

Nocturnal hypoventilation – identifying & treating syndromes

Amanda J. Piper

*Respiratory Failure Service, Department of Respiratory Medicine, Royal Prince Alfred Hospital
Camperdown, Woolcock Institute of Medical Research, University of Sydney, Australia*

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Nocturnal hypoventilation is a common feature of disorders affecting the function of the diaphragm or central respiratory drive mechanisms. The ensuing change in gas exchange is initially confined to rapid eye movement (REM) sleep, but over time buffering of the raised carbon dioxide produces a secondary depression of respiratory drive that will further reduce ventilation not only during sleep but eventually during wakefulness as well. Failure to identify and treat nocturnal hypoventilation results in impairments in daytime function, quality of life and premature mortality. While some simple daytime tests of respiratory function can identify at risk individuals, these cannot predict the nature or severity of any sleep disordered breathing present. Nocturnal monitoring of gas exchange with or without full polysomnography is the only way to comprehensively assess this disorder, especially in the early stages of its evolution. Non invasive ventilation used during sleep is the most appropriate approach to reverse the consequences of nocturnal hypoventilation, although continuous positive airway pressure (CPAP) may be effective in those individuals where a significant degree of upper airway obstruction is present. When appropriately selected patients use therapy on a regular basis, significant improvements in quality of life, exercise capacity and survival can be achieved, irrespective of the underlying disease process.

Key words Hypercapnia - nocturnal hypoventilation - non invasive ventilation - respiratory failure

Background

Hypoventilation occurs when the level of alveolar ventilation is insufficient to meet metabolic needs. This is characterised by a rise in arterial carbon dioxide (CO₂) tension, usually measured from arterial blood gases. The ability to maintain an adequate level of ventilation relies on three main factors: the capacity of the respiratory muscles, the load that is placed on these muscles and the adequacy of the central drive to breathe. If one or more of these factors become unbalanced, the individual is placed at risk of hypoventilating. Although identifying and investigating daytime hypercapnia is routine in respiratory practice particularly in the acute

setting, many clinicians and patients fail to appreciate the extent to which sleep may promote and exacerbate chronic hypoventilation. This article briefly reviews the impact of sleep on breathing in health and respiratory disease, outlines the major disorders known to be associated with nocturnal hypoventilation, discusses the methods of identifying those at risk and reviews the evidence for various strategies used in managing nocturnal hypoventilation.

The impact of sleep on breathing

A number of important alterations in respiratory physiology occur with the onset of sleep. The

wakefulness drive to breathe is lost, with a reduction in tonic neural input to the respiratory system. Reduced drive to the chest wall and upper airway muscles results in an increase in upper airway resistance, while the reflexive compensatory mechanisms for added mechanical loads are simultaneously reduced¹ along with the respiratory centre responsiveness to hypoxia and hypercapnia. As a consequence of these changes a small fall in minute ventilation of around 10 per cent occurs in normal subjects from wakefulness to non-rapid eye movement (NREM) sleep, resulting in a small rise in PaCO₂ and reduction in oxygen saturation (SpO₂)². In addition, sleep induces a change in the pattern of respiratory muscle activation such that during NREM sleep there is an increase in the rib cage contribution to ventilation compared to wakefulness. In contrast, during rapid eye movement (REM) sleep active inhibition of motoneurons produces a generalized postural muscle atonia, so that maintenance of ventilation in this sleep stage is reliant primarily on diaphragm activity, and to a lesser extent the parasternal intercostals. Tidal volume and respiratory rate during REM sleep are also more variable than NREM sleep, although overall minute ventilation is similar².

These physiological changes cause a small degree of sleep hypoventilation in normal subjects but are of little clinical consequence. However, when superimposed on individuals who already have respiratory muscle weakness, altered chest wall mechanics, compromised gas exchange or abnormal respiratory drive, significant alterations in nocturnal ventilation and gas exchange can occur. In a group of patients with nocturnal desaturation, minute ventilation fell by around 20 per cent from wakefulness to NREM, with further falls during REM sleep of almost 40 per cent, irrespective of the underlying primary disease process². This fall was mainly due to a reduction in tidal volume, with only minor changes in respiratory rate seen. In contrast, in normal subjects and those with continuous positive airway pressure (CPAP) treated obstructive sleep apnoea (OSAS), minute ventilation during NREM and REM sleep fell only marginally compared to wakefulness, with no significant difference between these two sleep stages².

When nocturnal hypoventilation is present, it will first become apparent during REM sleep. The fall in oxygen saturation initially induces arousal from sleep, impacting on sleep quality and duration. This limits the magnitude of desaturation and the rise in CO₂, at least initially, by briefly changing state and restoring

levels of ventilation. In some cases REM sleep is lost or reduced to minimise these changes³⁻⁵. However, over time and with increasing pressure for sleep, more extreme changes in nocturnal blood gases are tolerated especially during REM sleep. As periods of hypoventilation become more prolonged, bicarbonate levels in the cerebrospinal fluid rise in response to increasing CO₂. This further depresses respiratory drive, not only during sleep but in wakefulness as well. The resultant development of diurnal respiratory failure may be mistaken for the patient reaching the terminal stages of their disease. Frequently, the extent of the problem is only recognised after the patient is hospitalised with acute respiratory failure triggered by a seemingly minor intercurrent illness such as a viral chest infection^{6,7}.

Disorders associated with nocturnal hypoventilation

Any disorder that reduces the capacity of the inspiratory muscles especially the diaphragm to generate pressure, increases the load placed on these muscles, or impairs the drive to breathe may produce hypoventilation (Table I). Although the pathogenesis underlying disorders associated with nocturnal hypoventilation varies considerably, the impact on sleep breathing, gas exchange and daytime function is similar. Upper airway obstruction may also be present

Table I. Disorders associated with nocturnal hypoventilation

<i>Neuromuscular disorders</i>	
	Stable or slowly progressive
	Previous poliomyelitis
	High spinal cord injuries
	Spinal muscular atrophy
	Myotonic dystrophy
	Congenital myopathy
	Rapidly progressive disorders
	Motor neurone disease
<i>Chest wall abnormalities</i>	
	Kyphoscoliosis
	Post tuberculosis sequelae
	Thoracoplasty
	Obesity hypoventilation syndrome
<i>Lung disorders</i>	
	Chronic obstructive pulmonary disease
	Cystic Fibrosis
	Overlap syndrome (lung disease with obstructive sleep apnea)
<i>Ventilatory control abnormalities</i>	
	Brainstem injuries: Stroke, infection, tumour
	Congenital central hypoventilation
	Primary alveolar hypoventilation

in these individuals, related to the primary disease process itself or secondary to other factors such as obesity, and this may further exacerbate the problem of abnormal gas exchange during sleep.

