Effects of non-invasive ventilation on sleep in chronic hypercapnic respiratory failure

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ABSTRACT

Chronic respiratory disease can exacerbate the normal physiological changes in ventilation observed in healthy individuals during sleep, leading to sleep-disordered breathing, nocturnal hypoventilation, sleep disruption and chronic respiratory failure. Therefore, patients with obesity, slowly and rapidly progressive neuromuscular disease and chronic obstructive airways disease report poor sleep quality. Non-invasive ventilation (NIV) is a complex intervention used to treat sleep-disordered breathing and nocturnal hypoventilation with overnight physiological studies demonstrating improvement in sleep-disordered breathing and nocturnal hypoventilation, and clinical trials demonstrating improved outcomes for patients. However, the impact on subjective and objective sleep quality is dependent on the tools used to measure sleep quality and the patient population. As home NIV becomes more commonly used, there is a need to conduct studies focused on sleep quality, and the relationship between sleep quality and health-related quality of life, in all patient groups, in order to allow the clinician to provide clear patient-centred information.

INTRODUCTION

Hypercapnic respiratory failure is a severe complication of several underlying neuromuscular and cardiopulmonary conditions. Symptoms typically present with breathlessness, but in most individuals, prior to the presentation of daytime hypercapnia, sleep-related deterioration of ventilation can be observed. This can manifest as hypercapnia in rapid eye movement (REM)-sleep at first, but eventually throughout the night.

In the healthy subject, ventilation is diminished with sleep onset and the partial pressure of arterial carbon dioxide ($PaCO_2$) rises slightly but with little clinical consequence[1 2]; in patients with chronic respiratory disease, pathophysiological changes occur that lead to hypercapnic respiratory failure. Patients with chronic hypercapnic failure frequently report poor sleep quality, which facilitates symptoms of sleepiness, perception of breathlessness and has a significant impact on the quality of life. This review will discuss the complex interaction between sleep quality and chronic hypercapnic respiratory failure. First, the physiological changes in ventilation (eg, breathing frequency and pattern) during sleep will be summarised, and a model to explore the pathophysiology of hypercapnic respiratory failure will be introduced. Next, the review will focus on four clinical conditions, chronic obstructive pulmonary disease (COPD), obesity-related respiratory failure (ORRF), slowly progressive neuromuscular disease (NMD) and rapidly progressive NMD and report the relationship between chronic respiratory failure and sleep quality and the effect of non-invasive ventilation (NIV) treatment. The aim of this review is to demonstrate that in patients with chronic respiratory failure, sleep quality is an important contributor in the aetiopathophysiology and influences clinical outcomes, frequently opening a diagnostic window to anticipate respiratory issues and allow for secondary prevention of deterioration, and, lastly, that NIV, by improving sleep quality, has a role in enhancing health-related quality of life. Of course, it should be noted that patients with hypercapnic respiratory failure are still at risk of reduced sleep quality due to causes other than hypoventilation, including organic sleep disorders, restless leg syndrome and psychological disorders, among many others.

METHODS

Literature for this review was identified using the following terms in Medline and Embase: sleep, sleep pathophysiology, sleep disorders, sleep disordered breathing, polysomnography, sleep apnoea, obstructive sleep apnoea (OSA), hypoventilation, respiratory failure, COPD, obesity hypoventilation, neuromuscular disorders, motor neuron disease (MND). No restrictions on dates or study design. English language articles were included. The databases were searched from inception to April 2023.

Physiological changes to ventilation during sleep in healthy individuals

Normal restorative sleep in healthy subjects results in a subclinical state of reduced alveolar ventilation when compared with wakefulness. Tidal volume decreases progressively through the stages of sleep, down to almost 13% of the awake tidal volume in REM sleep.[1] As a result, minute ventilation also decreases in parallel. This is affected by increased activity of gamma-aminobutyric acid-secreting neurones during sleep that act as a depressant of the central respiratory centre.[3] Consequently, a small increase in the $PaCO_2$ and a small decrease in the partial pressure arterial oxygen (PaO_2) is observed.[1] Ventilatory responses to hypoxia and hypercapnia are attenuated during normal sleep, due to altered chemosensitivity. During REM sleep, chemosensitivity is less than a third than in wakefulness.[4] This minimises any increase in neural drive in response to the small increase in $PaCO_2$. Upper airway resistance is increased during sleep, due to loss of nasopharyngeal muscle tone, resulting in increased load on the respiratory system.[5 6] A degree of bronchoconstriction is also observed during healthy sleep,

