Hypoventilation Syndromes

Amanda J. Piper[*1] *and Brendon J. Yee*[1]

ABSTRACT

In patients with impaired inspiratory muscle function or altered respiratory system mechanics, an imbalance between load and capacity can arise. The ventilatory control system normally compensates for this by increasing drive to maintain adequate alveolar ventilation levels, thereby keeping arterial CO_2 within its normal range. To reduce work of breathing, a pattern of reduced tidal volume and increased respiratory rate occurs. This pattern itself may eventually reduce effective ventilation by increasing dead space ventilation. However, the impact of sleep on breathing and its role in the development of diurnal respiratory failure is often overlooked in this process. Sleep not only reduces respiratory drive, but also diminishes chemoresponsiveness to hypoxia and hypercapnia creating an environment where significant alterations in oxygenation and CO_2 can occur. Acute increases in CO_2 load especially during rapid eye movement sleep can initiate the process of bicarbonate retention which further depresses ventilatory responsiveness to CO_2. Treatment of hypoventilation needs to be directed toward factors underlying its development. Nocturnal noninvasive positive pressure therapy is the most widely used and reliable strategy currently available to manage hypoventilation syndromes. Although this may not consistently alter respiratory muscle strength or the mechanical properties of the respiratory system, it does appear to reset chemosensitivity by reducing bicarbonate, resulting in a more appropriate ventilatory response to CO_2 during wakefulness. Not only is diurnal hypoventilation reduced with noninvasive ventilation, but quality of life, functional capacity and survival are also improved. However, close attention to how therapy is set up and used are key factors in achieving clinical benefits. © 2014 American Physiological Society. *Compr Physiol* 4:1639-1676, 2014.

Introduction

Hypoventilation occurs when the level of alveolar ventilation becomes insufficient to match the body's metabolic carbon dioxide (CO_2) production resulting in a rise in the partial pressure of CO_2 ($PaCO_2$) in the arterial blood. At rest, the normal range of $PaCO_2$ is generally accepted as 35 to 45 mmHg. Maintaining an adequate level of ventilation relies on a balance between the load placed on the respiratory system and the capacity of the system to respond appropriately to that load. Respiratory drive is then able to further modify this balance. Disorders that significantly impair respiratory muscle function, alter chest wall mechanics, or depress ventilatory drive have the capacity to reduce ventilation on a chronic basis, resulting in a rise in arterial CO_2 levels and the development of hypercapnic respiratory failure.

In the mid 1980s, an appreciation of the extent to which sleep could pose a significant challenge to the respiratory system and its ability to maintain adequate awake ventilation began to develop. Continuous monitoring of gas exchange and ventilation highlighted the marked abnormalities in breathing that could occur during sleep, even in patients with relatively mild degrees of daytime respiratory compromise (65, 262). This led to a realization of the key role nocturnal hypoventilation plays in the development and progression of daytime respiratory insufficiency in a range of respiratory disorders. It also became apparent there was an opportunity to identify individuals with a high risk of developing daytime respiratory failure earlier, based on the nature and severity of abnormal breathing present during sleep (412). In parallel, the development of simple, relatively low cost positive pressure ventilators and improved interface designs enabled home ventilation to be realistically extended to patients with milder degrees of hypoventilation and at an earlier time point than had been possible with previous forms of home ventilation equipment. The ability to effectively treat nocturnal hypoventilation in a simple and accessible fashion has had a major impact not only on the lives of at-risk individuals, but has altered our understanding of the natural evolution of many of these disorders (15, 114, 181, 301).

Broadly speaking, there are four major clinical groups likely to present with nocturnal hypoventilation: neuromuscular diseases affecting the diaphragm, restrictive chest wall disorders affecting the geometry of the thorax, parenchymal lung diseases affecting pulmonary mechanics, and central hypoventilation syndromes (Table 1). This latter group makes up a relatively small proportion of patients presenting with hypoventilation, and will not be covered further in this

[*]Correspondence to amanda.piper@sydney.edu.au

[1]Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Camperdown; Woolcock Institute of Medical Research, University of Sydney, NSW, Australia

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Table 1 Major Disorders Commonly Associated with Nocturnal Hypoventilation

Restrictive thoracic disorders
• Kyphoscoliosis
• Thoracoplasty
• Post tuberculous sequelae
• Obesity hypoventilation syndrome
Neuromuscular disorders
• Duchenne muscular dystrophy
• Spinal muscular atrophy
• Myotonic dystrophy
• Congenital myopathies
• High spinal cord injury
• Acid maltase deficiency
• Previous poliomyelitis
• Idiopathic diaphragmatic paralysis
• Rapidly progressive disorders such as amyotrophic lateral sclerosis
Obstructive lung disease
• Chronic obstructive pulmonary disease
• Cystic fibrosis
• Overlap syndrome
Control of breathing abnormalities
• Congenital central hypoventilation syndrome
• Brainstem injury (infection, trauma, or tumor)

article. Understanding the mechanisms promoting nocturnal hypoventilation is important not only for the early identification of those at risk but also in guiding treatment options most likely to stabilize or delay the development of diurnal hypercapnic respiratory failure.

Normal Breathing and Ventilation During Sleep

To appreciate the alterations in breathing and ventilation that occur during sleep in patients with nocturnal hypoventilation syndromes, it is important to first understand the expected physiological changes sleep has on normal breathing.

With the onset of sleep, a reduction in centrally mediated output to the chest wall and upper airway muscles occurs. Upper airway resistance increases (194,236) while the reflexive compensatory mechanisms for increased mechanical loads are reduced (171). As a consequence, a small fall in minute ventilation of 10% to 15% normally occurs from wakefulness to nonrapid eye movement (NREM) sleep (28,106,383), producing rises in $PaCO_2$ up to 7 mmHg and falls in PaO_2 of a similar magnitude (48, 106, 363). At the same time, ventilatory responsiveness to hypoxia and hypercapnia are reduced compared to wakefulness (46,47,107,108).

The most notable changes in breathing and ventilation occur during REM sleep. In this sleep stage, chemoreceptor responsiveness to hypoxia and hypercapnia is blunted even further (46, 47, 107, 108). Additionally, electromyographic (EMG) activity of the intercostal muscles is reduced during REM sleep compared with NREM sleep and wakefulness, whereas diaphragmatic EMG is preserved or even increases (383). The maintenance of ventilation during REM sleep remains critically dependent on the diaphragm. During phasic REM periods (i.e., where active eye movements are present), breathing becomes irregular, with a rapid respiratory rate and reduced tidal volume (28, 106, 148), with more stable breathing seen during tonic REM. Although a further fall in minute ventilation from NREM to REM sleep in normal subjects has been reported (106), other investigators have not found this to be the case (28, 148). This disparity in findings likely arises from differences in measurement methodologies and the proportion of tonic to phasic REM captured during different sampling periods.

Changes in drive, upper airway resistance, respiratory muscle activation, and chemoresponsiveness during sleep pose only minor stresses for individuals in whom the respiratory system is normal, although the development of upper airway obstruction is not an uncommon finding. However, for those with pre-existing diaphragmatic inefficiency or weakness, reduced ventilatory drive or abnormal gas exchange, changes in breathing and ventilation during sleep can be quite profound. In a study of subjects with a range of respiratory disorders associated with nocturnal desaturation, Becker et al. (28) found a fall in minute ventilation of 19% in NREM and 39% in REM sleep compared to wakefulness, mainly associated with a fall in tidal volume (Fig. 1). These changes in ventilation were consistent across disease processes. In addition to nocturnal hypoventilation, obstructive and central events occurring in both NREM and REM sleep can occur (37, 169, 381). The nature of hypoventilation itself may also vary considerably between and within patient groups, with some individuals exhibiting no discernible breathing effort during periods of hypoventilation, while in others continued breathing will be seen but with reduced effort (hypopneas). Prolonged periods of flow limitation (obstructive hypopneas) can also produce sleep hypoventilation in disorders such chronic obstructive pulmonary disease (COPD) (287) and obesity hypoventilation syndrome (OHS) (37). Distinguishing the type of sleep-disordered breathing present is clinically helpful in determining the most appropriate type of therapy to reverse these nocturnal events.

Sleep and Breathing Abnormalities in Hypoventilation

Neuromuscular disorders

Weakness of the respiratory muscles occurs at some point in the clinical evolution of many neuromuscular disorders, producing chronic hypoventilation, unstable respiratory failure and eventually death. Although the development of hypoventilation and respiratory failure is inevitable in disorders such as amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy (DMD), in others the distribution of muscle involvement is such that only small numbers with the disorder will be affected (e.g., facioscapulohumeral dystrophy). Occasionally, the presentation of a patient in daytime hypercapnic respiratory failure will be the first indication of the presence of a neuromuscular disorder (261,336). Other conditions such as

