, which introduces "crosstalk" signals from nearby musculature that interfere with measurement of parasternal activity [37].

Ventilatory neural drive and mechanical output in healthy individuals during sleep

Sleep introduces significant changes to ventilatory neural drive, respiratory mechanics and gas exchange in healthy individuals. Early studies demonstrated progressive decreases in minute ventilation as a result of

lowered tidal volume (V_T) [38] as individuals transition from wakefulness into non-rapid eye movement (NREM) and then into rapid eye movement (REM) sleep [39]. This is in part due to progressive increases in upper airway resistance throughout NREM sleep stages [40, 41] which become even more pronounced during REM sleep. It is thought that a decrease of tonic activity of the genioglossus muscle, which contributes to maintenance of airway patency during NREM sleep, in addition to a large suppression of pharyngeal muscle tone in REM sleep, contribute to airway narrowing and are key contributors to this resistance increase [42]. The gravitational impact of supine positioning may also contribute to the increased resistance through airway narrowing and tongue displacement [43, 44]. This increase in resistance has been shown to cause a minor but detectable increase in CO_2 retention in healthy subjects specifically during NREM sleep [45]. In addition, the diaphragm is displaced in the supine position assumed during sleep, and this displacement has been shown to compress the lungs and airways, reducing lung volumes [43, 46]. Hypoxaemia, which sometimes occurs during REM sleep, has been partially attributed to increased V'/Q' mismatching and shunt throughout this phase, as functional residual capacity is lowered as a result of absent tonic diaphragm and intercostal activity [47].

In health, chemosensory responses to both hypercapnia [48] and hypoxia [49] are reduced in NREM and REM sleep [50]. Typically, responses to hypercapnia have been measured through Read's rebreathing protocol, in which P_{aCO_2} is increased by taking an individual's expired air and having them re-inspire it [48, 51–53]. Hypercapnic sensitivity can also be assessed through artificial increases in CO_2 through a breathing circuit [54]. Although measuring chemosensitivity is a surrogate assessment of ventilatory neural drive to breathe during sleep, a more comprehensive and direct measurement technique is needed to appreciate mechanical, chemical and functional elements contributing to ventilatory drive.

Ventilatory neural drive in chronically hypercapnic patients with COPD: wakefulness and sleep

Ventilatory neural drive in awake hypercapnic patients with COPD

The pathophysiological hallmark of COPD is expiratory flow limitation with consequent air trapping and hyperinflation. The resultant increased mechanical loading of the respiratory system, leading to increased work of breathing, contributes to inability of the respiratory muscles to meet ventilatory drive requirements in many COPD patients. If the ventilatory system response is consistently unable to meet drive requirements, alveolar hypoventilation develops and the ability to expel CO_2 is compromised, leading to hypercapnia. Severe and persistent hypercapnia, termed hypercapnic respiratory failure, is defined as chronically high P_{aCO_2} (>45 mmHg) [5]. Hypercapnia can also occur acutely, as when acute hypercapnic respiratory failure develops during exacerbations of COPD [55]. Prior acute hypercapnic respiratory failure is a predisposing factor to the development of chronic hypercapnia [56]. A recent multicentre prospective trial from Germany found the prevalence of daytime hypercapnia to be 25% in COPD patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 disease [57]. Daytime hypercapnia is also a predictor of poor prognosis. In a prospective cohort from China, hypercapnic patients had shorter median survival than normocapnic COPD patients [58].

Chemical, mechanical and direct ventilatory neural mechanisms of chronic hypercapnic respiratory failure

Ventilatory drive to the diaphragm [59] and other muscles of inspiration (including the scalene and parasternal intercostal muscles) [60] is markedly increased in patients with severe COPD, secondary to complex chemical, mechanical and neural changes. However, the effect of chronic hypercapnia on this elevated ventilatory drive is less well characterised.

Chemical sources of ventilatory drive in hypercapnic patients

Central chemoreceptors located in the medulla sense decreased pH within the brain extracellular fluid as well as changes in arterial CO_2, altering ventilation to maintain pH within a certain range [61, 62]. In contrast, peripheral chemoreceptors within the carotid body and aorta are predominantly sensitive to hypoxia, a sensitivity that is enhanced during conditions of decreased pH [63]. CO_2 behaves as an acid in aqueous solution, such that the central and peripheral chemoreceptors have P_{aCO_2} thresholds of ~45 mmHg and ~39 mmHg, respectively, after which ventilation increases linearly with increasing P_{aCO_2} [64].