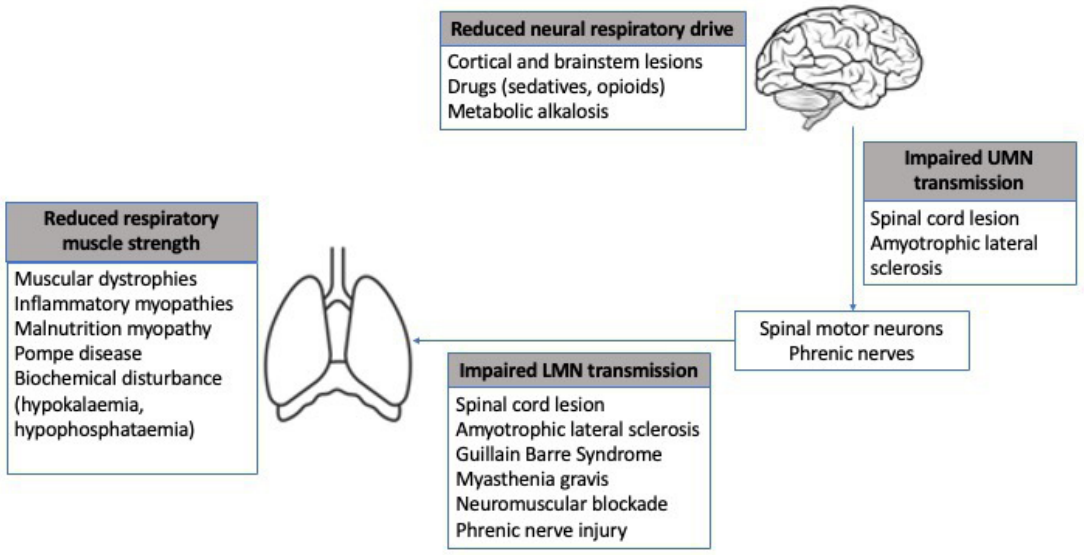

Figure 1 The neural pathway conducting impulses from the central respiratory centre to the respiratory muscles, displaying where different conditions cause impairment and therefore hypoventilation. LMN, lower motor neuron; UMN, upper motor neuron.

resulting in a mild increase in lower airway resistance.[7] During REM sleep, a marked loss of intercostal muscle activity has also been reported[8] resulting in a decrease in tidal volume, and a reliance on an intact diaphragm to maintain ventilation during this period. In healthy individuals, these changes are limited and do not result in any clinical sequelae, although oxygen saturation during sleep is lower than during wakefulness. These changes tend to be exaggerated in individuals with chronic respiratory diseases and exacerbate nocturnal alveolar hypoventilation, and thereby contribute to the development of hypercapnic respiratory failure.

Pathophysiology of hypercapnic chronic respiratory failure

The arterial partial pressure of carbon dioxide is inversely proportional to alveolar ventilation such that hypercapnic chronic respiratory failure occurs as a consequence of inadequate alveolar ventilation associated with ineffective elimination of carbon dioxide.[9] Alveolar ventilation is determined by the difference between minute ventilation and dead space ventilation, and in turn, minute ventilation is controlled by neural respiratory drive, which determines respiratory muscle pump activity in order to meet metabolic demand. Clinical conditions that impact on the integrity of the neural pathways between the central nervous system and the respiratory muscles (figure 1), and those that increase dead space ventilation contribute to the development of hypercapnic respiratory failure. The respiratory muscle load-capacity ratio is a useful construct to determine the pathophysiological contribution of respiratory and neuromuscular conditions that lead to hypercapnic respiratory failure.[9] Increased load on the respiratory system, reduced respiratory muscle capacity and reduced neural respiratory drive, in isolation or in combination lead to an imbalance in the load-capacity ratio, and can cause alveolar hypoventilation (figure 2). Furthermore, sleep fragmentation is typically a consequence of respiratory-related arousals that are associated either with hypoxic, hypercapnic or resistive breathing-related events caused by the underlying condition.[10]

Respiratory muscle load is composed of resistive load (eg, airways resistance), elastic load (eg, lung and chest wall compliance) and threshold load (eg, intrinsic positive end-expiratory pressure). An excess respiratory load can be compensated for by an increase in neural respiratory drive that recruits increased respiratory muscle pump activity, leading to increased ventilation.