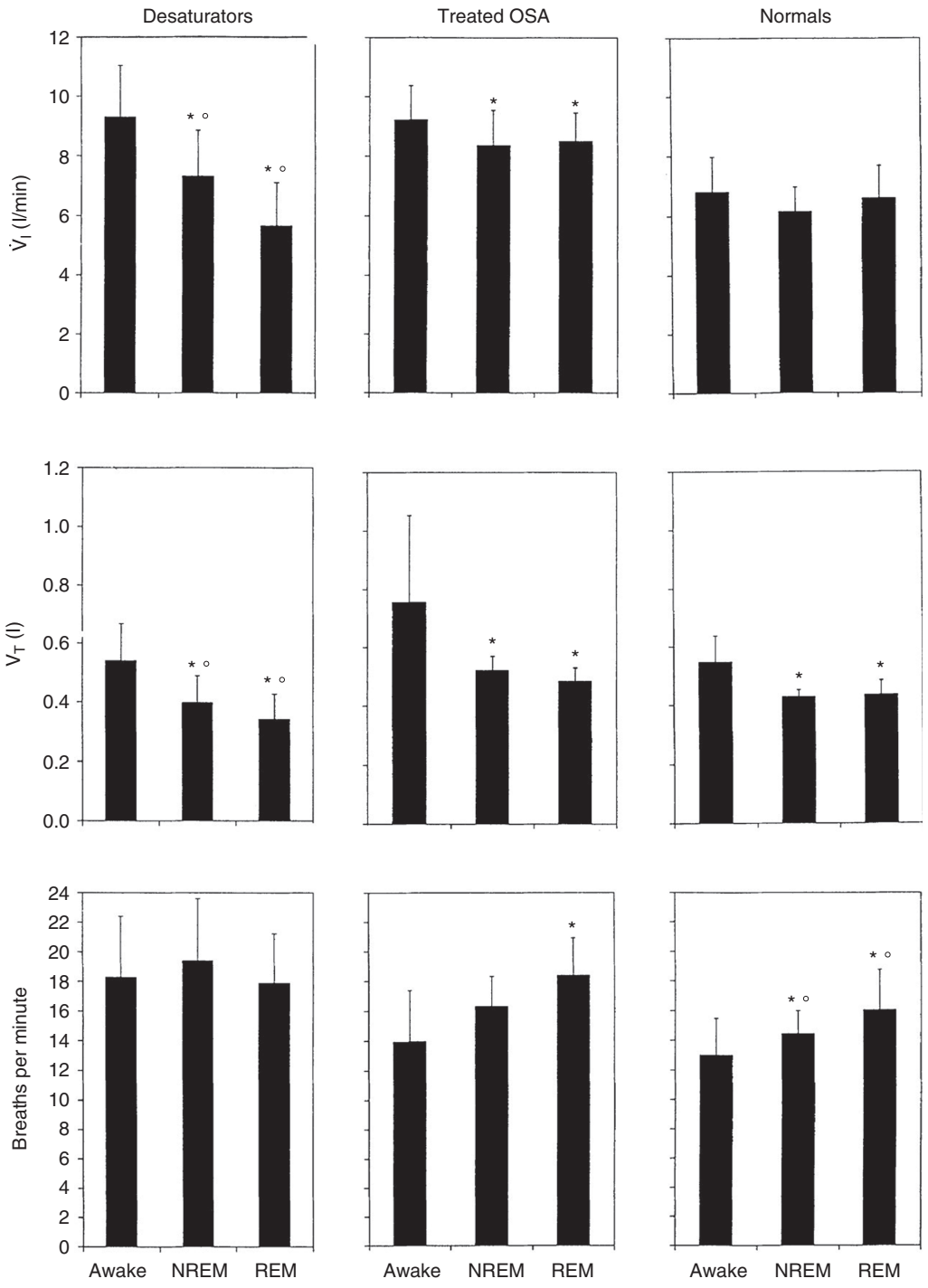

Figure 1 Changes in minute ventilation (V_I), tidal volume (V_T) and respiratory rate from wakefulness to sleep in patients with nocturnal hypoventilation (Desaturators), patients with eucapnic OSA during effective CPAP, and healthy normal controls. In the nocturnal hypoventilation group, the larger relative falls in V_T were not offset by changes in respiratory rate so that an overall reduction in V_I occurred. [Adapted, with permission, from Becker et al. 1999; *Breathing during sleep in patients with nocturnal desaturation*. Am J Respir Crit Care Med, 159:112-118. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Official Journal of the American Thoracic Society (28.)]

obesity, scoliosis, aspiration, or concurrent lung damage are additional factors that may influence if and when hypoventilation emerges in the course of a disorder, and the extent to which the patient is able to compensate for respiratory muscle impairment.

In neuromuscular disorders involving the respiratory muscles, weakness of the inspiratory muscles (principally the diaphragm) reduces lung volumes, promotes sleep-disordered breathing and contributes to the development of daytime respiratory failure. Expiratory muscle weakness usually accompanies inspiratory weakness and while not an independent predictor of hypercapnia (317) will affect the ability to cough and clear secretions effectively if severe. Retained secretions expose the patient to atelectasis, recurrent chest infections, and respiratory failure. In a number of disorders, the bulbar muscles are also involved, affecting swallow, increasing the risk of aspiration and possibly contributing to the development of upper airway obstruction. Consequently, in assessing and treating patients with hypoventilation related to respiratory muscle weakness attention needs to be paid not only to the inspiratory muscles, but also the muscles of expiration and the upper airway, recognizing their potential contribution to reduced ventilation and CO_2 retention.

Although the term "neuromuscular disease" encompasses a broad spectrum of pathologies, those that are associated with nocturnal hypoventilation all share the same physiologic abnormalities that will eventually lead to hypercapnic respiratory failure. Weakness of the diaphragm is central to this process, and may appear as an early (336) or late manifestation of the neuromuscular process (10). Since REM sleep relies on diaphragmatic activity to sustain adequate ventilation, weakness or paralysis of the diaphragm will produce abnormalities in breathing that are initially confined to this sleep state, but over time will eventually become apparent during NREM sleep and wakefulness.

When a neuromuscular process involves the respiratory muscles, reductions in inspiratory and expiratory muscle strength and endurance will occur. As a consequence of losing the ability to inhale fully a restrictive pattern is seen on lung volume measurements, with reductions in total lung capacity (TLC) and vital capacity (VC), while functional residual capacity (FRC) is normal or slightly increased (55, 95, 122). Usually, forced expiratory volume in 1 s (FEV_1) is reduced proportionately to reductions in forced vital capacity (FVC) so that the ratio remains normal or high (264). The relationship between VC and respiratory muscle strength is curvilinear (55, 95), so that VC may be relatively well maintained until a marked reduction in inspiratory muscle strength occurs (55). Pulmonary mechanics are also altered, with reduced chest wall and lung compliance (95, 215) and increased elastic loading (31, 264). These changes are presumed to be due to reduced distensibility of the lungs or from stiffening of the rib cage arising from reduced chest wall movement (95). In a significant number of patients, chest wall deformity will also be present, which can contribute further to pulmonary function impairments.

As muscle weakness progresses, the reduced inspiratory force coupled with the increased elastic load produces a rapid shallow breathing pattern (31, 264). This is a strategy which attempts to reduce perceived effort (211), and has been reported in a number of neuromuscular disorders (25, 142, 264, 393). Such a pattern reduces the elastic work per breath and the oxygen cost of breathing, and may be a mechanism to avoid fatigue and possible damage to the respiratory muscles caused by the imbalance between load on the respiratory system and muscle capacity (264, 295, 393). A direct relationship between inspiratory time and tidal volume has been demonstrated in patients with neuromuscular disorders such that the shorter the inspiratory time the lower the tidal volume generated (264). By minimizing inspiratory time and decreasing transdiaphragmatic pressure through a reduction in the size of each breath, the risk of performing a level of work that could lead to fatigue is reduced (138). There is also some evidence to suggest that the fatigue threshold may be lower in patients with neuromuscular disorders compared to healthy controls (249, 279). However, such a pattern also increases dead space ventilation, contributing further to the development of chronic hypercapnia (264). Although altered ventilation perfusion can be present, in the absence of significant parenchymal lung damage or scoliosis patients with neuromuscular disorders tend to have well preserved oxygenation compared to other groups at risk of nocturnal hypoventilation (213).

Central respiratory drive remains intact and in many cases is augmented in patients with neuromuscular disorders (25, 30, 138, 142). To compensate for progressive respiratory muscle weakness, an increase in respiratory neural output to the muscles occurs to maintain alveolar ventilation and eucapnia (149). Minute ventilation and mouth pressure generated in the first 0.1 s following an occlusion ($P_{0.1}$) are widely used methods for assessing central respiratory drive in normal subjects. However, minute ventilation alone is a poor measure of respiratory center output in patients with neuromuscular disease since respiratory muscle weakness especially when severe can limit the extent to which an increase in drive can be translated into an appropriate change in ventilation. Holle et al. (166) induced respiratory muscle weakness in a group of healthy volunteers by partial curarization to compare the impact of muscle weakness on $P_{0.1}$ and minute ventilation. While there was a linear increase in $P_{0.1}$ in response to increased CO_2, simultaneously measured minute ventilation was reduced as the severity of respiratory muscle weakness worsened. The authors suggested that $P_{0.1}$ was a reasonable index of central respiratory drive and response to CO_2 even in patients with severe respiratory muscle impairment (166). However, severe muscle weakness, abnormal chest wall configuration or a compliant upper airway can influence $P_{0.1}$ measures, and these limitations need to be taken into consideration when evaluating respiratory drive in neuromuscular patients (142, 419). Monitoring EMG activity of the diaphragm or other respiratory muscles provides a better measurement of neural activation of the inspiratory muscles, and while there

are still limitations with this approach (142,419), when used in conjunction with other measures such as $P_{0.1}$ or flow derivatives, a more complete assessment of respiratory center drive can be obtained (1).

Many studies have reported a blunting of the responsiveness of respiratory centers to hypoxia and hypercapnia in patients with neuromuscular disorders (32, 98, 142, 281). However, assessing ventilatory responsiveness to chemostimulation is also difficult in these patients. In the presence of weak respiratory muscles, ventilation may not be able to be increased appropriately despite an increase in neural drive (33, 142, 149). In an early study of patients with DMD, the chemoreceptors were shown to be appropriately responsive to hypoxia and hypercapnia, but that the pattern of responsiveness was one of increased respiratory rate rather than the increase in tidal volume seen in normal controls (33). In patients with limb girdle muscular dystrophy, the ventilatory response to CO_2 was found to be low when assessed using a change in tidal volume or minute ventilation in response to a change in CO_2. However, when responsiveness was evaluated using neural drive measured by changes in diaphragmatic and parasternal intercostal muscle EMG activity in response to changes in CO_2, there were no differences between patients and an age-matched control group (142). This suggests that neural output from the respiratory centers in response to chemostimulation remained intact, but that respiratory muscle weakness prevented this being converted into an appropriate ventilatory response.