Neuromuscular disorders

Sleep associated breathing and gas exchange abnormalities are common in neuromuscular disorders^{8,9}. The type of sleep disordered breathing present will reflect the distribution of respiratory muscle involvement⁹, which can vary considerably between disorders. For example, involvement of the diaphragm usually occurs late in the disease process in Duchenne muscular dystrophy (DMD) while in motor neurone disease (MND) and acid maltase deficiency, diaphragmatic weakness may be the first presentation of the disorder¹⁰. Although diaphragmatic weakness primarily underpins the appearance of hypoventilation during sleep, the problem will be further exacerbated if a scoliosis is present as it places the muscles at a mechanical disadvantage. Obstructive apnoeas or hypopnoeas are also frequently reported in many of these disorders¹¹⁻¹³. Scoliosis, obesity, craniofacial abnormalities and upper airway instability from pharyngeal muscle weakness can all predispose the patient to developing upper airway obstruction, which can occur in both NREM and REM sleep. Abnormalities in ventilatory control, either as a component of the primary disorder such as in myotonic dystrophy or congenital myopathy¹⁴, or secondary to nocturnal hypoventilation and bicarbonate retention may also contribute to reduced respiratory drive both during sleep and eventually during wakefulness as well. Consequently, it is not surprising that obstructive and central events as well as hypoventilation have been variously described across neuromuscular disorders and within the same disease process.

Inevitably, the most severe desaturation is seen during REM sleep^{5,15} (Fig. 1), and is most obvious

during periods of phasic eye movements, when central hypopnoeas associated with suppression of intercostal muscle activity and reduced chest wall movement are frequently seen⁵. However, an imbalance between the inspiratory force generated by the inspiratory muscles including the diaphragm and the activity of the muscles responsible for stabilising the upper airway can lead to frank upper airway obstruction, with traumatic quadriplegia below the level of C5 being the most common example of this. In many patients with severe respiratory muscle weakness, recruitment of accessory inspiratory muscles such as the scalenes and sternomastoid muscles will occur during wakefulness and NREM sleep to aid diaphragmatic efforts^{3,5,15}. Contraction of the abdominal muscles during expiration may also be observed^{5,15} (Fig. 2a). This strategy can improve the effectiveness of the inspiratory muscles by increasing abdominal pressure and moving the diaphragm in a cranial direction. Relaxation of the abdominal muscles at the commencement of inspiration allows passive descent of the diaphragm, facilitating inspiratory flow^{5,15}. However, in REM sleep the suppression of postural muscles renders these compensatory manoeuvres ineffective, producing reduction or loss of inspiratory flow and chest wall movement, and the emergence of “central” events (Fig. 2b).

The severity of sleep disordered breathing and whether it is dominated by obstructive events or hypoventilation is likely to be influenced by the clinical stage at which any investigation is undertaken. Initially it was presumed that MND patients with bulbar muscle involvement would show a high incidence of obstructive events¹⁶. However, no significant association between bulbar dysfunction and severity of sleep disordered breathing or type of event has been found¹⁶⁻¹⁸. In a retrospective analysis of sleep data in 114 patients with MND, sleep related breathing abnormalities were common



Fig. 1. Sleep hypnogram and oximetry recording from a patient with neuromuscular disease. As is typically seen, the most severe periods of oxygen desaturation occurred during REM sleep.