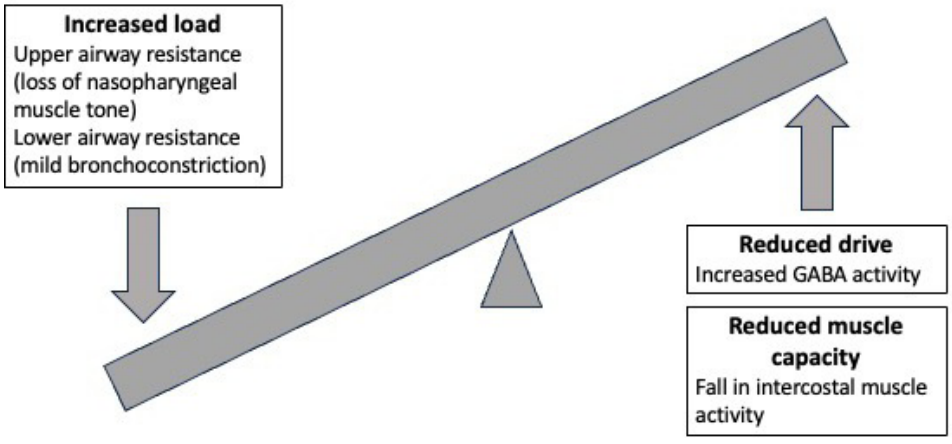

Figure 2 Respiratory muscle load-capacity-drive relationship displaying changes in sleep in normal subjects and how they contribute to alveolar hypoventilation. GABA, gamma-aminobutyric acid.

Table 1 Changes to the respiratory muscle load-capacity-drive relationship in each condition during sleep, leading to alveolar hypoventilation

	Load	Capacity	Drive
COPD	► Dynamic hyperinflation ► Bronchoconstriction	► Loss of intercostal muscle activity during sleep	► Reduced drive during sleep does not compensate for increased load/decreased capacity
Obesity	► Smaller lung volumes ► Airway narrowing ► Dynamic hyperinflation ► Airway inflammation ► Small airway tidal closure	► Adipose tissue impairing chest expansion ► Reduced diaphragm neuromuscular coupling	► Reduced drive during sleep does not compensate for increased load/decreased capacity
Slowly-progressive neuromuscular disease	► Fibrosis of rib cage/spinal deformities ► Reduce nasopharyngeal dilator muscle function	► Respiratory muscle weakness	► Reduced drive during sleep does not compensate for increased load/decreased capacity ► Disruption along the neural pathways
Motor neuron disease	► Reduced nasopharyngeal dilator muscle function ► Increased secretions	► Respiratory muscle weakness ► Phrenic nerve-induced diaphragm paralysis/paresis	► Reduced drive during sleep does not compensate for increased load/decreased capacity ► Disruption along the neural pathways

COPD, chronic obstructive pulmonary disease.

The capacity of the respiratory muscle pump is largely determined by inspiratory muscle strength and endurance, primarily by the diaphragm and the extradiaphragmatic muscles. Neural respiratory drive indicates the efferent signal of the central nervous system required to match the work of breathing in response to the afferent information, including the metabolic demand (eg, high body temperature, metabolic acidosis). Neuronal signals are transmitted from the respiratory centre in the brainstem to the respiratory muscles via the spinal cord and peripheral nerves, including the neuromuscular junctions. Without an intact neuronal tract, the respiratory muscles will not respond to increased metabolic demand leading to reduced elimination and accumulation of alveolar carbon dioxide. There is no difference between the hypercapnic ventilatory response in older people compared with younger healthy controls both in wakefulness[11] and during sleep.[12] This demonstrates that the altered ventilatory response observed in individuals with chronic respiratory failure cannot be explained by the effect of advancing age on neural respiratory drive. Throughout this review, the respiratory muscle load-capacity ratio will be used to explain how COPD, ORRF, slowly progressive NMD and rapidly progressive NMD lead to hypercapnic respiratory failure (table 1), why it contributes to sleep fragmentation with development of symptoms, and how NIV can support the patient accordingly.