Sleep itself is associated with a number of changes in breathing even in normal individuals, including reduced responsiveness of the respiratory muscles to respiratory center outputs and diminished ventilatory responsiveness to mechanical and chemical stimuli (254). Consequently, the normal reduction in respiratory center output and alteration in breathing pattern that occurs particularly in REM sleep will attenuate any compensatory increase in respiratory drive that may be maintaining adequate ventilation during wakefulness. The resultant sleep hypoventilation then produces secondary alterations in the chemical drive to breathe, blunting ventilatory responsiveness to hypoxia and hypercapnia (8,98). However, once effective nocturnal ventilatory support is commenced, improvements in chemoresponsiveness are seen, even in the absence of alterations in respiratory muscle strength or pulmonary function (8, 98, 281). In a study of 20 hypercapnic individuals with chest wall restriction, 12 of whom had neuromuscular disease, nocturnal ventilation significantly reduced CO_2 after 5 days of therapy, with further improvements at 3 months. In parallel, the mean hypercapnic ventilatory response increased by 30% at day 5, and was 50% higher than baseline by 3 months (281). Measures of inspiratory muscle strength including twitch transdiaphragmatic pressure, lung function, and respiratory system compliance showed no change across the same period. Furthermore, the improvements in ventilatory response are significantly correlated with changes in daytime CO_2 (8, 281). It is believed that the increase in hypercapnic ventilatory response occurs as a result of reduced bicarbonate retention, permitting the chemoreceptors to be reset to be more responsive to CO_2 (144, 281). This would support the notion that depressed ventilatory responsiveness is largely a secondary phenomenon arising from hypoventilation which first appears during sleep.

Sleep breathing in neuromuscular disorders

The presence of sleep-disordered breathing is common in patients with neuromuscular disorders (197, 208, 367, 381, 412) even when daytime blood gases are normal. The most frequent form of sleep-disordered breathing is hypoventilation (10, 310, 327), and may precede the appearance of daytime respiratory failure by months or even years (310, 412).

Nocturnal hypoventilation is initially confined to REM sleep, and identified by markedly reduced or absent chest wall movement accompanied by falls in oxygenation and rises in carbon dioxide. These changes in gas exchange provoke a brief arousal from sleep, limiting the degree of desaturation and rise in CO_2 by restoring ventilation. Frequent arousals also impact on sleep quality and structure, and in some cases REM sleep is markedly reduced or absent (10,314,417). Sleep loss has been associated with diminish ventilatory responsiveness to hypoxia and hypercapnia (88, 416). Over time, bicarbonate levels in the cerebrospinal fluid will rise in response to increasing CO_2. This further depresses chemoresponsiveness, which in turn would promote more hypoventilation, with the individual not increasing ventilation appropriately to increases in CO_2. Such a cycle will lead to the eventual emergence of hypoventilation during wakefulness.

Patients with bilateral diaphragm paralysis develop compensatory breathing strategies to try and maintain ventilation during sleep. A common strategy employed is recruitment of accessory respiratory muscles such as the sternomastoid and scalene muscles during wakefulness and NREM sleep in an attempt to compensate for poor diaphragmatic function (10, 65, 372, 417). Abdominal muscle contraction during expiration can also contribute to the efforts of the inspiratory muscles by increasing abdominal pressure, which moves the diaphragm in a cranial direction. Release of this contraction at the start of inspiration then assists in the passive descent of the diaphragm, facilitating inspiratory flow (65, 417). Activity of these extradiaphragmatic muscles is lost in many individuals when they enter REM sleep and suppression of the postural muscles occurs. As a consequence, reduction or loss of inspiratory flow and chest wall movement is seen, most obvious during periods of phasic eye movement.

Interestingly, in some disorders involving bilateral diaphragm paralysis continued activity of the accessory respiratory muscles, including the sternocleidomastoids, parasternal intercostals, and the abdominal muscles may occur, maintaining ventilation during both tonic and phasic REM sleep (10, 35). In ALS patients with diaphragmatic dysfunction, the persistence of sternomastoid activity in REM sleep was associated not only with the ability to maintain longer periods of REM sleep, but also improved survival time (10). The

possibility that this represents plasticity of the respiratory control system, operating to preserve both REM sleep and minimize hypoventilation during this period has been raised (10, 35). If patients are unable to adopt this compensatory maneuver, or if it is lost with disease progression, then REM sleep reduction or complete REM suppression may occur (10).

It was thought that patients with unilateral diaphragm paralysis or weakness would be able to sustain normal ventilation during sleep unless other comorbidities were present (212). However in a study of 11 patients with unilateral paralysis, Steier and colleagues (372) identified a high incidence of central hypopneas and apneas in REM sleep, with 26.0 ± 17.8 events/h compared to 0.7 ± 0.9 events/h in healthy sex-, age-, and body mass index (BMI) matched controls. These events were deemed pathological, as the unilateral paralysis group reported significantly reduced quality of life (measured by two disease specific questionnaires: the St George Respiratory Questionnaire and the Chronic Respiratory Disease Questionnaire) compared to the controls. Dyspnea and daytime sleepiness scores were also higher. Neural drive to the diaphragm in NREM sleep as measured by transesophageal EMG activity was double that seen in the control group, with further increases during REM sleep while in the control group it remained unchanged (372). Activation of the accessory respiratory muscles in the unilateral diaphragm paralysis group was also observed. An interesting finding of this study was the activation of abdominal activity during inspiration in sleep which the investigators hypothesized might stabilize the abdominal wall, thereby preventing the weaker hemidiaphragm being pulled upward by negative intrathoracic pressure (372).

Upper airway obstruction during sleep has been reported in a number of neuromuscular disorders although its presence and severity is not as common as might be expected given the incidence of upper airway muscle dysfunction in disorders such as ALS and postpolio syndrome (97, 133, 199). Whether primarily obstructive apnea or hypoventilation is seen during sleep will be influenced by the clinical stage of the disease process when investigation is performed, as well as the pattern of respiratory muscle weakness. In patients with DMD, obstructive events are more commonly reported in younger patients (197, 381), with more frequent and severe central events (197) and hypoventilation (381) present in older age groups. In a retrospective analysis of sleep data in 114 patients with ALS, sleep related breathing abnormalities were common in the first year following disease onset (346). 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 years had significantly fewer events than patients diagnosed for less than 1 year. It was suggested that this change in frequency of events may reflect increasing inspiratory muscle weakness (346). It is reasonable to presuppose that with increasing diaphragmatic involvement, the ability of the subject to generate an inspiratory negative pressure below the critical pressure of the upper airway would be reduced, resulting in fewer events being recorded (2, 133).

Bulbar dysfunction does not appear to predispose individuals to an increased likelihood of obstructive events during sleep (133, 141, 199). However, the classical risk factors associated with obstructive sleep apnea (OSA) such as obesity and habitual snoring do (169, 208). Craniofacial abnormalities such as macroglossia or retrognathia present in some neuromuscular disorders (23, 52) may contribute to the development of upper airway obstruction, while disorders involving pharyngeal or laryngeal neuropathy could also affect the stability of the upper airway (100).

In most neuromuscular disorders, central events seen during sleep are considered to be related to respiratory muscle weakness. However, in some disorders abnormalities in respiratory control may be present. It has been suggested that in ALS, some patients may have impaired generation or transmission of central command from upper motor neurone lesions of the phrenic nerve nuclei (362), affecting diaphragm function. In postpolio syndrome, patients with bulbar involvement have been shown to have more frequent sleep apnea, which are more likely to be central events that occur in NREM sleep, than those without bulbar signs (97). It is possible this reflects compromised brainstem respiratory centers in bulbar or bulbospinal postpolio syndrome (97). Myotonic dystrophy is another disorder in which respiratory muscle weakness does not fully explain the abnormalities in breathing seen during either wakefulness or sleep. These patients exhibit abnormal respiratory rhythm when awake and in light sleep (403, 404), and have more sleep-disordered breathing and greater degrees of nocturnal desaturation than other neuromuscular groups with similar levels of respiratory muscle strength (143). Excessive sleepiness is common in this disorder, and can be unrelated to sleep apnea or sleep fragmentation (401). A specific brainstem abnormality may be present in myotonic dystrophy affecting respiratory control (401, 403). Neuropathology studies have demonstrated severe neuronal loss and gliosis in the midbrain and pontine raphe, and the pontine and medullary reticular formation (289, 290).

Restrictive chest wall disorders

Chest wall deformity

Deformity of the chest wall may be idiopathic in nature, occur as a consequence of a neuromuscular disorder, arise from diseases affecting the vertebral bodies or connective tissue disease, or may be secondary to surgical or traumatic injury.

The most commonly encountered chest wall abnormality is kyphoscoliosis, with curvature of the spine laterally (scoliosis) and anteroposteriorly (kyphosis). In addition to spinal curvature, the ribs are also displaced, placing the respiratory and chest wall muscles at a mechanical disadvantage. In patients with idiopathic scoliosis, the extent to which breathing will be affected is related to the degree of spinal curvature present, as measured by the Cobb angle, with angles more than 100° needed before hypoventilation is seen (40).

Lung volumes in scoliosis show a profoundly restrictive pattern, with reduced TLC, VC, and FRC, and an inverse

relationship between these lung volumes and the angle of curvature in those with idiopathic scoliosis (188). In congenital scoliosis, more severe restriction of lung function for a given angulation of the spine is present compared to those with idiopathic scoliosis (292). Alterations in pulmonary mechanics are primarily responsible for these changes, although retarded lung growth or long-standing atelectasis could further add to lung volume reduction (205). In scoliosis, chest wall resistance is increased, while compliance of the chest wall and to a lesser extent the lungs is reduced (188,402). The stiffer chest wall reduces FRC by reducing the resting position of the chest wall which would then reduce lung compliance. Airway resistance may also be increased (402) related to chronic airway inflammation from secretion retention (54), or by distortion of the intrathoracic trachea and main stem bronchi (5).