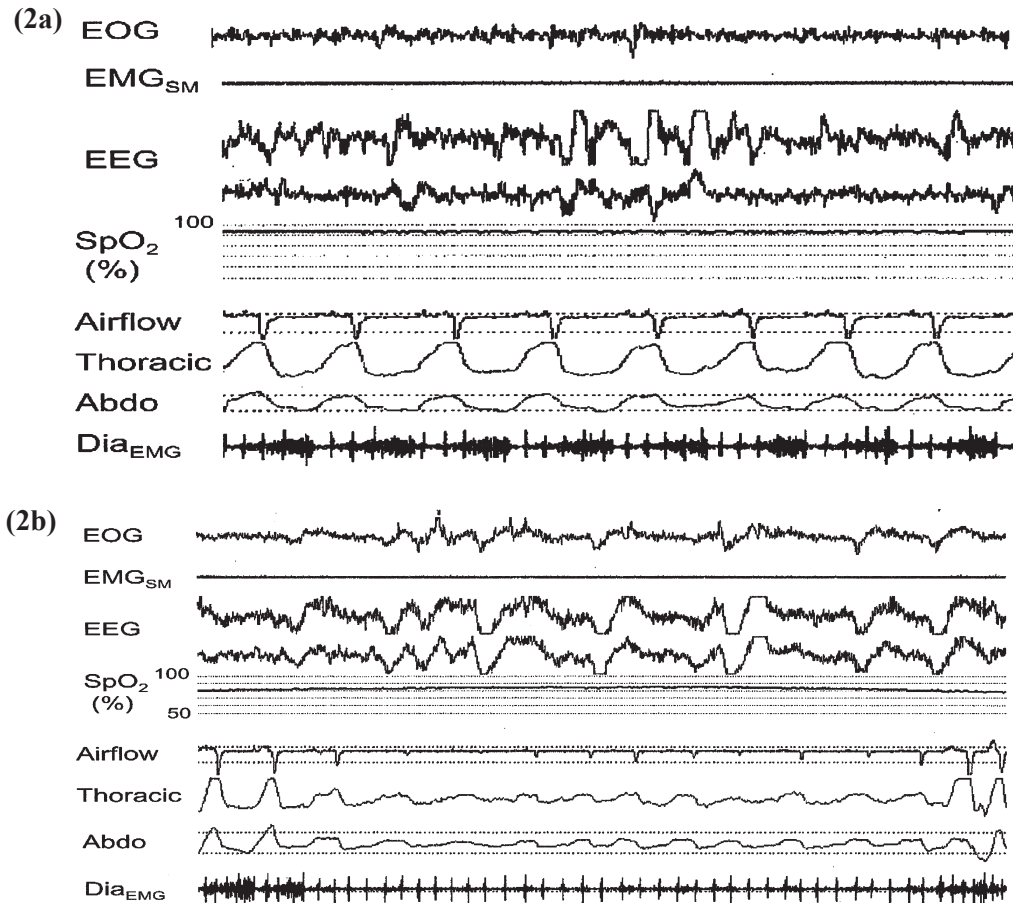


Fig. 2a. Breathing during sleep in a patient with congenital muscular dystrophy. During NREM sleep, airflow and chest wall movement is augmented by abdominal muscle contraction during expiration. This activity can be seen in the diaphragm (DiaEMG) channel. This expiratory activity, with sudden relaxation at the beginning of inspiration, aids passive descent of the diaphragm and hence augments inspiratory flow. **2b.** In REM sleep, inhibition of the postural muscles results in loss of this accessory expiratory activity, with consequent reduced chest wall motion and attenuated airflow.

in the first year following disease onset¹⁹. However, a progressive decline in the number of events over the duration of the disease was seen such that those patients with disease duration of more than 2 yr had significantly fewer events than patients diagnosed for less than 1 yr. It was suggested that this change in frequency of events may reflect increasing inspiratory muscle weakness¹⁹. With increasing diaphragmatic involvement, the ability of the subject to generate an inspiratory pressure above the closing pressure of the upper airway would be reduced, resulting in fewer events being recorded^{16,20}. Likewise in DMD, some studies have reported predominantly central events with hypoventilation, especially during REM sleep^{12,21}, while in other studies obstructive events have been reported^{11,13}. Although this finding may arise due to misclassification of obstructive events as central¹², it is also possible that sleep disordered breathing

evolves with age in this patient group¹³. Obstructive events have been more commonly reported in younger patients^{11,13}, with more frequent and severe central events¹¹ or hypoventilation¹³ appearing as the patient ages.

Chest wall deformity

The most common disorder associated with chest wall deformity is scoliosis, characterized by curvature of the spine either laterally (scoliosis) or laterally and anteroposteriorly (kyphoscoliosis). This disorder may occur idiopathically or as a secondary complication in a variety of conditions including neuromuscular disorders, primary displasias of the spine, connective tissue disease, or following trauma or surgery to the chest wall or spine. A restriction pattern of pulmonary function occurs, with reduced total lung capacity, increased residual volume and consequent

reduction in inspiratory capacity and vital capacity (VC). These changes may arise from impaired chest wall mechanics or from lung hypoplasia. In addition to restriction, airway obstruction may also be present due either to breathing at low lung volumes²² or from the displacement of the intrathoracic trachea and main stem bronchi arising from the secondary cervical curvature creating a mechanical airway obstruction²³.

Respiratory complications in scoliosis are related to the severity of the spinal deformity and degree of respiratory muscle weakness or inefficiency that is present. The abnormal chest wall mechanics may also create unco-ordinated chest wall movement and alter ventilation perfusion (VQ) distribution. If chest wall mechanics are abnormal enough, significant alterations in the pattern of breathing not only during sleep but at rest and on exertion will occur. Tidal volume is reduced and respiratory rate increases. While this pattern of breathing will reduce the work of breathing, dead space ventilation is increased and alveolar ventilation reduced²⁴. Although tidal volume is reduced, relative to VC it increases, but in order to achieve this the patient must generate inspiratory pressures greater than normal, requiring increased rib cage muscle activity as well as recruitment from the abdominal expiratory muscles^{24,25}. This permits a reduction in end-expiratory lung volume and promotes chest wall recoil during the next inspiratory effort, thereby sharing the increased work of breathing between the inspiratory and expiratory muscles²⁴. This ventilatory strategy may not be possible if the patient's scoliosis is associated with neuromuscular disease, and will be lost with the inhibition of postural muscles associated with REM sleep, thereby permitting significant desaturation to occur.

As with other groups exhibiting hypoventilation during sleep, the most common nocturnal breathing abnormality in scoliosis is hypopnoeas in REM sleep²⁶. However, upper airway obstruction may also be seen, especially in those patients who are overweight²⁷, or where there is significant displacement of the intrathoracic trachea. The severity of desaturation and the type of event seen does not appear to be influenced by whether the scoliosis is secondary to respiratory muscle weakness or to other causes²⁶. However, compared to subjects with chronic obstructive pulmonary disease (COPD) or interstitial lung disease with the same degree of daytime hypoxaemia, those with scoliosis have more severe falls in mean SpO₂ and larger rises in CO₂ during sleep²⁸.

Obesity hypoventilation

Severe obesity places a significant load on the respiratory system through changes in chest wall compliance and reductions in lung volumes including functional residual capacity (FRC) and expiratory reserve volume. Breathing at low volumes can promote air trapping, expiratory flow limitation and the development of intrinsic positive end-expiratory pressure, which will impose a threshold load on the inspiratory muscles and increase the work of breathing²⁹. In order to maintain eucapnia in the face of mass loading and abnormal chest wall mechanics, increased respiratory drive occurs³⁰. However, if this increased drive cannot be maintained, hypoventilation will develop³¹, and is termed obesity hypoventilation syndrome (OHS). Sleep breathing in these individuals is characterized by combinations of frank obstructive apnoea, prolonged periods of partial airway obstruction associated with hypoventilation and "central" hypoventilation³². The frequency and severity of obstructive events are similar between patients with OHS and those with eucapnic OSAS of similar body weight; although the time spent below SpO₂ 90 per cent is significantly greater in the OHS group³³.

Diminished chemosensitivity to hypoxia and hypercapnia during wakefulness is seen in patients with OHS^{34,35} with lower ventilatory responsiveness to carbon dioxide being associated with more time in hypoventilation during REM sleep³⁴. This attenuated responsiveness is thought to be an acquired phenomenon and is at least partially reversed with correction of sleep disordered breathing³⁴, suggesting that sleep apnoea itself may play some role in the development of daytime hypercapnia. However, since obstructive events are equally severe in hypercapnic as in eucapnic obese patients with obstructive sleep apnoea syndrome (OSAS), the possible mechanisms underlying the development of nocturnal hypoventilation and awake respiratory failure are still unclear. One proposal is the inability of patients with hypercapnia to augment ventilation during the inter-apnoea periods and therefore unload carbon dioxide accumulated during the apnoeic period³⁶. Hypercapnic patients have been shown to have a reduced post-event ventilatory slope compared to eucapnic individuals of similar body mass index (BMI) and lung function³⁶, which would lead to the accumulation of CO₂ overnight. This could initiate the retention of bicarbonate, thereby allowing a gradual adaptation of chemoreceptors and eventual persistence of hypercapnia through blunting of the ventilatory drive³⁷.