Chronic obstructive pulmonary disease

COPD is the most common cause of chronic hypercapnic respiratory failure. Many patients with severe COPD complain of 'poor sleep', with 50%–80% of patients reporting sleep disturbance.[13–17] However, despite this high prevalence, there are limited data detailing sleep fragmentation and quality in COPD.[18]

In patients with COPD, any regular physiological changes to ventilation during sleep are exaggerated due to the underlying pathophysiology. Due to the lung and airway contribution, patients with COPD often have lower oxygen saturation levels, typically on the steep part of the oxygen-dissociation curve; such that any further overnight reduction on oxygen saturation will result in a substantial fall in PaO_2. Lung hyperinflation associated with expiratory tidal flow limitation in COPD increases physiological dead space, reduces the capacity of the respiratory muscles, and increases the elastic load, resulting in further hypoventilation and consequently, hypercapnia. Ongoing bronchoconstriction in COPD facilitates the increase in the resistance of the lower airways and increase resistive load. Furthermore, there is an impaired dilating response of the supraglottic airways in response to hypercapnia in patients with COPD, resulting in increased upper airway resistance and resistive load.[19] Finally, patients with COPD use their intercostal muscles to maintain ventilation; loss of the intercostal neuromuscular tone during sleep will reduce respiratory muscle capacity further.[20] The combination of these pathophysiological changes in COPD directly exaggerates the normal ventilatory changes in healthy adults during sleep, resulting in sleep hypoventilation and development of hypercapnic respiratory failure.[21]

These pathophysiological constraints are reflected in the symptoms and quality of life, as measured by clinical outcomes and standardised validated questionnaires. The Pittsburgh Sleep Quality Index (PSQI) is a widely available tool used to evaluate subjective sleep quality; the higher the score, the worse the subjective sleep quality. Studies have demonstrated that poor sleep quality (higher PSQI) is associated not only with an increased risk of COPD exacerbations,[22] but also with reduced physical activity,[23] and worse health-related quality of life.[16 24 25] Sleep quality appears to be inversely proportional to the severity of COPD.[26] In addition, polysomnographic studies have demonstrated that sleep architecture is also disrupted in patients with COPD with reduced sleep efficiency,[15 27] reduced total sleep time[27] and reduced time spent in REM sleep.[28] Poor sleep in COPD has been associated with increased peripheral airway resistance,[29] and the presence of comorbid OSA in patients with COPD can result in worse subjective[14] and objective sleep efficiency.[15]

Over the past two decades, interest in the provision of domiciliary NIV for the treatment of chronic respiratory failure in COPD has increased. Two recent landmark studies resulted in conditional recommendations in the most recent European Respiratory Society guidelines[30] for the addition of domiciliary NIV to oxygen therapy in patients with COPD with persistent short-term hypercapnia following a severe exacerbation of COPD,[31] and in stable patients with COPD with chronic respiratory failure.[32] These landmark studies provide the clinical evidence to target carbon dioxide reduction to improve clinical outcome and health-related quality of life in patients with COPD. Indeed, recent studies have demonstrated the cost-effectiveness of domiciliary NIV in patients with COPD following a recent admission to hospital due to an exacerbation that required acute NIV.[33 34] Few studies have specifically investigated the effect of domiciliary NIV on sleep in COPD, although subjective evaluation has been performed in clinical studies as a secondary outcome measure

with a Cochrane review detailing the lack of data reporting sleep quality changes in patients with COPD receiving domiciliary NIV.[35] Studies have demonstrated no difference in sleep quality with domiciliary NIV when compared with long-term oxygen therapy[36] and usual care,[37] with either subjective questionnaire or objective polysomnographic measurements.[38] Studies comparing automated modes of NIV, for example, intelligent volume-assured pressure support and average volume assured pressure support (AVAPS) with fixed-pressure support ventilation, have investigated sleep quality as a primary outcome with mixed results in terms of reported subjective sleep quality.[39–41] As the use of domiciliary NIV for chronic respiratory failure and persistent hypercania following a severe exacerbation of COPD increases, there is an essential requirement to design clinical trials which focus primarily on sleep quality.