During wakefulness, severe distortion of the chest wall promotes uncoordinated chest wall movement, altering ventilation perfusion distribution (357) and increasing the work of breathing. Those with severe deformity adopt a pattern of breathing characterized by reduced tidal volume and a more rapid respiratory rate. However, this pattern also increases dead space ventilation, and reduces alveolar ventilation. Altered ventilation-perfusion relationships occur especially in the region of maximum convexity, leading to an increased arterial-alveolar oxygen gradient and hypoxemia (357). Concomitant respiratory diseases, especially COPD, are common in these patients (152, 379), and would have an additional impact on gas exchange. Inspiratory muscle strength is significantly reduced, especially in those patients with hypercapnia (228), and is likely a consequence of the mechanical inefficiency of the muscles related to chest wall geometry, and in the later stages from hypoxia and hypercapnia from respiratory failure (185, 186) rather than from an intrinsic abnormality of the muscles themselves. Intercostal and accessory inspiratory muscles recruitment occurs to maintain ventilation (228), and activation of the abdominal muscles during expiration is frequently seen (122). This latter maneuver reduces end-expiratory lung volume and promotes chest wall recoil during the next inspiratory effort, enabling the increased work of breathing to be shared between the inspiratory and expiratory muscles (122) (Fig. 2). Nevertheless, the load on the respiratory muscles is high and sustained. The oxygen cost of breathing, which is positively correlated with the work of breathing (250), is significantly higher than in normal subjects (41), putting these individuals at risk of developing respiratory insufficiency when even minor stressors are placed on the respiratory system. Exercise tolerance is reduced, even in mild scoliosis (196), and in those with significant chest wall deformity, severe dyspnea (50), and marked oxygen desaturation (255, 407) occurs with low level exercise, significantly impacting on functional activity and quality of life (70).

The term "thoracoplasty" covers a range of surgical procedures from removal of up to four ribs to complete involvement in the whole hemithorax (284), and was the major approach to the management of pulmonary tuberculosis before effective antituberculous chemotherapy was available. These individuals demonstrate a restrictive ventilatory defect, with reduced VC (56) and total respiratory system compliance (360). Collapse of functioning lung tissue at the time of the operation reduces lung volumes while lung compliance is reduced through residual pulmonary fibrosis and pleural thickening (284, 305). Chest wall compliance is reduced secondary to scoliosis, and inspiratory muscle function will be impaired both by the resection of muscle tissue during the procedure and by the mechanical disadvantage imposed by the chest wall deformity. Chronic airflow obstruction is also common in this group (56, 284, 305), and may arise from inflammation of the airways due to previous extensive tuberculous endobronchitis (284, 305) or smoking-related lung damage. The overlay of airflow obstruction on the restrictive ventilatory defect caused by chest wall deformity increases the work of breathing to a greater extent than that seen with chest wall deformity alone, thereby increasing the risk of developing respiratory failure and cor pulmonale (305).

Several studies have shown that the ventilatory responsiveness to CO_2 is normal in subjects with a normal awake CO_2 (41, 347). In contrast, hypercapnic patients invariably demonstrate abnormal responses, with lower responsiveness to CO_2 seen in those with higher levels of daytime hypercapnia (41), most likely related to the presence of sleep hypoventilation rather than indicating a primary defect in central respiratory drive. Mechanical abnormalities related to chest wall distortion make interpret of ventilatory and mouth occlusion pressure responses to chemical stimuli in this patient group difficult, as changes in these measurements could arise from the mechanical impairment alone. As occurs in patients with neuromuscular disorders, the development of sleep hypoventilation and gradual bicarbonate retention could also be expected to blunt central responsiveness to CO_2. Support for this occurring comes from studies showing improvement in ventilatory responsiveness to hypercapnia once when effective nocturnal ventilation is commenced even when respiratory muscle strength, lung function and respiratory system compliance remain unchanged (8,281). Nevertheless, responsiveness in these previously hypercapnic individuals remains diminished compared to normal subjects (281).

Breathing during sleep in chest wall deformity

Studies looking at breathing during sleep in patients with kyphoscoliosis have most commonly demonstrated hypopneic events in REM sleep (348), which are probably due to reduced chest wall movement rather than upper airway obstruction. Since patients may compensate for the high work of breathing and mechanical inefficiency of the diaphragm by recruiting accessory inspiratory and abdominal expiratory muscles during spontaneous daytime breathing, the postural muscle inhibition associated with REM produces a significant reduction in airflow and chest wall movement, with consequent oxygen desaturation and CO_2 rise. Upper airway obstruction may occur in those who are overweight (121,348),

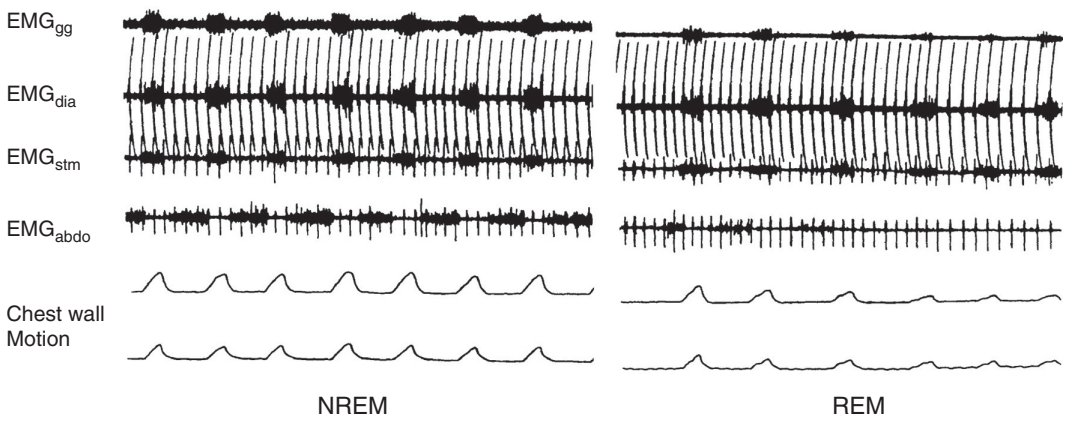

Figure 2 Recording of respiratory muscle activity and chest wall movement from a patient with scoliosis during sleep. There is widespread recruitment of accessory respiratory muscles during NREM sleep. Note also the activation of abdominal muscle activity (EMG_{ABDO}) during expiration. With the onset of REM sleep, a generalized reduction in inspiratory muscle activity occurs, with complete loss of abdominal EMG activity. This produces a marked reduction in chest wall movement with reduced airflow. [Adapted, with permission, from Becker et al. 1999; *Breathing during sleep in patients with nocturnal desaturation*. Am J Respir Crit Care Med, 159:112-118. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Official Journal of the American Thoracic Society (28.)]

or where there is significant displacement of the trachea. Whether the scoliosis is the result of a neuromuscular disorder or another cause does not appear to affect the severity or type of respiratory event seen during sleep (348). The magnitude of fall in SpO_2 during sleep has been shown to be related to the waking oxygen saturation (348). However, compared to patients with restrictive lung disease or those with COPD and similar levels of daytime hypoxemia, patients with scoliosis experience more severe falls in SpO_2 and greater rises in CO_2 during sleep (262). The low FRC seen in those with severe chest wall deformity compared to these other diagnostic groups would limit oxygen reserves and consequently increase the degree of desaturation seen during any period of abnormal sleep breathing (262). In one study, an indwelling radial artery catheter was placed in a patient during a diagnostic sleep study, allowing measurement of arterial blood gases. This illustrated the dramatic rises in CO_2 that can occur during sleep, with the CO_2 increasing from an awake value of 47 to 62 mmHg during REM, along with a fall in pH from 7.42 to 7.29 (150).

Obesity hypoventilation syndrome

This disorder is seen in patients who are obese (BMI > 30 kg/m^2) and in whom no other cause for daytime hypercapnia ($PaCO_2$ > 45 mmHg) such as significant lung disease, hypothyroidism, neuromuscular, or chest wall deformity can be identified (288). Between 10% to 20% of patients referred to sleep laboratories have OHS (76, 242, 267), with the incidence increasing as the BMI range increases (265,283). Since its early description in the medical literature, there has been a great deal of speculation regarding the mechanisms responsible for the development of hypoventilation in the morbidly obese, particularly given that daytime hypercapnia occurs in only a subgroup of even the most obese individuals. Factors that have been implicated in the development of OHS include alterations in central respiratory control, alterations in lung and chest wall function secondary to adiposity, and sleep-disordered breathing. However, no single mechanism adequately explains this syndrome, and the emergence of hypoventilation more likely arises from a complex interaction of a number of factors, culminating in the failure of the normal compensatory mechanisms that operate to maintain ventilation despite severe obesity.