Emerging evidence from animal and human data suggest there are other permissive factors that could contribute to alterations in breathing during sleep in OHS. These include neurohormonal factors such as leptin and neuromodulators such as adenosine. Leptin is a protein produced by adipose tissue and amongst other functions acts on the respiratory centres to stimulate ventilation. In a mouse model of obesity, leptin deficiency was associated with impaired respiratory mechanics and depressed respiratory control especially during sleep³⁸. Prolonged leptin replacement in this model attenuated the respiratory complications of obesity including the rapid shallow breathing pattern and diminished lung compliance³⁸. In humans, leptin levels are increased in obesity, and therefore may be contributing to the augmented drive needed to maintain eucapnia in the face of mass loading³⁹. Since leptin levels are further increased in hypercapnia³⁹, a state of leptin “resistance” has been proposed to explain the development of nocturnal and daytime hypoventilation in severely obese individuals⁴⁰. The sustained hypoxia characteristic of sleep breathing in OHS³³ may further contribute to the perpetuation and progression of abnormal breathing through impairment of the arousal response⁴¹, further adding to the inability of these individuals to unload CO₂ following apnoeic periods³⁶, and therefore worsening hypoventilation.

Chronic obstructive lung disease (COPD)

Sleep can be a major stressor on breathing in patients with COPD who have pre-existing abnormal respiratory mechanics and lower baseline oxygenation during wakefulness than normal subjects. Consequently, abnormalities in gas exchange during sleep appear to be common in these patients and can be broadly classified as isolated nocturnal desaturation despite adequate daytime oxygenation (PaO₂>55mmHg); sleep hypoventilation in those with daytime respiratory failure; and the co-existence of OSAS with COPD, referred to as overlap syndrome⁴².

Nocturnal desaturation in COPD patients with mild to moderate daytime hypoxaemia (PaO₂ 56-70mmHg) is common⁴³, and is generally confined to or worsened by REM sleep. The mechanisms underlying this pattern of nocturnal desaturation have been the subject of investigation for some years. Hypoventilation, especially in REM sleep, is thought to be the major contributing factor², although worsening ventilation-perfusion has also been implicated⁴⁴. In patients who are hyperinflated, recruitment of the accessory respiratory

muscles aids the flattened diaphragm in generating sufficient inspiratory pressure to maintain adequate ventilation both when awake and during NREM sleep. With the generalized muscle atonia associated with REM sleep, this accessory muscle activity is lost⁴⁵, resulting in reduced minute ventilation². Accessory muscle suppression is particularly pronounced during phasic periods of rapid eye movement, and can result in “central” hypopnoeas and desaturation⁴⁵. The reduction in accessory muscle activity could also cause a fall in FRC, which would further alter VQ relationships, and contribute to more significant desaturation⁴⁴.

In the most extensive evaluation of changes in respiratory function during sleep in COPD, Ballard *et al*⁴⁶ studied 5 normocapnic patients with severe, stable COPD using a horizontal body box. Contrary to previous studies, these investigators found no change in supine FRC across sleep stages, and suggested that VQ mismatch was not playing a major role in nocturnal gas exchange abnormalities. They did, however, find significant decreases in minute ventilation and inspiratory flow, associated with an increase in upper airway resistance and reduced inspiratory neuromuscular drive, particularly marked in REM sleep. It is suggested⁴⁶ that patients who have high resting ventilatory requirements during wakefulness would be unable to meet these ventilatory requirements during sleep as a result of these changes, impacting on oxygenation especially during REM sleep.

In most studies of sleep and COPD, subjects were normocapnic during wakefulness, and exhibited nocturnal desaturation which was mainly confined to REM sleep. Since a reduction in drive to the upper airway muscles⁴⁵ and increased inspiratory flow resistance⁴⁶ occur in COPD patients, it is not surprising that obstructive sleep apnoea or partial airway obstruction co-exists in a number of patients, particularly when BMI is increased^{47,48}. The presence of upper airway instability, even without frank obstruction, has been implicated in the development of sleep and daytime hypoventilation in some COPD patients^{47,48}, although a few studies have examined nocturnal breathing in hypercapnic COPD patients. Sleep hypoventilation is common in this group, occurring in more than 40 per cent of patients⁴⁸. Significant falls in minute ventilation from wakefulness to NREM sleep and from NREM to REM sleep occur, associated with a reduction in tidal volume². The severity of the ensuing sleep hypoventilation appears to be related not only to the awake PaCO₂ level and BMI, but also to the degree of

inspiratory flow limitation present during REM sleep⁴⁸. This is consistent with the findings of Chan *et al*⁴⁷ who observed that hypercapnic COPD patients had more sleep disordered breathing, higher BMIs and smaller upper airway cross sectional areas than eucapnic controls matched for lung function. Obesity in the presence of a smaller upper airway may tip the balance towards “obstructive” events, including hypopnoeas and flow limitation, when drive to the inspiratory muscles in REM sleep is reduced⁴⁵. This added load to breathing in the presence of abnormal chest wall mechanics could produce more extreme sleep hypoventilation. During more prolonged periods of underbreathing, a gradual retention of bicarbonate would occur, blunting the chemosensitivity to CO₂ and eventually promoting the emergence of chronic hypercapnia³⁷. The change in evening to morning PaCO₂ has been shown to be highly correlated with severity of sleep hypoventilation, suggesting that nocturnal hypoventilation can influence daytime hypercapnia in severe COPD⁴⁸.