In patients with chronic hypercapnia due to severe COPD, chemoreceptor sensitivity may be decreased [65] (figure 1c). Chronically hypercapnic patients with obstructive airway disease have lower ventilatory responses (*i.e.* sensitivity) to increased P_{aCO_2} (with and without hypoxia) than normocapnic patients with obstructive disease or healthy controls [65, 66]. It is important to consider, when reviewing these findings, that hypercapnic COPD patients are also typically those with the most severe mechanical limitations [67]. Thus, it is difficult to distinguish to what extent blunting of ventilatory responses within such individuals results from mechanical limitations *versus* decreased chemosensitivity [68]. When Burgraff *et al.* [69]

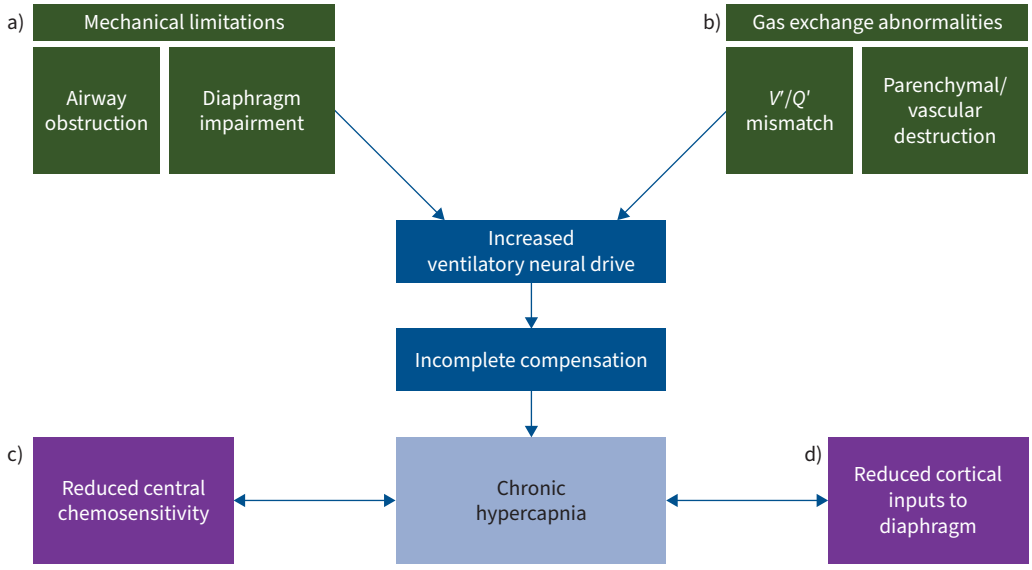

FIGURE 1 Proposed pathway of physiological contributions to hypercapnic respiratory failure. a) Mechanical limitations increase work of breathing and ventilatory neural drive through an increase in airway obstruction, which can result in air trapping and alveolar hyperinflation, as well as diaphragm weakness caused by displacement and molecular changes within the muscle. b) Gas exchange abnormalities include ventilation/perfusion ratio (V'/Q') mismatch (either a result of obstructed or collapsed airways or compromised pulmonary capillaries) and overall parenchymal and vascular destruction. The increased ventilatory drive and inability to compensate for drive due to mechanical and nonmechanical deficits described eventually lead to chronic elevations in arterial partial pressure of carbon dioxide (P_{aCO_2}) (chronic hypercapnia). Chronic hypercapnia itself can then lead to several deficits, including c) a reduction in chemosensitivity and d) reduced efferent signals to the diaphragm from cortical motor centres. Both deficits can in turn increase P_{aCO_2}, creating positive feedback loops, which worsen existing hypercapnia.

simulated hypercapnia in goats through 30 days of exposure to high CO_2 levels, they demonstrated no significant alteration in chemoreflex response.

Neuroplasticity of regions of the brain responsible for ventilatory sensing and neural drive may play a role in the altered responses seen in chronic hypercapnic patients, although this hypothesis has thus far only been explored in animal studies. Within the retrotrapezoid nucleus (RTN; a region containing many chemosensory cells relevant to respiration), expression of several neuropeptides decreases with short-term hypercapnia, but increases with chronically elevated P_{aCO_2} [70]. One of these is galanin, which inhibits ventilatory signals including the acute chemosensory response to hypercapnia and hypoxia when injected into the Bötzinger and pre-Bötzinger complexes of rats [71]. This offers a potential mechanism to explain findings of blunted acute chemosensitivity in hypercapnic patients, although the limitations of applying animal physiology to human physiological function must be considered [70]. However, the neuropeptide neuromedin B, which is an excitatory neurotransmitter potentially implicated in increased minute ventilation, is also expressed in increasing quantities in rat RTN neurons as hypercapnia progresses, which may explain the sustained increase in ventilation during chronic hypercapnia [70].