One of the most obvious features of morbid obesity is the physical limitation of lung and chest wall movement related to the accumulation of adipose tissue around the thorax and abdomen. However, it is not simply the presence of excess weight but how it is distributed that influences the degree to which lung function is impaired. Waist-to-hip ratios reflect the degree of central obesity present, and this has been shown to be more closely associated with abnormalities in lung volumes and gas exchange than either weight or BMI (83, 214, 429). Patients with OHS have more marked central obesity, with larger neck circumferences and higher waist-to-hip ratios than either patients with OSA or those with eucapnic obesity, even at a similar BMI (331). They also have a more marked restrictive pattern on pulmonary function testing, with reductions in both FEV_1 and FVC but with preservation of the FEV_1/FVC ratio. While TLC may also be reduced compared to eucapnic morbid obesity, it is the reduction in expiratory reserve volume (ERV) which is most pronounced in those with OHS (160, 311). In conjunction with impairment of lung volumes, pulmonary mechanics are also significantly altered, with marked reductions in respiratory system compliance (275, 302) and increases in airway resistance (302, 430). These changes contribute to an increased work of breathing, which is markedly greater in patients with OHS compared to

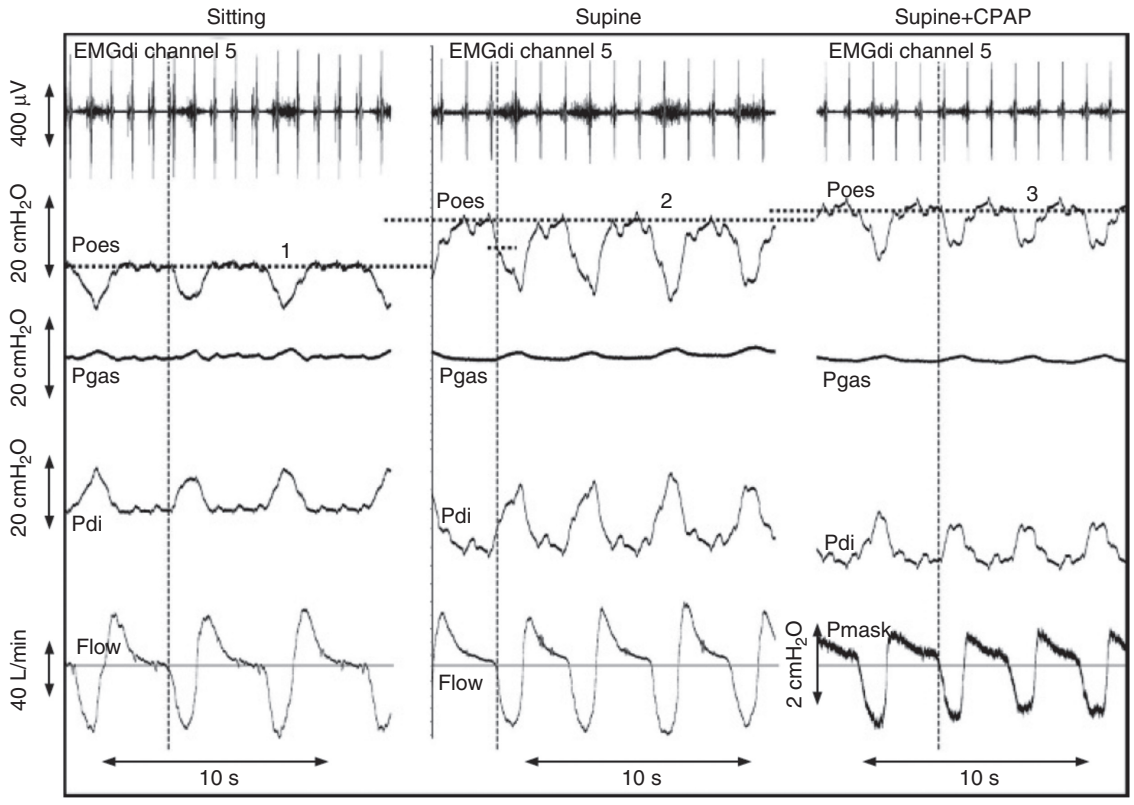

Figure 3 Resting breathing in an obese subject (BMI 42 kg/m^2) when seated (left), supine without CPAP (middle) and with CPAP (right). The change in end-expiratory esophageal baseline pressure is reflected by the horizontal dotted lines (nos 1-3). There is PEEPi of around 6 cmH_2O (vertical broken lines indicate the start of inspiratory flow, with the difference between horizontal line 2 and 4 indicating PEEPi). Zero flow is indicated by the horizontal line. In the right panel the patient is supine breathing with CPAP at 6 cmH_2O. Neural respiratory drive to the diaphragm increases when changing posture from sitting to supine and reduces with CPAP; PEEPi is offset by CPAP and pressure swings of Poes and Pdi are smaller. CPAP, continuous positive airway pressure; EMGdi, electromyogram of the diaphragm; Poes, esophageal pressure; Pgas, gastric pressure; Pdi, transdiaphragmatic pressure (= Pgas-Poes); PEEPi, intrinsic positive end expiratory pressure. [Reproduced, with permission, from Thorax, Steier et al. 64:719-725, 2009 with permission from the BMJ Publishing Group Ltd (373.)]

eucapnic obesity (217,296). Reductions in FRC and more particularly ERV will also favor small airway closure. Not only will this worsen ventilation-perfusion relationships and hence gas exchange, it also promotes air trapping and the development of intrinsic positive end expiratory pressure (PEEPi) (297,373), a situation where alveolar pressure remains above atmospheric at end-expiration caused by incomplete expiration. By imposing a threshold load on the inspiratory muscles, PEEPi further increases the work of breathing, particularly when the patient lays supine (217,297,373). (Fig. 3) Adding to this increased work of breathing is increased upper airway resistance which occurs in patients with OHS both sitting and supine. In contrast, in eucapnic obese patients with simple OSA this increase in resistance is only seen in the supine position (226). (Fig. 4).

At the same time loads on the respiratory system are increased, respiratory muscle performance may be impaired (82,209). Maximum voluntary ventilation, reflecting respiratory muscle endurance, is lower in OHS compared to eucapnic morbid obesity (202), and may arise from breathing at low lung volumes (414) or from the hypoxia related to greater ventilation-perfusion mismatch in this group. Maximum inspiratory muscle strength is also reduced compared to both normal subjects and those with eucapnic obesity, and worsens in the supine position (358). This may be due to a splinting of the diaphragm from the increased abdominal mass (358), placing the inspiratory muscles at a mechanical disadvantage (338). Intrinsic changes to the inspiratory muscles themselves may also occur, although this has not been well studied in humans. In obese Zucker rats, a remodeling of the diaphragm occurs, resulting in thickening of the muscle (128). An increase in the oxidative capacity of the inspiratory muscles has also been shown (321). Such changes would enhance force generation and the ability to maintain ventilation while promoting fatigue resistance despite the high work of breathing related to extreme obesity. However, if such compensatory adaptations failed or were overwhelmed, this could contribute to reduction ventilation. Fatty infiltration of the diaphragm of a patient with OHS who died from cardiorespiratory failure has also been reported (124), but data regarding morphological differences in the diaphragm between OHS, eucapnic obese and normal subjects is not available.

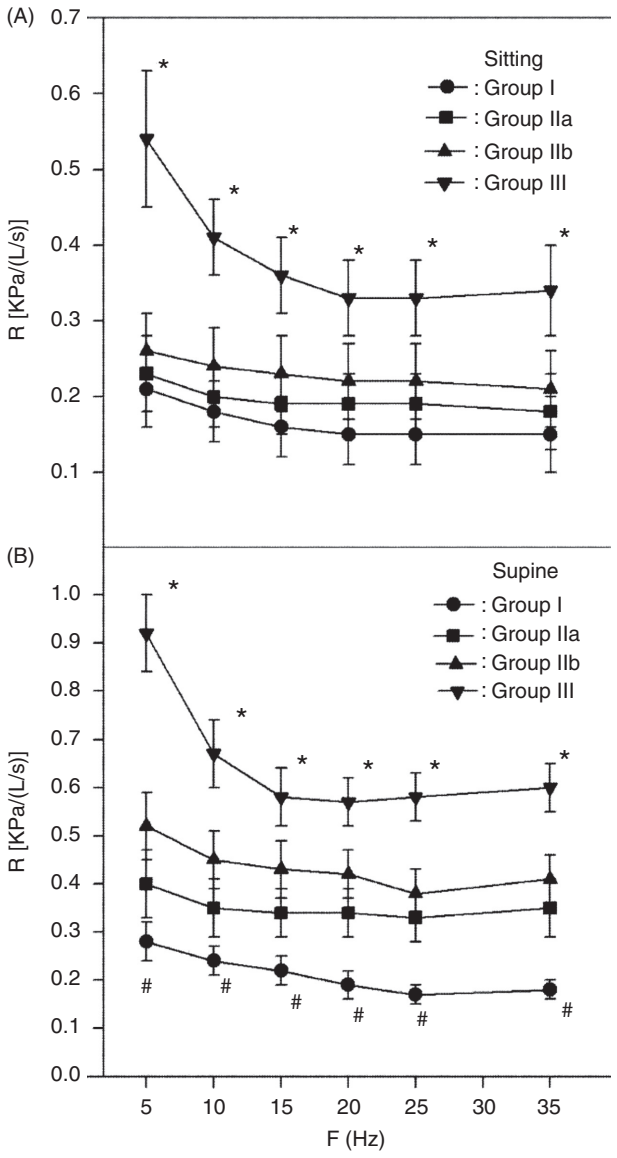

Figure 4 High upper airway resistance is present in OHS patients not only when supine but during sitting. Total respiratory resistance (Rrs) at different oscillometry frequencies measured in awake sitting (A: upper panel) and supine (B: lower panel) in normal controls without OSA (Group I), in patients with moderate-severe OSA and BMI $\leq$ 35 kg/m^2 (Group IIa) or BMI $>$ 35 kg/m^2 (Group IIb) and patients with OHS (Group III). In sitting, there was no significant difference in Rrs at any oscillometry frequency between normal subjects and those with eucapnic OSAS, although Rrs at all frequencies was higher in the eucapnic OSAS compared to normal controls when supine ($^{\#}P < 0.05$). In patients with OHS, significantly higher Rrs was seen at all oscillometry frequencies compared to the other three groups in both sitting and when supine ($^{*}P < 0.05$). [Reprinted from Respir Physiol Neurobiol. Vol 139, Lin et al, *Oral airway resistance during wakefulness in eucapnic and hypercapnic sleep apnea syndrome*. pg 215-224, 2004, with permission from Elsevier. (226.)]