Obesity-related respiratory failure

Obesity increases the load on the respiratory system through a number of pathophysiological mechanisms, making obese individuals particularly vulnerable to chronic hypercapnic respiratory failure. Obese individuals breathe at lower lung volumes, specifically a reduced expiratory reserve volume (ERV), such that resting breathing occurs at a less compliant part of the pressure-volume curve, resulting in increased elastic load,[42] close to the closing volume of the small airways, potentially leading to tidal airway closure. Furthermore, airway calibre is dependent on lung volume; with the change in airway diameter proportional to the cube root of lung volume.[43] As obese individuals breathe at this lower lung volume, airway smooth muscles are unloaded, allowing them to shorten excessively resulting in further airways narrowing which is exacerbated by the obese proinflammatory state of airways inflammation.[44] The airways narrowing results in tidal expiratory flow limitation and a resistive load which is accompanied by dynamic hyperinflation and intrinsic positive end expiratory pressure, and subsequent increase in inspiratory threshold load.[45] Pulmonary compliance is reduced due to the physical impact on chest wall expansion of obese tissues, and due to peripheral small airway closure, again secondary to breathing at low volumes, leading to atelectasis.[46] In addition, there is a reduction in diaphragm neuromuscular coupling in response to inspired carbon dioxide resulting in less respiratory muscle activity for any unit of drive.[47] Furthermore, respiratory muscle endurance is inversely proportional to increasing body mass index.[48] In order to meet the demands of the increase in resistive and threshold loads and reduced respiratory muscle capacity, neural respiratory drive increases to attempt to maintain adequate alveolar ventilation.[49] Indeed, in obese patients with chronic respiratory failure, the neural respiratory drive in the awake state, normalised for maximum neural respiratory drive, is fourfold higher than that observed in healthy subjects.[50] As expected, if the load overwhelms the system's ability to match the demand, alveolar hypoventilation will follow and lead to hypercapnic respiratory failure for example, during sleep, resulting in sleep-disordered breathing and resultant nocturnal respiratory failure. During sleep, the abdominal contents move in a cephalic direction, impeding diaphragm excursion and further reducing ERV, increasing the elastic load. Fatty deposits in the pharyngeal tissue increase the upper airway collapsibility observed during sleep due to muscle hypotonia, increasing the resistive load. As respiratory drive is reduced during sleep, the increased load can overwhelm the compensatory mechanisms resulting in alveolar hypoventilation.[51] The above pathophysiology establishes in the obesity hypoventilation syndrome (OHS), where obese individuals exhibit daytime hypercapnia in the absence of any other cause. The majority of individuals with OHS (90%) also suffer from concomitant onbstructive sleep apnoea (OSA),[42] but there is evidence to support a continuum for progression of hypercapnia in patients with severe OSA through a combination of OSA and OHS to OHS[52 53]

Obese individuals report shorter sleep duration and lower sleep efficiency,[54 55] and worse sleep quality[56 57] than controls. Respiratory effort-related arousals may partly explain this sleep disturbance. These are a period of abnormal breathing during sleep, associated with an increased effort and arousal, that do not fulfil the criteria for apnoea or hypopnoea.[58] Current data reports that both physiological and psychological factors such as mood disturbances impact on sleep quality.[59 60] Of interest, in OHS patients without OSA, time spent in REM sleep was lower than in controls[61] and the presence of OSA did not have any impact on subjective sleep quality,[62] suggesting that hypercapnia may contribute, rather than the nature of sleep-disordered breathing, as the level of PaCO2 elevation is often greater in the OSA and OHS phenotype than the OSA phenotype.