Mechanical modulation of ventilatory drive in hypercapnic patients

COPD results in airways obstruction, ventilation/perfusion (V'/Q') mismatch, respiratory muscle dysfunction and hyperinflation, the latter of which leads to diaphragmatic flattening, impaired length–tension relationship of the diaphragm for force generation and consequent changes in breathing pattern (*i.e.* decreased V_T) [72–75]. Hyperinflation further contributes to greater intrinsic positive end expiratory pressure that must be overcome to generate inspiration [76]. In concert, the increased work of breathing resulting from these mechanical deficits requires increased ventilatory neural drive from the respiratory centres within the brain to maintain or attempt to maintain appropriate ventilation per metabolic load in face of reduced ventilatory capacity (figures 1a and 2) [77, 78]. Interestingly, hypercapnia itself may contribute to the perpetuation of this cycle, as even 21 days of chronic hypercapnia increases airway smooth muscle contractility and constriction in response to acetylcholine through a caspase-7-mediated

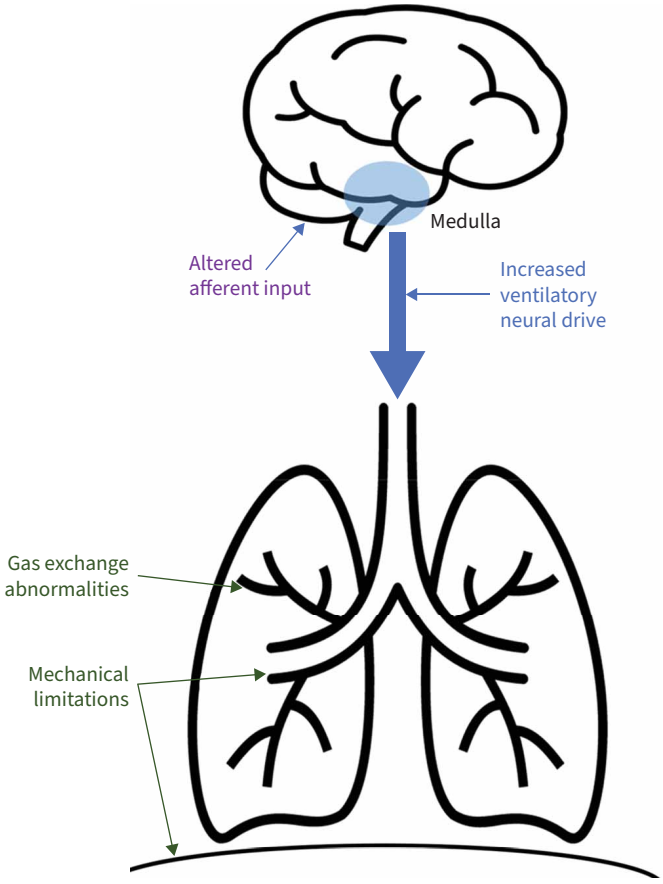

FIGURE 2 Physiology of increased ventilatory neural drive in COPD patients with hypercapnic respiratory failure. Gas exchange abnormalities (including ventilation/perfusion mismatch and parenchymal and vascular destruction) as well as mechanical limitations (airways obstruction and respiratory muscle impairment from hyperinflation) ultimately lead to hypercapnia when ventilation is no longer able to match metabolic demand. In turn, altered signalling to the central respiratory centres from chemical and mechanical receptors leads to an increase in ventilatory neural drive to the muscles of respiration.

mechanism in murine models [78]. This hypercapnia-mediated increase in contractility may potentiate airways resistance and load in hypercapnic COPD patients, which in turn could further increase ventilatory drive through mechanosensory afferent pathways [79]. In addition, cellular and molecular changes within the diaphragm contribute to mechanical limitations in chronic hypercapnic respiratory failure. On the level of individual cells, diaphragmatic muscle fibres from patients with severe COPD generate less force than those within the diaphragms of healthy controls (figure 1a) [80]. However, the proportion of slow-twitch fibres within the diaphragm is increased in COPD patients, indicating a potential increase in fatigue resistance to compensate for higher ventilatory load [81]. It is still unclear whether this compensation is able to prevent or delay the onset of hypercapnic respiratory failure; more investigation is needed in this domain.