When work of breathing is high and inspiratory muscle strength is reduced, individuals frequently adopt a pattern of breathing characterized by high respiratory frequency and low tidal volume. Such a strategy optimizes the work of breathing by reducing the load-related increased elastic force obese patients need to breathe against (78). Eventually, however, the higher respiratory rate increases dead space and the oxygen cost of breathing (78), which is already high (206).

To maintain eucapnia in the face of these alterations in lung volumes and pulmonary mechanics, neural drive at rest is increased in eucapnic obese patients compared to normal weight healthy subjects (63, 78, 115, 235, 373). Using transesophageal measurements of diaphragm EMG activity, Steier and colleagues (373) observed a neural drive at rest that was two to three times higher in morbidly obese subjects than that seen in normal weight controls. Patients with OHS lack this augmented drive (235,341). Airway occlusion pressures (226) and diaphragmatic EMG responses to hypercapnia (342) are reduced compared to eucapnic obesity. Ventilatory responses to both hypoxia (224,431) and hypercapnia (79, 93, 155, 224) are blunted compared with normal weight controls and those with morbid obesity. A relationship between hypercapnic ventilatory responsiveness and severity of REM hypoventilation has also been demonstrated, so that individuals with lower CO_2 ventilatory response spend a greater percentage of REM sleep hypoventilating (79).

Initially, it was proposed that there may have been a genetic basis to explain this loss of chemoresponsiveness. However, subsequent studies have failed to find differences in respiratory chemosensitivity between family members of OHS patients and healthy control subjects (180, 183). More likely blunted ventilatory responsiveness is acquired. Treatment of sleep-disordered breathing improves this responsiveness, with changes occurring within days and weeks of therapy, even in the absence of significant alterations in weight (45, 79, 93, 155, 224). The increased CO_2 during sleep related to abnormal breathing (discussed below), leads to increased bicarbonate which would blunt ventilatory responsiveness to CO_2 (39, 144).

Recently, interest has turned to the role leptin, a protein produced by adipose tissue, may play as a potential link between obesity, respiratory depression and altered upper airway dysfunction. The leptin deficient obese (ob/ob) mouse exhibits changes in ventilation very similar to that seen in humans with OHS. This includes daytime hypercapnia and a blunted ventilatory response to CO_2 during wakefulness and sleep (286, 319, 384). Acute leptin replacement produces a marked increase in minute ventilation, particularly during REM sleep, as well as improving CO_2 chemosensitivity during NREM and REM sleep (285). Wild type mice fed a high-fat diet to induce obesity demonstrate a rise in plasma leptin levels, along with a significant increase in baseline ventilation despite a decrease in hypercapnic ventilatory response during wakefulness. However, ventilatory responsiveness to CO_2 is maintained during NREM and REM sleep to a level similar to that seen in lean wild-type mice, suggesting that the raised endogenous leptin levels acts as a protection against respiratory depression in the face of obesity, particularly during sleep (285). Also in a mouse model, leptin deficiency has been shown to promote pharyngeal collapsibility, independent of obesity, likely related to reduced neuromuscular

control of upper airway muscles through diminished ventilatory drive (318). In humans, leptin deficiency is rare, with obesity inducing an increase in leptin levels, while further increases are seen in those individuals with OSAS or OHS (293, 306, 386). Hence, elevated leptin levels are seen as a compensatory mechanism to maintain an appropriate level of respiratory drive and ventilation despite the increased ventilatory load associated with obesity (306). If the stimulatory effects of leptin on ventilation are attenuated by the development of "leptin resistance" or "central leptin insufficiency" (189, 285), then hypercapnia can emerge. This would be particularly important during sleep, where a reduction in hypercapnic ventilatory responsiveness promotes the development of hypercapnia by blunting the ventilatory compensation that normally follows apneic events (39). Findings from a number of studies support this premise. In severely obese subjects, an association between higher concentrations of serum leptin and reduced ventilatory responsiveness to hypercapnia has been shown (67). In patients with OSA, Shiruma et al. (359) found that serum leptin was the only predictor of the presence of hypercapnia. Makinodan et al. (243) reported a significant positive relationship between serum leptin levels and hypercapnic ventilatory responsiveness in control subjects and eucapnic patients with OSA. In contrast, those subjects with hypercapnic OSA had significantly lower hypercapnic ventilatory responses compared to eucapnic subjects despite similar serum leptin levels, lung volumes and BMI (243). Taken together these findings suggest that leptin augments hypercapnic ventilatory responsiveness to maintain eucapnia despite the significant load placed on the respiratory system by obesity. However, if the stimulating effects of leptin are attenuated, hypercapnia and a diminished response to CO_2 emerge.

Alterations in other neurohormonal factors may also be involved in the emergence of hypoventilation. Significant reductions in Insulin-like growth factor-1 (IGF-1) in OHS patients compared to eucapnic obese patients with OSA has also been reported (268), with serum IGF-1 levels strongly and negatively correlated with $PaCO_2$ and bicarbonate, two of the major clinical indicators of OHS. Reduced growth hormone and IGF-1 levels have also been associated with reduced inspiratory drive and CO_2 sensitivity in Prader Willi (227) as well as diaphragmatic weakness in animal models (223).

Sleep breathing abnormalities in obesity hypoventilation

Most commonly, patients with OHS demonstrate some abnormality of upper airway stability, ranging from prolonged periods of partial flow obstruction (obstructive hypoventilation) (37) to frank OSA (22, 37, 79, 316). Only around 10% of individuals with this disorder will demonstrate pure sleep hypoventilation (195, 288), with sustained nocturnal desaturation and rises of more than 8 to 10 mmHg with attenuation in the airflow signal but no change in its morphology. Whether this represents two different phenotypes of this disorder or simply reflects differences in the drive to the diaphragm and upper airway muscles at the time of diagnosis is unclear. However, in a study which initially recruited only patients with sleep hypoventilation (defined as an apnea hypopnea index [AHI] < 10 events/h), seven out of the 12 patients studied demonstrated OSA during a follow up period off their usual ventilatory support, even though weight and pulmonary function had not changed (94). Improved respiratory drive following therapy to eliminate sleep-disordered breathing could conceivably have increased output to the diaphragm during sleep. Greater intrathoracic pressure swings would favor upper airway collapse and the emergence of OSA where previously this had been absent (309).

The role upper airway obstruction plays in the development of sleep hypoventilation in OHS has stimulated considerable debate over the years. A meta-analysis looking at factors involved in the development of chronic hypercapnia in obese patients with OSA, found a significant association between AHI and daytime hypercapnia (192). However, the mean difference in events/hr between eucapnic and hypercapnic patients was only 12.51 (95% confidence interval: 6.59-18.44), with both groups having a mean AHI of more than 50 events/hr. While it is true that relieving upper airway obstruction can reduce or normalize awake CO_2 (37, 266, 316), the majority of patients, even those with severe OSA, do not develop awake hypoventilation. Consequently, other factors must be in play for chronic hypoventilation to occur in those with OHS.

A model that ties upper airway obstruction to the development of chronic daytime hypercapnia has recently been proposed (39). Apneic and hypopneic episodes during sleep permit a transient increase in CO_2, which should be normalized by an appropriate level of hyperventilation between events (38, 328). In hypercapnic patients, ventilation for a given CO_2 load is reduced post apnea (38), while the interapnea duration relative to the apnea duration is shortened compared to OSA patients maintaining daytime eucapnia (13). This would diminish the time such individuals have to "blow off" CO_2 that has accumulated during the apneic period (13) (Fig. 5). As a consequence of repetitive poorly compensated hypercapnic events, an overall rise in CO_2 over the night occurs (39). This rise in CO_2 is accompanied by a rise in serum bicarbonate, and if not excreted prior to the next sleep period, its accumulation would begin to blunt ventilatory responsiveness to CO_2 (39, 282). By using computer modeling of whole body CO_2 kinetics, Norman et al. (282) demonstrated that repetitive apneic episodes produce modest rises in CO_2 over time when ventilatory CO_2 response is low or renal bicarbonate excretion is inadequate. However, when both circumstances occurred together, the retention of CO_2 is significantly greater.

There are clinical data to support the concepts proposed by this model. In patients with hypercapnic OSA, a marked increase in overnight transcutaneous CO_2 occurs along with a significant rise in morning $PaCO_2$ compared to values obtained the previous night. Such a finding is not seen in those who are able to maintain eucapnia (77). Using a highly

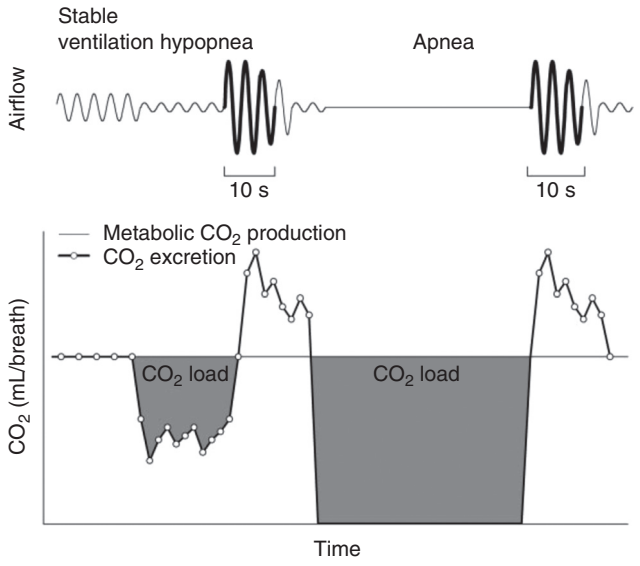

Figure 5 Conceptual illustration of the impact of the interapneic period on the accumulation of CO_2 during sleep in patients with upper airway obstruction. The accumulation of CO_2 during the hypopnea is offset during the interapnea period by sufficient ventilation over a sufficient period to eliminate the previous CO_2 build up. However, if more CO_2 is accumulated than can be excreted in the interapneic period, a small net rise in CO_2 occurs. If this process is repeatedly frequently, a rise in $PaCO_2$ will occur. [Reprinted with permission from Berger et al., 2002. J of Appl Physiol 93:917-924) (38).]

sensitive threshold, Mokhlesi and colleagues (267) found that only 3% of OHS patients with a serum bicarbonate level $<$27 mEq/L had hypercapnia compared to 50% with a serum bicarbonate $\geq$27 mEq/L.