Both COPD and OSAS are relatively common, so it is not surprising that the two disorders will occur together, with early studies suggesting that the prevalence of OSAS in COPD may be higher than expected by chance⁴⁹. However, a study of a middle aged to elderly community population found that the prevalence of OSAS was not higher in subjects with COPD (albeit fairly mild disease) than those without COPD⁵⁰. It is, however, important to identify patients with overlap, since individuals with both disorders demonstrate more severe nocturnal desaturation, and are at a greater risk of developing pulmonary hypertension and right heart failure, than those with either disorder in isolation^{49,51}. In patients with overlap, diurnal hypoxaemia, hypercapnia and pulmonary hypertension occur when pulmonary function is only mildly or moderately impaired⁴⁹, which is very different to COPD patients with isolated nocturnal desaturation. Health related quality of life is also markedly impaired in overlap patients compared to those with COPD alone, with the degree of OSA accounting for the majority of the difference seen⁵².

Central alveolar hypoventilation

This is a group of disorders characterized by primary abnormalities in ventilatory control leading to hypoventilation and central apnoea during sleep. The congenital form of the disorder is known as congenital central hypoventilation syndrome (CCHS) or “Ondine’s Curse” and produces severe sleep

hypoventilation although adequate ventilation during wakefulness is usually maintained. In addition to the respiratory manifestations of this disorder, CCHS is also associated with a more global autonomic nervous system dysfunction⁵³. The disorder is diagnosed in the absence of primary neuromuscular, lung cardiac disease or the presence of an identifiable brainstem lesion^{53,54}. The abnormality arises from mutations of the *PHOX2B* gene⁵⁵. During sleep, these children have little or no ventilatory sensitivity to CO₂, and a variable or absent sensitivity to hypoxia⁵³. Ventilatory responsiveness to chemical stimuli is also abnormal during wakefulness⁵³. Consequently, severe alveolar hypoventilation during sleep develops during spontaneous breathing, necessitating long term nocturnal ventilation. However, CCHS differs from other respiratory disorders causing hypoventilation during sleep in that the level of ventilation, though abnormal, is better in REM than NREM sleep⁵⁶. Although generally thought of as a paediatric disorder, a recent case series identified 5 adults presenting after the age of 21 with respiratory failure without early overt manifestations of CCHS yet heterozygous for a polyalanine expansion mutation in the *PHOX2B* gene⁵⁷.

Central hypoventilation may also be acquired following neurologic disorders that affect the brainstem, such as stroke, vascular malformations, infections and brainstem tumours. If no cause for the hypoventilation can be found the disorder is labelled idiopathic. However, it is possible that many of these individuals have milder forms of disorders known to cause hypoventilation.

Opioid-induced central apnoea and hypoventilation may be another cause of abnormal sleep gas exchange and daytime respiratory failure. Central sleep apnoea is common in this population⁵⁸ along with prolonged periods of hypoventilation. In stable methadone managed patients, central chemosensitivity is reduced while peripheral chemosensitivity is increased⁵⁹. Although the exact mechanisms underlying the development of sleep disordered breathing in this population remain unclear, the interplay between depressed respiratory drive and abnormalities in chemoreceptor sensitivity undoubtedly plays an important role⁵⁹.

Assessing nocturnal hypoventilation

Identifying changes in nocturnal breathing and gas exchange is not merely a clinical curiosity but constitutes a crucial stage in the clinical care of these individuals since effective and acceptable therapy in

the form of non-invasive ventilatory support is now widely available.

The method and frequency of any assessment will depend on the nature of the primary disorder, the clinical stage at which the patient presents, and any signs or symptoms the patient may have (Table II). Foremost however, clinicians need to be armed with a high level of suspicion when seeing patients with disorders known to be associated with nocturnal hypoventilation. Thyroid function should be checked in any person with symptoms of hypoventilation, and a sleep history should form part of the general assessment. However, the development of nocturnal hypoventilation and daytime hypercapnic respiratory failure is often insidious, especially in patients who are non-ambulant^{8,60}. Symptoms such as dyspnoea, morning headache, impaired sleep quality, sleep restlessness and drowsiness may be reported or elicited on questioning. However, these are also non specific, and if not aware of the possibility of sleep hypoventilation the patient and clinician may attribute such symptoms to the progression of the primary disease process.

Daytime measures which reflect breathing and gas exchange during sleep would be of great clinical relevance since undertaking nocturnal monitoring, especially polysomnography (PSG), can be difficult, costly and inconvenient^{61,62}. Although awake measures of lung function and gas exchange have not been shown to accurately predict the nature or severity of nocturnal hypoventilation, a number of simple measures can

assist in identifying at risk individuals in whom closer and more detailed monitoring is warranted.

Pulse oximetry is a simple and readily available tool that should be routinely used to screen patients. Although there is a moderate relationship between daytime SpO₂ and nocturnal desaturation in patients with COPD^{43,63,64}, this relationship is not robust enough to accurately identify who will desaturate during sleep and how severely. Nevertheless, nocturnal desaturation is unlikely where daytime SpO₂ >94 per cent, but likely when SpO₂ is below this^{43,63}.

Arterial blood gases provide more definitive information about current daytime gas exchange. However, this is an invasive procedure and can be uncomfortable and difficult to obtain in patients with contractures or in those with significant obesity. As an alternative, venous or capillary blood samples can be used, as base excess⁶¹ and bicarbonate⁶⁵ have been shown to be sensitive measures in identifying nocturnal hypoventilation in neuromuscular disorders and OHS.

While lung function does not predict nocturnal desaturation in COPD⁶³, this is not the case for patients with neuromuscular and chest wall deformities. Significant correlations between nocturnal saturation and VC have been shown^{15,60,61}. In a number of neuromuscular disorders including DMD, congenital and limb girdle muscular dystrophy, nocturnal hypoventilation can be predicted on the basis of a VC <40 per cent of predicted^{60,61}. In patients with thoracic cage disorders, a VC <1.0 - 1.5l and a high angle of curvature (>120 degrees) should prompt further investigation as these patients have been shown to be at high risk of developing respiratory failure⁶⁶.

A problem with VC though is that it can remain relatively well preserved even in the presence of significant muscle weakness. In contrast, measuring the fall in VC from upright to supine has been shown to be a specific and sensitive indicator of diaphragmatic weakness if the change is greater than 25 per cent⁶⁷, with significant negative correlations reported between overnight oxygenation and erect to supine fall in VC^{5,15}.