An additional and significant factor contributing to gas exchange derangement and eventual hypercapnia, which is linked to both mechanical and chemical alterations, is V'/Q' mismatch (see figure 1b). In early COPD, V'/Q' inequality presents, in part, through early collapse of small airways and impaired alveolar ventilation prior to larger airways becoming impacted and altering spirometry [73]. Concurrent destruction of pulmonary capillaries increases the proportion of ventilation that enters poorly perfused alveoli (creation of physiological dead space), further contributing to V'/Q' mismatch. There is also more recent evidence to suggest that some COPD patients may present with a "vascular phenotype" of disease which leads to early V'/Q' inequality, in which vascular pruning and vascular dysfunction, as opposed to emphysematous destruction of capillary beds, is the predominant contributor to V'/Q' mismatch as a result of poor perfusion [82]. Finally, the creation of dead space as a result of airway collapse and perfusion limitation

leads to a higher required level of minute ventilation in order to facilitate sufficient gas exchange. Patients with severe COPD and mechanical limitation are often unable to meet this requirement and CO_2 retention is the result.

Direct neural inputs to the diaphragm

Direct neural inputs to the diaphragm *via* the corticospinal pathway allow for voluntary control of the diaphragm and facilitate nonventilatory activities such as speech [83]. These pathways have been assessed by way of transcranial magnetic stimulation and measurement of resultant motor evoked potentials of the diaphragm [84]. Signalling to the diaphragm initiated in the cortex through the corticospinal pathway contributes to neural drive in the waking state and is essential for resisting apnoeas induced by hypocapnia [85]. This drive is predominantly provided by excitatory stimulation of the cortex *via* the reticular activating system during wakefulness, allowing for continuation of breathing even without medullary centre input [86].

Evidence suggests that the corticospinal tract is almost maximally activated in awake COPD patients [87] and there is a ceiling effect of the corticospinal signal in COPD patients not seen in healthy controls [88]. However, in COPD patients with elevated P_{aCO_2}, findings are inconsistent, with some studies suggesting that corticospinal inhibition of the diaphragmatic motor cortex is increased in hypercapnia [87], while others demonstrating increased voluntary activation of the diaphragm possibly conferring protective advantages in face of worsened mechanics [89]. Such findings have been obtained in relatively small sample sizes, and further work is needed to definitively identify the impact of chronic hypercapnia on ventilatory neural drive. Relative changes in input from medullary respiratory centres may also contribute to changes in drive, but their respective contributions in severe COPD and/or hypercapnia have not been characterised.

Ventilatory neural drive in sleeping patients with hypercapnic COPD

Despite persistently elevated daytime ventilatory neural drive in patients with COPD, neural drive changes occurring during sleep may especially predispose patients with impaired respiratory mechanics to nocturnal hypoventilation. To date, EMG_{di} has been acquired in few overnight studies in patients with COPD. Luo *et al.* [18] demonstrated greater declines in EMG_{di} during the transition from wakefulness to NREM and REM sleep in normocapnic COPD *versus* heathy controls despite consistently higher overall drive in COPD patients, concluding that such decreases in drive may contribute to hypoventilation and hypercapnia during sleep (figure 3a). This is supported by recent findings showing greater loss of EMG_{di} in the transition from wakefulness to sleep in normocapnic COPD than in health [90]. Such nocturnal hypercapnia is predicted to precede the onset of persistent daytime hypercapnia [91]. As described in the preceding section, corticospinal input to the respiratory centres contributes to neural drive in the waking state, but much of this input is lost during sleep. This has potential to contribute to the drop in EMG_{di} observed in the transition to sleep. It may also be postulated that the loss of this wakefulness drive could have exaggerated impacts on COPD patients as compared to the healthy population, due to impaired ability to compensate for the increasing mechanical and chemical deficits which we have described in hypercapnic COPD, thus increasing vulnerability to hypoventilation. Interestingly, decreases in EMG_{di} in the transition to sleep may occur in the presence of preserved ventilatory effort (oesophageal and transdiaphragmatic pressure) in normocapnic COPD [90].