Individuals with OHS also spend a greater proportion of sleep time and, in severe disease wakefulness, with SpO_2 $<$90%. Periods of sustained hypoxemia are most likely to be seen in REM sleep, and a significant relationship between the amount of hypoventilation in REM sleep and CO_2 sensitivity has been shown (79). The proportion of total sleep time spent with a SpO_2 $<$90% is strongly associated with the development of daytime hypercapnia (192). Severe hypoxia during sleep may in itself worsen breathing by affecting hypothalamic function or increasing central leptin resistance, although such mechanisms remain purely speculative (427). Sustained hypoxia could also interfere with the synthesis of a number of neurotransmitters, which in turn could adversely affect ventilatory responses and central respiratory control (218). In a study of healthy nonobese males during sleep, arousal in response to external resistive loading was significantly delayed by sustained hypoxia (165). Hypoxia-related blunting of arousal has the potential to prolong periods of abnormal breathing, worsening sleep hypoventilation not only in those with OHS, but in any disorder associated with prolonged nocturnal hypoxemia (165).

Chronic obstructive pulmonary disease

A number of abnormalities in pulmonary function occur with COPD. Forced expiratory flow rates are reduced related to both fixed narrowing of the airway and airway instability. As a consequence of flow limitation, RV increases along with TLC but not to the same extent, resulting in an increase in RV/TLC ratio. This hyperinflation assists in maintaining maximum expiratory flow by increasing the elastic recoil pressure and enlarging airways but it also places the inspiratory muscles, especially the diaphragm, at a mechanical disadvantage. This increases the work of breathing by imposing an additional inspiratory threshold load. Damage to both the airways and lung parenchyma in COPD creates uneven distribution of both alveolar ventilation and pulmonary blood flow resulting in significant ventilation-perfusion mismatch and arterial hypoxemia with or without hypercapnia, reducing the supply of oxygen to the respiratory muscles. Increased physiological dead space necessitates the individual generating higher levels of minute ventilation and tidal volumes to maintain eucapnia.

To achieve this, respiratory drive is increased in patients with COPD compared to age-matched healthy controls, whether measured using $P_{0.1}$ (12,269) or diaphragmatic EMG activity (184). It was initially speculated that the development of awake hypercapnia arose from a blunting of respiratory drive (6). However, later work has shown that increased neural drive occurs to the same extent in patients with and without hypercapnia (96,269). While inspiratory drive is increased in most patients with severe COPD (61), the capacity to translate this drive into increased ventilation may become impaired when the mechanical load is too great and neural drive cannot be increased further, resulting in a decrease in ventilation and subsequent rise in CO_2 (269). As CO_2 accumulates, the ventilatory response to CO_2 would be blunted by the compensatory retention of bicarbonate, permitting the development of daytime hypercapnic respiratory failure. While a positive relationship between the degree of hypoventilation and severity of airflow obstruction has been shown (269,335), there is a wide spread in the severity of airways obstruction required before CO_2 retention occurs. However, CO_2 retention is unlikely to occur when FEV_1 is above 1 L (269) unless other factors such as severe obesity or sleep-disordered breathing come into play.

Since OSA and COPD are both common disorders in the general population, it is not surprising that the two conditions are not infrequently seen in the same patient (referred to as "overlap"), with a prevalence estimated to be around 1% of adult males (29). Patients with an overlap of these two disorders tend to be more obese, have more severe daytime hypercapnia and hypoxemia independent of lung function (72,195), experience lower mean nocturnal oxygenation (73), and have higher pulmonary artery pressure than those with COPD alone (73,158,195). Radwan et al. (326) studied 20 obese patients with OSA and compared mouth occlusion pressures at rest and awake ventilatory response to CO_2 to 11 equally obese patients with overlap. At rest, minute ventilation and mouth occlusion pressure were similar between groups but increased compared to healthy, nonobese controls, indicating a higher neuromuscular output. However, during CO_2 rebreathing, ventilatory, and mouth occlusion pressures

were significantly decreased in the overlap patients, while responses in OSA patients were similar to controls.

Breathing during sleep in chronic obstructive pulmonary disease

It has been recognized for many years that gas exchange can worsen markedly during sleep in patients with COPD (105, 204, 395). These changes arise from alterations in lung volumes, ventilation perfusion matching, and respiratory drive associated with sleep, lead to worsening of gas exchange in sleep compared to wakefulness. Three patterns of abnormal gas exchange during sleep in patients with COPD have been noted: isolated nocturnal desaturation in those with mild daytime hypoxemia; worsening sleep hypoventilation in patients with daytime respiratory failure; and frank OSA coexisting with COPD (the overlap syndrome).

In COPD patients with mild to moderate daytime hypoxemia (i.e., PaO_2 in the range 56-70 mmHg), nocturnal desaturation is not uncommonly encountered in clinical practice (72, 222, 410), although it is estimated to have a prevalence of less than 5% in the whole COPD outpatient population (222). Mostly, these periods of desaturation occur in REM sleep only, or are at their most severe during this time (271). Not unexpectedly, a moderate relationship between the degree of daytime hypoxemia and the severity of sleep-related oxygen desaturation in COPD patients has been shown, such that those that are most hypoxic awake become most hypoxemic during sleep (222, 229, 410). Patients with respiratory muscle dysfunction (159) or a low ventilatory response to CO_2 (410) are also at risk of developing nocturnal hypoxemia.

In COPD, the worsening of oxygenation during sleep may be due to either hypoventilation secondary to reduced ventilatory drive or from changes in ventilation-perfusion matching related to alterations in respiratory muscle activation, lung volumes and airflow obstruction (170, 271). Concurrently, arterial CO_2 levels increase during these periods of oxygen desaturation, and while rises are usually relatively small in most patients (271), significant CO_2 retention is more likely to occur in patients already exhibiting awake hypercapnic respiratory failure (251, 340, 385). It has been suggested that the change in $PaCO_2$ largely reflects the mechanism of gas exchange abnormality occurring, such that small increases relative to the fall in oxygen saturation would be associated with ventilation-perfusion mismatching while larger increases would be seen when hypoventilation was the predominant mechanism (415). Mulloy and McNicholas (271) reported that the degree of hypoventilation in patients with COPD during sleep was similar regardless of whether they were major (defined as SpO_2 during sleep $<90\%$ for at least 5 min and reaching a minimum of at least 85%), or minor sleep desaturators, suggesting that other factors such as ventilation-perfusion mismatching were responsible for the greater degree of desaturation seen. Using an inductance vest to estimate ventilation, Hudgel et al. (170) found that there was a larger decrease in FRC during hypopneic periods in desaturating COPD patients compared to nondesaturators which would favor worsening ventilation-perfusion matching as the cause of nocturnal desaturation. However, the variability of breathing during REM and the higher body stores of CO_2 compared to oxygen have made it difficult to quantify the extent to which worsening ventilation-perfusion contributes to nocturnal hypoxemia in these patients, and more recent evidence points to hypoventilation as being the predominant mechanism underlying desaturation during sleep (21, 28).

In an extensive evaluation of alterations in respiratory function during sleep, Ballard and colleagues (21) converted an iron lung to a body plethysmograph and studied five normocapnic patients with severe, stable COPD during sleep. While they were unable to find any change in lung volume or lower airway resistance across sleep stages, they did identify large reductions in minute ventilation related to reduced tidal volume, especially in REM sleep. Likewise, using a pneumotachograph Becker et al. (28) showed that average decrease in minute ventilation from wakefulness to NREM sleep was 16%, with a 32% fall in REM compared to awake values. A marked increase in upper airway resistance and significantly reduced inspiratory neuromuscular drive appears to underlie these falls in ventilation (21). Consequently, individuals who have high resting drive awake to maintain ventilation, would be unable to meet these ventilatory requirements during sleep, resulting in hypoventilation.

Most typically hypopneas during REM sleep are seen resulting in prolonged periods of desaturation with failure of SpO_2 to return to baseline levels during recovery breathing (170, 418). In patients with severe hyperinflation, the flattening of the diaphragm creates a mechanical impairment which limits its ability to generate inspiratory pressure. Consequently, the activity of other rib cage inspiratory muscles such as the intercostal, scalenes, and sternomastoid increases. The movement of the rib cage has been shown to be strongly correlated with peak inspiratory scalene activity and to a lesser extent with sternocleidomastoid activity (182). Suppression of this activity during REM from a generalized postural muscle atonia particularly during periods of phasic eye movement in REM sleep would lead to a decrease in inspiratory pressure development and hence hypoventilation (182, 418). However, a wide variation in breathing and inspiratory muscle activity during sleep has been noted between individuals (170,418), and a differential suppression of inspiratory muscle groups has been suggested to explain differences in the nature of the hypopneas seen (418). In those patients where a generalized reduction in inspiratory muscle activity occurs, there would be a reduction in chest wall movement associated with reduced effort. On the other hand, a greater reduction in output to the upper airway muscles compared to the chest wall muscles would produce increased inspiratory flow resistance and partial flow obstruction. Such "obstructive" hypopneas would more likely be seen in patients with a higher BMI or an anatomical narrower upper airway (71). In a group of COPD patients with severe, stable hypercapnic respiratory failure, O'Donoghue et al. (287)

found that even after the exclusion of patients with overt OSA, the severity of inspiratory flow limitation in REM was predictive of REM-related hypoventilation, while BMI was significantly correlated with sleep hypoventilation across the whole night. It has also been demonstrated that the length of these hypopneic events is important in altering nocturnal gas exchange, with individual episodes being longer and a greater proportion of REM sleep spent hypopneic in patients who desaturate compared to nondesaturators (170). This more prolonged period of underbreathing would permit the gradual retention of bicarbonate, which in turn would blunt the ventilatory response to CO_2, allowing even greater changes in gas exchange during sleep to occur, promoting the development of awake hypercapnia (287).