The gold-standard treatment for ORRF is significant weight loss, which can be successfully achieved by calorie control, exercise, bariatric surgery and novel metabolic treatments. Much less significant weight loss can be achieved with NIV alone[63] and NIV accompanied by a comprehensive weight loss programme.[64] Individuals who undergo bariatric surgery demonstrate improvement in sleep architecture (percentage time spent in non-REM sleep stage III and REM stages of sleep and apnoea/hypopnoea index),[65 66] with associated improvement in subjective sleep quality.[67 68]

More immediate correction of obesity-related alveolar hypoventilation and upper airways obstruction can be achieved with domiciliary nocturnal NIV. However, there are limited data reporting the effect on sleep quality after initiation of NIV. In a clinical trial comparing NIV in patients with mild OHS, NIV resulted in an improvement in percentage time spent in REM sleep, a reduction in respiratory arousals, a reduction in apnoea/hypopnoea index, and an increase in nocturnal oxygenation.[69] Another clinical trial comparing NIV and continuous positive airway pressure (CPAP) in patients with severe OSA and OHS demonstrated that both treatment modalities increased the percentage REM sleep time and reduced the arousal index and AHI,[70] supporting that nocturnal respiratory support is beneficial for sleep quality in patients with ORRF.

Slowly progressive neuromuscular disorders

Slowly progressive NMDs include conditions such as congenital muscular dystrophies, myotonic dystrophy, spinal muscular atrophies, inflammatory myopathies, metabolic muscle diseases and peripheral nerve diseases. While these conditions are rare, the NMD group account for 25% of patients treated with domiciliary NIV[71] as these patients often develop chronic hypercapnic respiratory failure with associated morbidity and mortality. As with COPD and ORRF, sleep disturbance and poor sleep quality is a frequently reported complication by patients with NMD.[20 72]

The common feature of these conditions is that there is a disruption along the neural pathways, with a negative effect on the efferent signal from the central respiratory centres to the respiratory muscles. This results in respiratory muscle weakness, altered respiratory mechanics and abnormal central control of breathing. Many NMD develop fibrotic changes of the rib cage and spinal deformities that result in an increased elastic recoil (and therefore increased elastic load), limiting inspiratory

capacity and causing a restrictive ventilatory pattern. In addition, to reduce the respiratory muscle load and reduce the risk of respiratory muscle fatigue, patients with NMD adopt a rapid shallow breathing pattern. This ventilatory pattern is characterised by decreased tidal volume and increased breathing frequency, leading to an increased dead space ventilation and decreased alveolar ventilation. Decreased alveolar ventilation increases the likelihood of developing hypercapnic respiratory failure. Reduced nasopharyngeal dilator muscle function further leads to increased upper airway resistance due loss of upper airway calibre, and therefore, increases the resistive load. An increased resistance in the upper airway causes greater work of breathing, further adding to the load on the diaphragm during inspiration, and in combination with the decreased upper airway tone during sleep, and diminished neural respiratory drive in different sleep stages leads to nocturnal alveolar hypoventilation. There are sparse data on individual NMD due to relatively low prevalence rates, particularly with regards to sleep quality. A single study reporting on polysomnographic data in patients with NMD demonstrated that apart from nocturnal hypoxia, which is unsurprising, sleep architecture was preserved.[73] The prevalence of sleep-disordered breathing is widely disparate in the literature due to multiple definitions of hypoventilation, heterogeneity of cohorts studied and the degree of weakness involved. Prevalence of hypoventilation in NMD has been reported from anywhere between 10% and 62%, depending on the definition of hypoventilation (daytime $PaCO_2$, daytime base excess, nocturnal SpO_2 or nocturnal $TcCO_2$).[74]

The use of domiciliary NIV to control hypercapnic respiratory failure has been well established in NMD for several decades. The majority of patients with NMD require domiciliary NIV during the course of their illness, and with increasing uptake of the therapy, life expectancy has considerably increased.[75] The major indication for initiating domiciliary NIV is nocturnal hypoventilation with or without sleep-disordered breathing.[76] There is evidence for the initiation of NIV prior to the onset of daytime hypercapnia and there are reports of the benefits of NIV in these patient groups,[77] and a number of international guidelines have been published,[78 79] although all referring to the low quality of evidence available. Most frequently, patients are established on NIV during an inpatient stay titrating required settings according to polysomnography or limited respiratory polygraphy monitoring. There is increasing interest in the effectiveness of home-based or outpatient set-up of NIV, to reduce the use of resources, time spent in hospital and increase cost-effectiveness. Pathways to employ autotitrating devices and telemedicine support are currently being developed to support a more outpatient or home-based delivery of the initial titration phase. Autotitrating devices are non-inferior in terms of outcomes to standard titration of NIV devices,[80] and home setup of NIV has been demonstrated to be both feasible and non-inferior when compared with inpatient setup.[81] However, as with COPD and obesity-related respiratory failure, few studies investigating the impact of NIV on sleep quality in NMD have been performed. Polysomnographic data in muscular dystrophy type I[82] and late-onset Pompe disease[83] demonstrated no deterioration in sleep quality after NIV initiation. A cross-sectional subjective assessment of sleep quality in a group of various NMD who were already established on domiciliary NIV demonstrated that more than 50% of patients reported experiencing poor sleep quality.[84] Sleep quality remains an important clinical outcome to evaluate when conducting NIV efficacy trials in this patient group.