In addition to disturbed mechanical inputs to the respiratory centres, disrupted chemical afferent inputs to the central rhythm generator in the medulla in COPD patients during sleep may facilitate hypoventilation and promote CO_2 retention (figure 3d). The decreased sensitivity of chemoreceptors to both hypercapnia and hypoxia throughout sleep [92] which causes minimal disturbance in healthy subjects can be deleterious when compounded by the mechanical limitations and blunted chemosensory responses in COPD patients [93]. Furthermore, diaphragmatic flattening due to hyperinflation may cause COPD patients to increase use of accessory inspiratory muscles to maintain ventilation during the daytime and portions of the night [94]. However, REM sleep-associated muscle atonia disproportionately affects inspiratory muscles other than the diaphragm [95, 96], leading to a presumed reliance on the diaphragm to maintain adequate ventilation [97] during REM sleep (figure 3c). This may leave COPD patients who rely in larger part on nondiaphragmatic inspiratory muscles without adequate means to generate pressure during REM sleep, contributing to sleep hypoventilation. Insufficient pressure generation from the diaphragm also encourages patients to adopt a rapid shallow breathing pattern [98], which leads to a higher percentage of ventilation within anatomical dead space, and less efficient gas exchange [99]. Accordingly, hypopnea and associated hypercapnia typically first present during REM sleep [20]. However, emerging evidence suggests that REM sleep atonia of inspiratory muscles apart from the diaphragm may not be as universal as previously believed. In patients with severe COPD recovering from exacerbation, evidence of additional

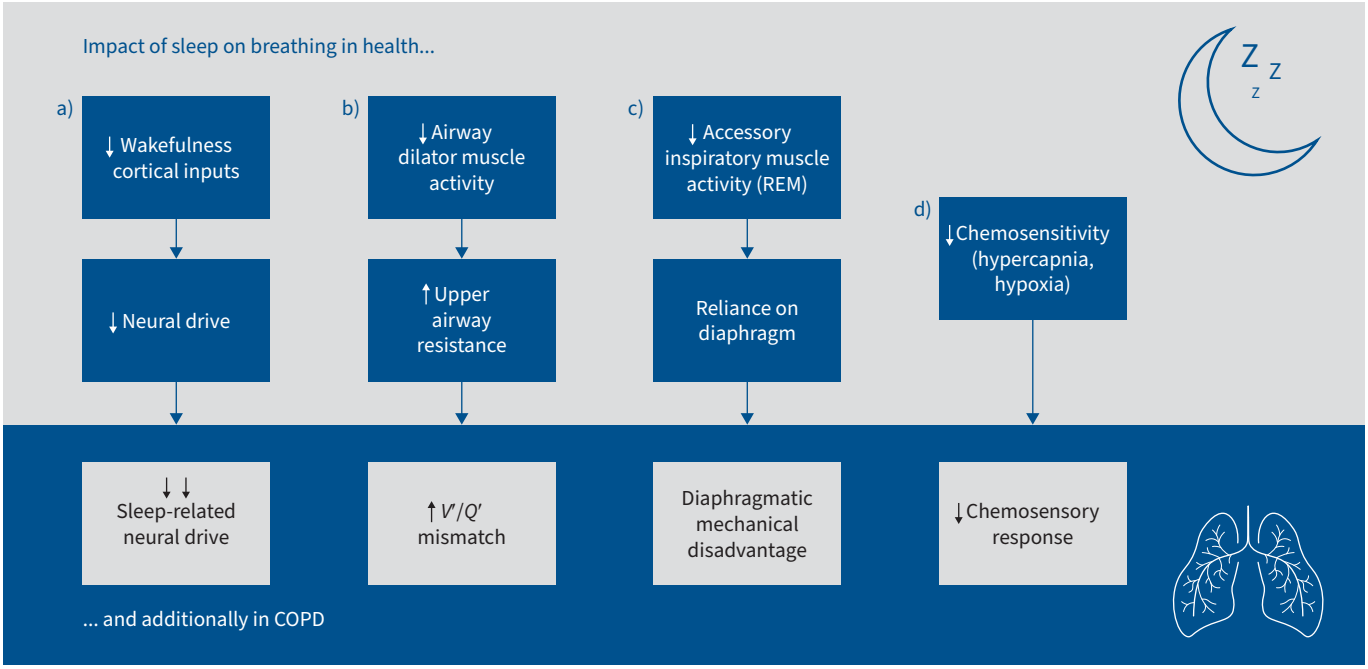

FIGURE 3 Physiological changes during sleep in normal subjects and COPD. a) During sleep, a decrease in ventilatory neural drive is observed. Despite higher baseline drive in COPD patients, a larger drop from wakefulness to sleep is typically noted in this population. b) Increased airway resistance during sleep may exacerbate the ventilation/perfusion (V'/Q') mismatching experienced in COPD. c) Accessory inspiratory muscle activity is typically eliminated during rapid eye movement (REM) sleep, necessitating a reliance on the diaphragm. However, in COPD patients with compromised diaphragm activity, hypoventilation may result from this loss of accessory muscle activity. d) Finally, decreased chemosensitivity in sleep compounds the existing reduction in chemosensitivity experienced by COPD patients, especially those with elevated arterial partial pressure of carbon dioxide. These changes in sleep compounded on the limitations on COPD patients can contribute to sleep hypoventilation in this population.

inspiratory muscle activity has been documented during REM sleep [100]. Similarly, maintained activity of other inspiratory muscles, including the parasternal intercostals, has been demonstrated in healthy individuals during REM sleep [101], suggesting that inhibition of inspiratory muscles may be a less significant factor in sleep hypoventilation than once believed.