Respiratory muscle weakness is common in patients with neuromuscular disorders, but may or may not be associated with other disorders such as idiopathic scoliosis and obesity hypoventilation, making assessment of respiratory muscle strength an important aspect of evaluating patients with suspected nocturnal hypoventilation. Respiratory muscle strength

Table II. Assessing nocturnal hypoventilation

<i>Symptoms</i>	
	Morning headaches, restless sleep, daytime sleepiness, orthopnea, recurrent respiratory problems, cor pulmonale
<i>Lung function</i>	
	Simple spirometry – FEV1 and VC (erect and supine)
	Peak cough flow
<i>Respiratory muscle strength</i>	
	Maximum inspiratory and expiratory muscle pressures
	Sniff nasal inspiratory pressures
<i>Gas exchange</i>	
	SpO ₂
	Venous blood bicarbonate or base excess
	Arterial blood gases
<i>Nocturnal monitoring</i>	
	Overnight oximetry
	Transcutaneous carbon dioxide monitoring
	Cardiorespiratory monitoring (SpO ₂ , airflow and chest wall movement)
	Polysomnography

has traditionally been assessed by measuring maximal inspiratory (MIP) and expiratory (MEP) pressures generated against an occluded airway. Although relationships between nocturnal gas exchange and respiratory muscle strength are not always clear, nocturnal hypoventilation is likely to occur when MIP is $<40\text{cmH}_2\text{O}$ ⁶⁰, with the appearance of diurnal respiratory failure when MIP falls below $30\text{cmH}_2\text{O}$ ^{15,60}.

Although these tests are easy to perform, recorded values may be inaccurate in neuromuscular patients with weakness of the oral musculature. Sniff nasal pressure (SNIP) is a short voluntary inspiratory manoeuvre measured in an occluded nostril during a maximal sniff through the contralateral nostril, and has been shown to correlate well with invasive and nonvolitional tests of inspiratory muscle strength^{68,69}. Although SNIP and MIP are correlated, the values are not interchangeable since the type of effort and pattern of muscle activation in the two manoeuvres are different. However, SNIP can be an easier test for patients with more advanced disease to perform even when they are unable to carry out other tests such as FVC and MIP⁶⁸. In patients with MND, a SNIP $<40\text{cmH}_2\text{O}$ was associated with nocturnal desaturation⁶⁸. Current recommendations are for non invasive ventilation to be commenced in MND when FVC falls below 50 per cent predicted. However in one study, 66 per cent of patients with a FVC >50 per cent were also found to have a SNIP <40 per cent predicted⁶⁸, suggesting that this latter test is a more sensitive marker for identifying sleep-associated breathing problems and determining the need for intervention.

Apart from assessing the presence of sleep hypoventilation and guiding the appropriate time to commence therapy, there is evidence that some of these measurements may also provide prognostic information. In DMD, a VC of less than 1l has been shown to be the best single predictor of survival over a 3 yr period⁷⁰. In patients with MND, once SNIP fell to less than $40\text{cmH}_2\text{O}$, median time to death was 6 months⁶⁸.

In addition to loss of inspiratory muscle strength, expiratory muscle strength also plays an important role in the acceleration of respiratory failure, especially during periods of upper respiratory tract infections. The inability to cough effectively and clear secretions will add to hypoventilation through atelectasis and increased load on the respiratory muscles. Peak cough flow (PCF) rates are directly associated with the ability to clear secretions effectively, with values lower than

160 l/min considered inadequate^{71,72}. Since respiratory muscle strength is impaired during viral infections⁷³, it is recommended that a PCF $< 270\text{l/min}$ be used to determine when to introduce training in assisted cough techniques⁷⁴. This threshold for PCF was recently shown to predict patients with stable MND who were unable to effectively cough and clear secretions during a chest infection⁷⁵.

The simple measurements outlined previously provide indicators of the presence of sleep disordered breathing and can routinely be carried out in clinics or in the patient's home to monitor changes in respiratory function and aid in determining the need for more extensive monitoring during sleep. Polysomnography is considered the gold standard for identifying and classifying sleep disordered breathing in patients with restrictive chest wall disorders^{15,76}, where obstructive sleep apnoea is suspected, or where complications such as polycythemia or cor pulmonale cannot be explained by the awake PaO_2 ⁷⁷. In patients with neuromuscular or chest wall disorders in whom daytime hypoventilation is already present, PSG is unlikely to be of major benefit as it is well established that nocturnal hypoventilation proceeds daytime respiratory failure^{7,78}. The role of limited nocturnal monitoring involving SpO_2 and other respiratory parameters in those with a few sleep symptoms and normal daytime CO_2 levels has yet to be fully defined. A number of studies have reported using continuous monitoring of nocturnal respiratory parameters to successfully identify and treat sleep disordered breathing and hypoventilation^{8,70,79,80}. Although a positive study is informative, a negative study cannot rule out the possibility of sleep disordered breathing since the presence of REM sleep cannot be confirmed from these limited monitoring systems. Consequently, sleep hypoventilation may be underestimated if the patient has poor sleep efficiency, a low proportion of REM sleep or a high REM arousal index^{9,81}. A lack of REM sleep in itself is diagnostically important³. Overnight oximetry may also be relatively insensitive to changes in oxygenation in patients in whom resting PaO_2 is above 70mmHg ⁷⁶, as is commonly seen in those with neuromuscular disorders. In patients with COPD, continuous nocturnal SpO_2 is often used to identify nocturnal desaturation. However, depending on what metric is reported, whether an individual should be classified as a nocturnal desaturator or not can vary considerably night to night, with more variability found in measures of time spent below 90 per cent compared to mean nocturnal saturation⁸².

Treatment of nocturnal hypoventilation

While hypoventilation during sleep can occur in a range of disparate disorders, the feature in common is the rise in CO₂ that occurs during sleep and the compensatory retention of bicarbonate by the kidney in response to this. These changes blunt central drive, generating further CO₂ retention, so that eventually hypoventilation is present not just during sleep but during wakefulness as well^{37,78,83}. For most individuals, little can be offered to alter the progression of the underlying disorder. However, by identifying and treating sleep hypoventilation appropriately, significant improvements in clinical outcomes, quality of life and survival can be achieved irrespective of the underlying disease process involved^{3, 7, 84-87}. Potential approach to managing nocturnal hypoventilation are listed in Table III.