Rapidly progressive neuromuscular disorders

MND is the most common adult-onset rapidly progressive neurogenerative disorder of both the central and peripheral nervous system. It results in the loss of motor neurones in the cerebral cortex, the brainstem and the anterior horn of the spinal cord. Respiratory failure is a common consequence of MND due to a combination of its effect on the brainstem control of breathing,[85 86] and the motor neurones supplying the respiratory muscles; it was the reason for hospital admission in approximately 30% of patients with MND[87 88] and a frequent cause of death.[89–92]

Alveolar hypoventilation is caused by respiratory muscle weakness as the disease progresses. Progressive degeneration of the motor neurones innervating the respiratory muscles results in significant respiratory muscle weakness and reduced capacity of the respiratory muscle pump. Loss of phrenic nerve function results in diaphragm weakness or paralysis, which promotes the unopposed caudal movement of abdominal organs in the supine posture, further reducing vital capacity. Expiratory muscles that support an effective cough manoeuvre also weaken with disease progression, resulting in an inability to expectorate secretions adequately, facilitating mucoretention and increasing the risk of lower respiratory tract infections, as well as contributing to a high airway resistance and increased resistive load.

Impaired sleep quality is a frequent and pervasive complaint among patients with MND[93] and presents a particular burden on their carers as well.[94] More than 60% of patients with MND report a raised score in the PSQI, indicating worse sleep quality, compared with 37% of controls.[95] Sleep fragmentation may be caused by a combination of physical symptoms related to MND (muscle cramps, pain, spasticity and restless legs with period limb movements at night), mood disturbance leading to insomnia and sleep-disordered breathing.[96] Furthermore, neurodegeneration of central pathways regulating REM sleep may also lead to REM sleep disorders.[97] Time spent in REM sleep was significantly reduced in patients with MND with diaphragmatic dysfunction (suggesting more advanced disease) than those without.[98] Of note, in those with diaphragmatic dysfunction, individuals who demonstrated preserved sternomastoid activity spent more time in REM sleep than those that did not. This is consistent with data from patients with bilateral diaphragmatic paralysis who maintained REM sleep by recruiting extradiaphragmatic muscles.[99]

The mainstay of treatment for hypercapnic respiratory failure in MND is NIV. A single clinical trial was performed which demonstrated clear survival benefit in patients with MND without severe bulbar dysfunction.[100] A Cochrane review supported the recommendations of this study, commenting that further trials will not be possible as it would be unethical to withhold NIV in a control arm, given the existing supportive data.[101] Subsequent retrospective studies have provided further evidence for the use of NIV. When compared with matched controls who were not treated with NIV, patients with NIV had longer overall survival,[102] as well as tracheostomy-free survival, and NIV also provided survival benefit in bulbar-onset patients.[103] Current work is focused on identifying the specific cohort of MND patients who most benefit from NIV and the most appropriate timing of initiation. Bulbar dysfunction was thought to be a predictor of NIV failure.[104 105] Positive pressure applied to the airway in patients with MND has been demonstrated to cause vocal cord closure, particularly in those with bulbar dysfunction.[106] This has potential consequences for the effective delivery of NIV in this patient group. However, a recent systematic review has demonstrated that with attention to individual needs