The prevalence of sleep disordered breathing, in particular, obstructive sleep apnoea (OSA), is high in patients with severe lung disease [102], which can further exacerbate declines in lung function and derangement of blood gases overnight. High apnoea–hypopnea index scores, which indicate the existence of OSA, have been found to be inversely correlated with forced expiratory volume in 1 s (FEV_1)/forced vital capacity, indicating that this condition disproportionately affects severe COPD patients [103]. Increased airway inflammation and larger and more frequent oxygen desaturations may contribute to hypoventilation and eventual hypercapnia in OSA patients. Additionally, COPD patients frequently experience arousal from sleep, which can be made even worse by coexistent OSA [104]. These arousals have been associated with increased neural drive, which could complicate our understanding of ventilatory drive during sleep and changes in blood gasses [26, 70]. However, the details of COPD–OSA overlap and arousals are beyond the scope of this article, as we aim to predominantly review the physiological underpinnings of hypercapnic COPD in isolation.

Treatments targeted towards improving ventilation during sleep include nocturnal bronchodilator therapy and oxygen supplementation. While dual long-acting nocturnal bronchodilators decrease airways resistance and sleeping ventilatory effort and ventilatory neural drive in moderate COPD [105, 106], nocturnal long-term oxygen therapy improves oxygenation in patients with persistent hypoxaemia [107] decreasing minute ventilation through reduction of a chemosensory stimulus [108]. These approaches are often insufficient when treating severe COPD with hypercapnia [109]. Recently, nocturnal NIV has gathered significant interest as an effective means of improving blood gas levels in hypercapnic COPD patients and contributing to improved symptom profile [110].

Nocturnal NIV in COPD

Nocturnal NIV directly addresses some of the overnight mechanical and neural challenges which contribute to chronic hypercapnic respiratory failure in COPD patients, showing outcome benefits over other therapies including nasal high-flow therapy [111] or long-term oxygen therapy alone [112]. NIV became utilised for acute respiratory failure in patients with COPD shortly after its initial use on patients with neuromuscular disease and paralysis [113]. Investigation into the use of high-intensity NIV (a form of NIV that uses high inspiratory pressures to help normalise P_{aCO_2}, to treat stable chronic hypercapnic COPD) began in the early 2010s, with early studies delivering promising results: improved health-related quality of life, reduced sleep hypoventilation and improved daytime lung function [9, 10].

When is NIV indicated in COPD?

The European Respiratory Society, American Thoracic Society and Canadian Thoracic Society acknowledge the benefits of NIV in stable hypercapnic COPD, with the most recent clinical practice guidelines of each recommending the initiation of NIV once a stable patient reaches a specific P_{aCO_2} threshold [15–17]. While there is some variance in the precise threshold employed by each society, this probably reflects the diversity of mean P_{aCO_2} of patients using NIV across studies [16].

Mechanisms of NIV in hypercapnic COPD

Despite the large body of literature documenting clinical outcomes of NIV, many questions remain on the physiological mechanisms contributing to its efficacy. Here, we will introduce several proposed mechanisms of action of NIV while highlighting gaps in the literature warranting further exploration.

Unloading the diaphragm

NIV is proposed to improve outcomes in chronic hypercapnic respiratory failure, in part through reduction of diaphragm workload (figure 4b). Duiverman *et al.*'s [12] study, which looked at costal diaphragm activity *via* surface EMG in awake COPD patients with hypercapnia, found significant reductions in EMG activity during NIV *versus* unassisted breathing, with even more pronounced reductions when a high inspiratory pressure was used. A modified mode of noninvasive ventilation, proportional assist ventilation, which uses the patient's breathing effort as measured by a pneumotachograph to determine assistive pressure and flow [114] also reduces costal diaphragm EMG *via* surface electrode by ∼38% when accounting for changes in minute ventilation [115]. It should be noted that diaphragm activity has only been measured through surface electrodes during NIV. This comes with technical limitations, as surface signals from the costal diaphragm are often skewed by artefact from nearby muscles of the chest wall [116]. The oesophageal catheter technique of measuring crural diaphragm EMG activity can eliminate some of this extraneous muscle crosstalk, improving specificity of measurement. Moreover, the activity of the diaphragm (costal or crural) during NIV in sleep has not been directly reported in the literature and must be explored to confirm that diaphragm unloading contributes to the efficacy of NIV in improving ventilation overnight.