Oxygen therapy

Oxygen therapy is generally used to correct sleep-linked hypoxaemia. However, oxygen therapy alone is usually ineffective where the sleep hypoxaemia is associated with significant hypoventilation since the underlying respiratory abnormality is not addressed. Consequently, sleep hypoventilation may worsen, especially in patients with pre-existing hypercapnia^{26,27,85,88}.

Although widely prescribed, the benefits of nocturnal oxygen therapy in patients with COPD and isolated nocturnal desaturation have not been unequivocally established. While some groups have recommended its use to prevent the development of pulmonary hypertension and improve survival^{89,90}, other groups have found no evidence that such an approach modifies the evolution of pulmonary haemodynamics nor delays the need for long term oxygen therapy^{91,92}. Likewise, there is no evidence that nocturnal oxygen therapy improves survival in these patients^{91,93}. It has

also been suggested that nocturnal desaturation may be an independent risk factor for the development of chronic respiratory failure in COPD in those with daytime normoxia⁹⁴. However, other investigators have not found this to be the case⁹². Another important consequence of sleep-associated oxygen desaturation is impairment of health status, impacting on sleep quality and daytime functioning. Although sleep quality has been shown to be poor in COPD⁹⁵, no difference in sleep quality or health related quality of life has been found between desaturators and non-desaturators⁴³. Therefore the clinical importance of nocturnal desaturation in COPD, often isolated to REM sleep, and the benefits of correcting this abnormality remains unclear at the present time.

CPAP therapy

Where daytime hypercapnia is associated with obesity or a high AHI, a trial of CPAP is warranted. Improved sleep gas exchange and daytime blood gases can occur in many individuals once upper airway obstruction is relieved, and has been reported in patients with early stage neuromuscular disease¹³, scoliosis²⁷, overlap^{96,97} and obesity hypoventilation syndrome^{33,86}.

In some patients with neuromuscular disorders and chest wall deformity, upper airway obstruction may be a major feature of the sleep breathing abnormality and precede the appearance of nocturnal hypoventilation^{11,13,66}. In these cases, CPAP may be effective¹³, although a subsequent transfer to non-invasive (NIV) is usually required, especially in patients with progressive disorders, and often within a short time period¹³. Consequently, if CPAP is used in patients with neuromuscular disorders, frequent reassessment and monitoring has been advised⁶⁶, with some authors suggesting NIV rather and CPAP be used when nocturnal hypoventilation is present, regardless of the degree of OSAS¹³.

Table III. Treatment options for nocturnal hypoventilation

Option	Comments
Oxygen therapy	Appropriate where there is ventilation-perfusion mismatching producing hypoxaemia, <i>eg.</i> , in individuals with parenchymal lung disease in addition to hypoventilation. Can worsen the severity of hypoventilation.
CPAP therapy	Where upper airway dysfunction is the underlying cause of sleep hypercapnia, <i>eg.</i> , selected individuals with OHS, overlap syndrome and scoliosis
Bi-level ventilatory support	Most commonly used modality for managing sleep hypoventilation, producing significant objective clinical improvements and subjective symptoms.
Volume preset ventilation	Most commonly used for individuals where bi-level support has failed to control sleep hypoventilation, where tracheostomy ventilation is needed, or where ventilatory support is used continuously

The benefits of CPAP in patients with overlap syndrome have been demonstrated in a number of studies, including improvements in overnight saturation⁹⁸, lung function⁹⁶, diurnal blood gases⁹⁶, and hospitalization rates⁹⁷, although deterioration in lung function with CPAP use has also been reported⁹⁹. Long-term, randomized trials are needed to evaluate the outcomes of CPAP on lung function and quality of life. Where nocturnal hypoventilation persists despite the administration of CPAP with or without oxygen therapy, NIV may be effective (Fig. 3).

The majority of patients with OHS also have OSAS, and many will respond favourably to CPAP therapy either initially^{33,86} or after a short period of noninvasive ventilatory support^{86,100}. However, there is a lack of data regarding long term outcomes in those treated with CPAP and a systematic evaluation of differences in clinical response between CPAP and NIV has not been undertaken.

Non invasive ventilatory support

Over the past two decades, NIV has emerged as the treatment of choice in the management of patients with disorders associated with nocturnal hypoventilation^{101,102}. Most commonly, NIV is delivered using a pressure preset device (*e.g.*, a bi-level machine), although volume preset machines continue to have a role, especially in cases of bi-level ventilation failure or where more extensive periods of ventilatory support are required. Nasal and full face masks are most commonly used¹⁰³, although effective ventilatory support can also be achieved through nasal prong style interfaces and mouthpieces.

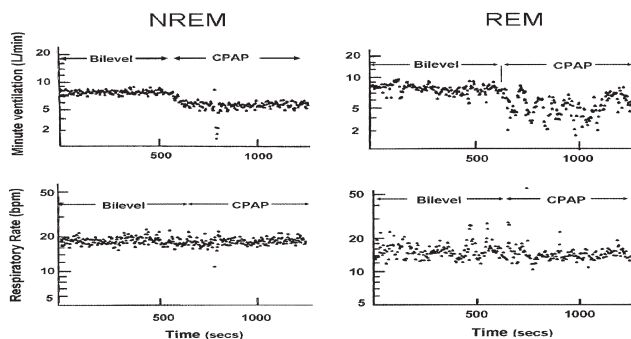


Fig. 3. Recordings of minute ventilation and respiratory rate during periods of NREM and REM sleep in a patient with hypercapnic COPD. With both bi-level and CPAP support, respiratory rate was relatively stable in NREM sleep. In REM sleep there was more respiratory variability but with no significant difference between bi-level and CPAP therapy. Note the improvement in minute ventilation in both NREM and REM sleep during bi-level support compared to CPAP.

The relative ease of initiating this therapy and its high long term acceptability by patients meant that NIV became well established in clinical practice in many countries before randomized trials were undertaken. Consequently, a Cochrane review found that the evidence for benefit of NIV in neuromuscular and chest wall disorders was weak¹⁰⁴, although this was due to a lack of suitable trials available for evaluation rather than any lack of response to therapy. In fact, the clinical experience with NIV is overwhelmingly positive, with a substantial body of literature attesting to its benefits in terms of improved diurnal blood gases^{22,83,86,87,100,101}, quality of life^{84,87}, exercise performance^{105,106}, health care utilization^{6,101} and survival^{22,84,87}.