(eg, secretion management, interface optimisation and closer ongoing monitoring) bulbar patients can derive considerable benefit from NIV therapy.[107] Survival is increased in patients who are more effectively ventilated (minimal time spent with oxygen saturation below 90%) overnight than those who are not,[108] and so careful initiation and monitoring is key in these patients. The optimal timing of NIV initiation remains under investigation. Outpatient-based and home-based initiation models are increasingly being investigated and compared with the traditional inpatient-based model; however, novel pathways appear to be at least non-inferior, and may, at best, result in improved clinical outcomes.[109] Sleep in MND has been investigated more often as a primary outcome following NIV initiation than in other NMD conditions. Subjectively, NIV initiation improved sleep quality (with a reduction in the PSQI) one month following initiation, and this change was sustained at twelve months.[110] Available polysomnographic data are inconclusive and relate primarily to patient selection for NIV initiation and study design. A small pre/post initiation study demonstrated that NIV improved overnight oxygenation without any improvement in the regular sleep architecture.[111] Other retrospective studies have demonstrated that NIV initiation increased the time spent in slow wave and REM sleep,[112] with an improvement in the sleep efficiency and the apnoea/hypopnoea index in non-bulbar patients only,[113] as well as in both bulbar and non-bulbar patients.[114] However, the current literature provides sufficient evidence that NIV significantly improves sleep outcomes in MND patients. Identification of patients who benefit the most (phenotypically and metabolically) and the most appropriate setting for initiation (inpatient, outpatient or home based) remain key considerations when initiating NIV in this cohort.

Monitoring sleep quality

Long-term NIV is initiated in patients with chronic respiratory disease not only to improve ventilation, but also to improve symptoms, quality of life and sleep quality. It is, therefore, important to monitor all of these goals. Monitoring sleep quality must be practical and easy to perform both for patients and the clinical team. Frequently used patient-reported outcome measures are the Severe Respiratory Insufficiency questionnaire, which is a quality of life assessment tool designed for individuals receiving home mechanical ventilation with a specific sleep domain and the PSQI, an assessment of sleep quality.[115] Pulse wave amplitude, which is measured using overnight oximetry, can be used to assess sleep fragmentation.[116] This is a simple home-based user-friendly tool to measure sleep quality. Mask leak is a common cause of poor sleep quality. Telemonitoring technology on the ventilator can be utilised to assess for leaks remotely.[117] Automated remote sleep staging by the ventilator has also been proposed[118] which would allow sleep architecture to be assessed while using NIV.

In patients using long-term NIV, correction of hypercapnia did not correlate with sleep quality. On the other hand, poor sleep quality was associated with adverse effects of NIV such as mouth dryness, mask leak, aerophagia, mask-related pain and pressure sores.[119] Therefore, it is important that these adverse effects are addressed to optimise sleep quality. The addition of humidification into the ventilator circuit can minimise mouth dryness. Frequent review, remote monitoring and offering alternative interfaces can help to identify and mitigate against mask leak, pain and pressure sores. Aerophagia can be treated with prokinetics and medications such as simethicone. Although sleep quality may be preserved after initiation of NIV,[120] it is important to monitor and address potential causes as they arise.

Summary

The physiological changes in ventilation during normal sleep in healthy adults are exacerbated in chronic respiratory diseases that result in alveolar hypoventilation. Simultaneously, sleep quality is attenuated in patients with conditions leading to chronic hypercapnic respiratory failure. This review has detailed the pathophysiological changes that lead to alveolar hypoventilation and poor sleep quality in COPD, ORRF, slowly progressive and rapidly progressive neuromuscular conditions. A combination of increased respiratory load, reduced neural respiratory drive and respiratory muscle capacity results in a state of alveolar hypoventilation; these pathophysiological changes are accentuated during sleep and can lead to hypercapnic respiratory failure. Although the pathophysiological mechanisms across these groups are well described, the focus of the clinical studies to date have targeted clinical outcomes and health-related quality of life. Despite this, there are limited published data investigating the effect of long-term NIV on sleep quality. The current data appear to suggest that NIV may have a positive impact on sleep quality, with the data for rapidly progressive NMD being more convincing than other groups. Multiple confounding factors, including study design, patient selection, intervention and different reported outcomes does not permit conclusions to be clearly drawn. With the increasing use of domiciliary NIV in all of these patient groups, supported by the physiological, clinical and patient-centred improvement, there is an urgent requirement to focus the effect of treatment with nocturnal ventilatory support on both subjective and objective sleep quality with a goal of enhancing adherence and further improving outcomes of patients with chronic respiratory failure.

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