Reduction of hyperinflation

Hyperinflation, which is a hallmark of COPD, can worsen overnight (figure 4a) [90, 105]. Combined with the deleterious impact of sleep on airway resistance, inspiratory muscle activity and breathing pattern, this hyperinflation can also lead to exaggerated hypoventilation and hypercapnia overnight [117]. Dynamic hyperinflation, characterised by positive end-expiratory pressure changes, is significantly reduced in COPD patients randomised to daytime NIV for 3 h, 5 days per week over 3 weeks, and this reduction is associated with decreased hypercapnia (−1.12 mmHg) [118]. It was postulated that the reduced hyperinflation may have been the result of a longer time available for expiration due to reduced respiratory rate facilitated by NIV, which resulted in more effective emptying and a reduction in gas trapping [118]. NIV used overnight may also significantly improve daytime hyperinflation, as described in a group of severe COPD patients (GOLD stage IV) undergoing simultaneous pulmonary rehabilitation [13]. Residual volume/total lung capacity (used to assess lung hyperinflation) significantly improved in patients using NIV and pulmonary rehabilitation and remained unchanged in patients completing pulmonary rehabilitation alone [13]. Improvements in hyperinflation may in turn improve lung function, with some literature pointing to a reduced decline, or even slight increase in FEV_1 in patients using NIV as compared to other forms of treatment alone [119].

Improvement in V′/Q′ mismatching

As described in the section on ventilatory neural drive in awake hypercapnic patients with COPD, V'/Q' mismatch due to small airway and alveolar collapse is common in COPD. Although some of the poorly ventilated pulmonary perfusion that results can be rerouted to more ventilated regions through pulmonary hypoxic vasoconstriction [120], areas of physiological shunt remain, which can result in the development