There are a number of uncontrolled trials and retrospective studies that have compared outcomes between NIV and oxygen therapy in patients with nocturnal hypoventilation. In patients with scoliosis, survival has been shown to be significantly better in those managed with NIV compared to long term oxygen therapy^{22,107,108}, even after adjusting for age, gender and concomitant respiratory disease²². In patients with neuromuscular disorders, significant CO₂ retention can arise if oxygen therapy alone is used⁸⁸. Hospitalization due to respiratory problems is higher in patients managed with oxygen therapy rather than NIV⁷⁴. Patients with nocturnal hypoventilation secondary to chest wall restriction but without overt daytime respiratory failure also benefit more from NIV than nocturnal oxygen therapy⁸⁵. Both NIV and oxygen therapy improved nocturnal oxygenation, but oxygen increased CO₂ during sleep, produced more apnoeas and hypopnoeas and worsened sleep quality⁸⁵. In contrast, NIV more effectively normalised nocturnal breathing and gas exchange as well as improving daytime symptoms. Despite these findings, many patients with disorders associated with nocturnal hypoventilation continue to be prescribed oxygen therapy as first line management^{22, 108}.

In contrast to restrictive chest wall disorders, a number of randomized trials evaluating NIV in patients with COPD have been undertaken. Current evidence suggests that NIV used for at least 3 months has no clinically or statistically significant effect on lung function, gas exchange or sleep efficiency in patients with stable hypercapnic COPD¹⁰⁹. Despite the lack of evidence to support the routine use of NIV even in severe COPD, it is apparent that some patients do respond positively; in general, those with higher daytime CO₂ levels or

more severe degrees of nocturnal hypoventilation¹¹⁰. The pressure settings used in the reported studies may underlie the differences in outcome so far reported. Data from both controlled¹¹⁰ and uncontrolled trials¹¹¹ using higher IPAP pressures (*i.e.*, 18cm H₂O and above) have reported more favourable outcomes than studies using pressures of 14cmH₂O or less¹¹²⁻¹¹⁴. Although evidence for the widespread use of NIV in this population is lacking, between a third and half of all patients currently prescribed NIV for long term home use have a primary diagnosis of COPD^{101,102,115}.

Since its introduction, there has been a great deal of speculation surrounding the mechanisms by which nocturnal ventilation so effectively improves daytime physiological and clinical parameters. Improved respiratory mechanics, alterations in VQ distribution, relief of respiratory muscle fatigue and improved ventilatory response to CO₂ have all been forwarded to explain improved daytime ventilation¹¹⁶. However, current data support the hypothesis that improvements in awake ventilation are due to an increase in ventilatory responsiveness to CO₂^{83,117}, with more significant improvements in spontaneous awake CO₂ being achieved where nocturnal CO₂ is better controlled with NIV^{110,111}. Although lung function and respiratory muscle performance may improve with the introduction of NIV, such changes are not mandatory for a significant clinical response to occur.

The appropriate time to introduce NIV in patients with nocturnal hypoventilation syndromes is another issue that has generated considerable interest. On one hand, a number of published guidelines provide recommendations for initiating NIV based primarily on awake CO₂ levels, lung function, or the presence of symptoms consistent with sleep disordered breathing^{118,119}. On the other hand, initiating NIV only after a patient becomes symptomatic or develops daytime hypercapnia runs the risk of overlooking individuals who already have significant daytime respiratory failure. In a group of patients with mixed neuromuscular disorders presenting with symptoms typical of chronic hypercapnic respiratory failure, mean PaCO₂ varied considerably depending on the underlying diagnosis; from 44mmHg in patients with DMD to 62mmHg in those with MND¹²⁰. Consequently, the issue of initiating NIV at an earlier stage in the evolution of chronic respiratory failure has been investigated. Ward *et al*⁷ tested the hypothesis that applying NIV when nocturnal hypoventilation is first identified, in the absence of daytime hypercapnia

or symptoms, was the most appropriate time to intervene. Twenty six patients with neuromuscular and chest wall disease were randomly assigned to either nocturnal NIV or no support and followed over a 24 month period. Significant improvements in nocturnal hypoventilation as well as SF-36 general health scores were only seen in the NIV managed group. In addition, 70 per cent of patients in the control group developed diurnal hypercapnia or respiratory symptoms within 12 months. These results shift the indication for NIV toward earlier intervention in order to avoid uncontrolled respiratory decompensation⁷. However, using NIV prior to the development of nocturnal hypoventilation or symptoms does not appear to confer any benefit, and in a randomized trial in Duchenne muscular dystrophy appeared to increase mortality rate compared to controls managed with standard care¹²¹. Hence, current evidence would support identifying patients at risk of developing nocturnal hypoventilation, and monitoring nocturnal gas exchange. If an abnormality is detected, discussion and decisions regarding the need and appropriateness of NIV for the individual's particular circumstances should be undertaken.

Conclusions

Disorders that affect diaphragmatic function, cause chest wall restriction or impair respiratory drive can have profound effects on ventilation and gas exchange during sleep, well before alterations in daytime gas exchange emerge. Identifying individuals at risk of developing nocturnal hypoventilation permits cost-effective monitoring and timely intervention, with the aim of avoiding the development of unstable respiratory failure and the need for acute hospitalisation. By understanding the mechanisms responsible for the deterioration in gas exchange during sleep appropriate therapy can be initiated which targets the physiologic abnormalities present. Despite only a handful of randomized trials available, NIV is now the primary technique used for correcting nocturnal hypoventilation. The simplicity of the technique makes it easier to initiate and more acceptable to patients than older treatment modalities such as negative pressure or tracheostomy ventilation. The rapid growth of home NIV therapy demonstrates the need for clear indications and goals for initiating therapy, and ongoing clinical and economic evaluation to ensure the right target population is accessing therapy and expected benefits are being realised. However, non-invasive ventilatory support offers a real opportunity for individuals with

nocturnal hypoventilation to finally rest, and breathe easily.

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Reprint requests: Dr Amanda J. Piper, Sleep Investigation Unit, Level 11, E Block, Royal Prince Alfred Hospital, Missenden Rd
Camperdown NSW 2050, Australia
e-mail: ajp@mail.med.usyd.edu.au