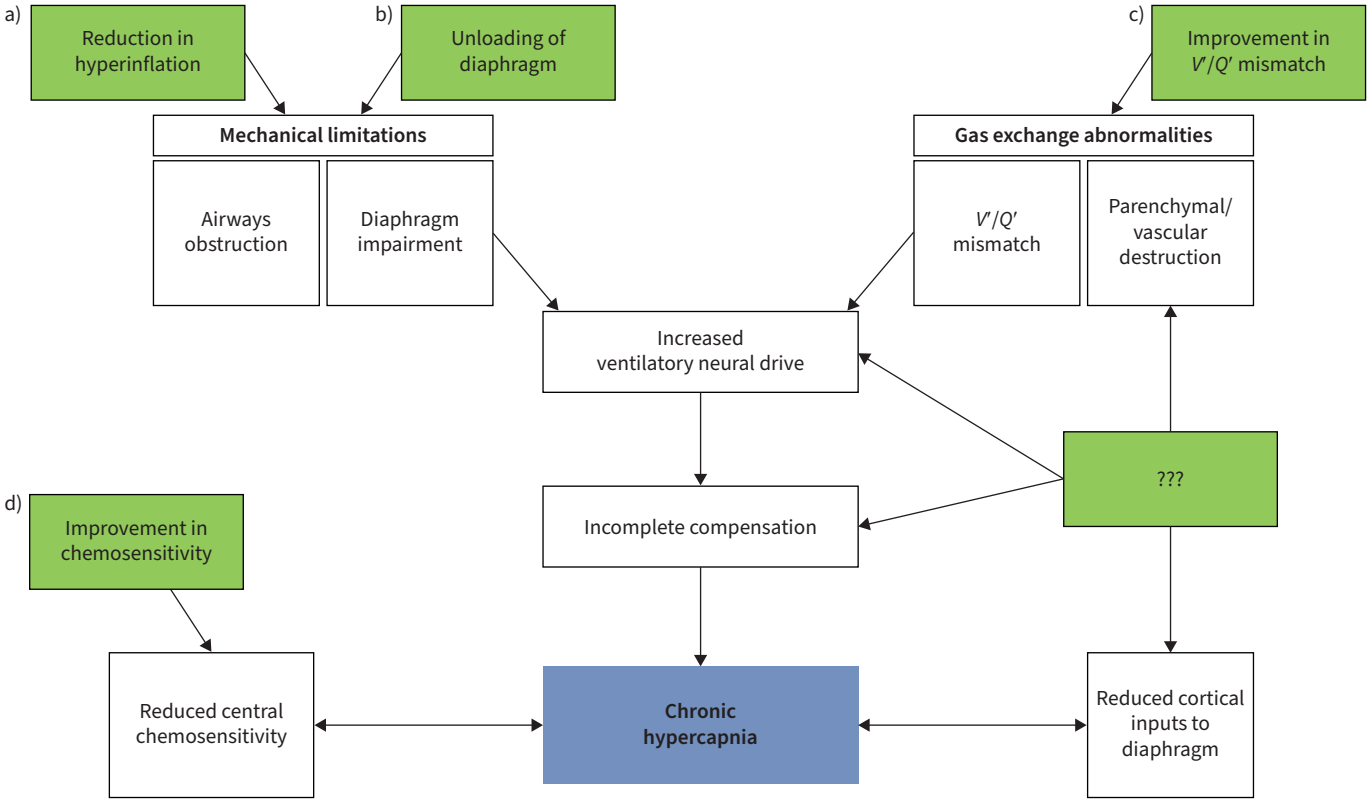

FIGURE 4 Mechanisms of noninvasive ventilation (NIV) in hypercapnic respiratory failure in COPD. a) The extended expiratory time provided by NIV is thought to facilitate lung emptying and reduce hyperinflation. b) The high inspiratory pressure provided by NIV therapy is also intended to directly reduce the work of the diaphragm in initiating inspiration. c) Positive pressure provided by NIV may allow for the reopening of previously collapsed small airways, leading to improvement in ventilation/perfusion (V'/Q') matching. These improvements may contribute to a reduction in ventilatory neural drive and improve ventilation capacity, leading to reductions in hypercapnia. d) Improved chemosensitivity may result from decreased hypercapnia, and lead to further reductions in arterial partial pressure of carbon dioxide.

of hypoxia. The ability of NIV to provide positive end-expiratory pressure functions to maintain airway patency and improve expiratory flow [121]. This pressure has been shown to recruit previously collapsed alveoli when used in patients with hypoxaemic acute respiratory failure [122]. This could potentially allow for ventilation in previously shunted regions, improving V'/Q' matching, resulting in oxygenation along with CO_2 removal (figure 4c).

NIV resetting central drive

It has been theorised that the improvements seen in NIV during sleep may also be the result of a "reset" in respiratory drive initiated by normalisation of P_{aCO_2}, which persists during the daytime to improve daytime P_{aCO_2} in addition to acutely improving nocturnal P_{aCO_2} during sleep (figure 4d). This is supported by two small studies [123, 124] which used rebreathing protocols to measure chemosensitivity to CO_2 during the daytime, and found improvements in sensitivity after nocturnal NIV treatment and resultant decreases in daytime P_{aCO_2}.

To date, few investigators have attempted to acutely characterise the impact of NIV on ventilatory neural drive to breathe. One study acutely assessed neural drive *via* parasternal electromyography during overnight NIV in a cohort of hypercapnic COPD patients to detect patient ventilator asynchrony; however, the impact of NIV on magnitude of and possible alterations in neural drive were not thoroughly characterised through the use of EMG_{di} to measure diaphragm activation [36].

Conclusion

The deleterious effects of advanced COPD on lung and airway mechanics, gas exchange and respiratory muscle function [125] impair the ability of the ventilatory system to effectively clear CO_2, ultimately resulting in chronic hypercapnic respiratory failure [5]. Nocturnal NIV has been successfully integrated

into clinical practice guidelines, and studies have shown promising data on its ability to improve clinical outcomes. However, much of the research on physiological mechanisms behind the efficacy of NIV relies on surrogate rather than direct measurement of ventilatory neural drive or has investigated the use of NIV during wakefulness. These shortcomings are acknowledged by recent clinical practice guidelines, which recommend further research in the area of physiological underpinnings of NIV. Such an understanding is prerequisite to developing setting recommendations for individual patients and may be facilitated by measurement of ventilatory neural drive and consequent mechanical responses to nocturnal NIV. Advances in techniques for measuring these physiological indices are increasingly available, and reports on this exciting yet complex process are eagerly anticipated.

Future research questions

- What is the impact of NIV on ventilatory neural drive (as measured by diaphragm EMG) overnight?
- What is the impact of long-term use of NIV on daytime ventilatory neural drive (as measured by EMG_{di})?
- How do cellular changes within the diaphragm in COPD impact the progression of chronic hypercapnic respiratory failure?
- What is the precise P_{aCO_2} threshold at which NIV is beneficial for patient clinical outcomes?
- What are the relative contributions of ventilatory versus perfusion limitations to the development of chronic hypercapnic respiratory failure?
- Does the impact of long-term NIV on ventilatory neural drive affect daytime perceptions of dyspnoea and associated exercise intolerance?

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