There is reason to believe that the presence of OSA in patients with COPD may significantly worsen outcome if the treatment of apneic events is not adequately addressed. Quality of life has been reported to be more impaired in patients with overlap compared to COPD alone (260). The presence of sleep apnea may be the major factor accounting for this difference (260), as isolated nocturnal desaturation has not been shown to be associated with impairments in health related quality of life (222). While mortality rates are higher amongst overlap patients compared to those with OSA alone (74) or with COPD alone (245), the role hypoventilation plays in this has not been investigated.

Assessing Patients at Risk of Hypoventilation

As can be seen from the previous discussion, despite added loads on the respiratory system from abnormal pulmonary mechanics or reduced capacity arising from impaired muscle function, the development of daytime hypoventilation is delayed or avoided by an increase in respiratory drive in the majority of individuals, albeit at the expense of dyspnea in many. However, when hypoventilation develops it will first become apparent during sleep. In the clinical management of "at risk" individuals the aim is to identify the presence of nocturnal hypoventilation as early as possible to advise and plan interventions to best manage the abnormality before unstable chronic respiratory failure occurs. In a study of patients with ALS, the average period between first evaluation and the occurrence of chronic hypoventilation was 12 (95% CI: 9-20) months (232). Ward et al. (412) found 50% of neuromuscular patients demonstrating isolated nocturnal hypoventilation developed signs or symptoms of daytime hypercapnia within 6 months of evaluation. (Fig. 6) In patients with DMD, if awake hypercapnia is not treated, mean survival may be as low as 9 months (405). Similarly, in hospitalized patients with OHS discharged without respiratory management, mortality was fourfold higher than eucapnic obesity, with the majority of deaths occurring with 3 months of discharge (283). These

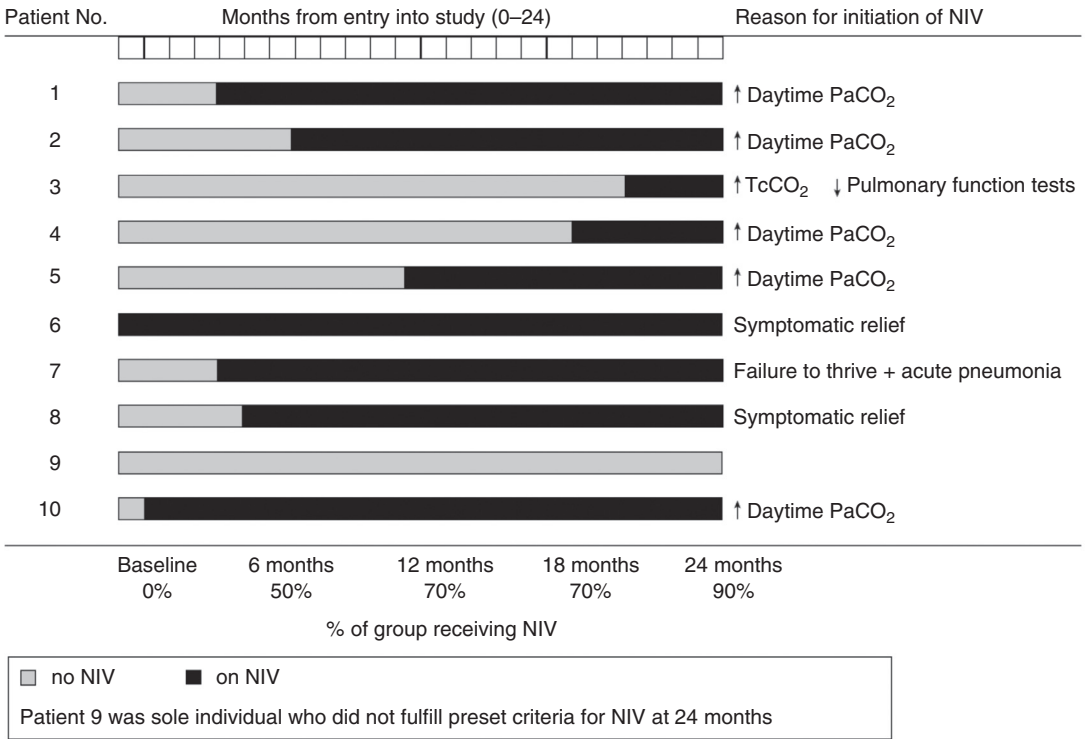

Figure 6 In patients with a neuromuscular and chest wall disorder, the development of nocturnal hypoventilation portends the development of awake hypercapnia within the next 12 to 24 months. These 10 patients represent a control group allocated to no NIV over a 2 year period. The light-colored bar represents the period of time the subject remained NIV-free. By 12 months, 70% of the group required NIV, and by 24 months only one subject did not fulfill the criteria to commence NIV. (Reproduced from Thorax, Ward et al. 60:1019-1024, 2005 with permission from the BMJ Publishing Group Ltd) (412).

Table 2 Clinical Features that Can be Associated with Nocturnal Hypoventilation

- Daytime fatigue or excessive daytime sleepiness
- Early morning headaches
- Nocturnal orthopnea or inability to lie flat
- Poor quality or fragmented sleep
- Cognitive impairment
- Worsening shortness of breath on activity
- Thoracoabdominal paradox
- Accessory respiratory muscle use
- Impaired cough
- Frequent respiratory infections
- Swallowing difficulties
- Weight loss
- Cor pulmonale

findings highlight the need for readily available and reliable techniques to identify as early as possible the presence of nocturnal hypoventilation.

Clinical evaluation

A high degree of clinical vigilance and monitoring needs to be undertaken in patients with disorders known to be associated with hypoventilation during sleep (Table 1). Even when overt daytime respiratory failure is present, it may not be clinically apparent, with patients reporting few symptoms, reflecting the insidious way in which chronic respiratory failure can develop in hypoventilation syndromes. Some patients will modify their life style in response to their deteriorating respiratory status, thereby minimizing symptoms. Other patients may not volunteer their respiratory symptoms believing them to be an expected part of their primary disease process. Consequently, direct and specific questions regarding sleep and daytime symptoms related to nocturnal hypoventilation need to be included in the routine clinical evaluation of patients with neuromuscular and restrictive chest wall disorders (208,381). Clinical features often associated with nocturnal hypoventilation are listed in Table 2, although symptoms are generally a poor predictor of the presence and severity of sleep breathing abnormalities. A self-administered symptom-based questionnaire, the SiNQ-5, has recently been developed and suggested as a potential clinical tool in prioritizing individuals with inspiratory muscle weakness for further investigations of sleep-disordered breathing (374). However, its clinical value has not yet been widely reported. In a retrospective analysis, Laub and colleagues (213) looked at the clinical motives for commencing home ventilation in nearly 270 neuromuscular patients. Daytime sleepiness was the most common reason, followed by abnormal awake arterial blood gases and dyspnea, although these reasons varied depending on the underlying disease process. As with sleep-disordered breathing, symptoms were found to be a poor marker of hypoventilation. In a study of patients with a range of neuromuscular disorders, the level of awake hypercapnia at which patients presented for investigation varied widely from a mean of 62 mmHg in patients with ALS to 44 mmHg in those with DMD (111). Using symptoms alone to identify sleep-disordered breathing and hypoventilation in patients with neuromuscular disorders may result in significant and potentially life threatening delays in intervention.

In patients with lung disease, obesity or the presence of cor pulmonale which is out of proportion to the degree of lung impairment should prompt specific questioning about sleep and OSA (91). Since the prevalence of OHS increases with increasing BMI, exclusion of the diagnosis should be undertaken in any patient with a BMI > 40 kg/m^2. These patients frequently report the classic symptoms of OSA, including loud snoring, nocturnal choking and hypersomnolence. However, in contrast to eucapnic OSA patients, those with OHS commonly report dyspnea on exertion and are more likely to present with lower limb edema and pulmonary hypertension (195). However, the nonspecific nature of the symptoms reported and their failure in reflecting either sleep-disordered breathing or the presence of hypoventilation necessitates the need for more objective monitoring of respiratory function.

Daytime respiratory function testing

A number of simple measurements have been identified as being useful predictors of those at risk of underbreathing during sleep. These can be carried out routinely in a clinic or by the bedside, and can assist in determining the need for more extensive or invasive monitoring procedures, as well as guiding the need for commencing nocturnal ventilatory support.

Neuromuscular disorders and thoracic cage deformities

The routine monitoring of pulmonary function and respiratory muscle strength has been widely recommended for patients with neuromuscular disorders. The frequency with which this needs to be carried out, and the best tests to provide information about progression of respiratory muscle impairment and the possibility of sleep-disordered breathing will vary slightly depending on the nature of the primary neuromuscular disorder.

VC reflects global respiratory muscle strength and as such is widely used in monitoring the progression of respiratory function in patients with a wide variety of neuromuscular and chest wall disorders. It has also been shown to be a useful in predicting the presence of sleep-disordered breathing and nocturnal hypercapnia in this population (172, 327). In patients with neuromuscular disorders such as DMD, acid maltase deficiency, congenital muscular, or limb girdle dystrophy, sleep-disordered breathing is unlikely to be present while supine VC remains greater than 60% predicted (327). However, hypopneas in REM sleep are likely to be seen once supine VC falls to 40% to 60% predicted. A supine VC $<$ 40% predicted was strongly linked to continuous nocturnal hypoventilation, while a VC $<$25% predicted daytime was associated with daytime respiratory failure (327) (Fig. 7). A

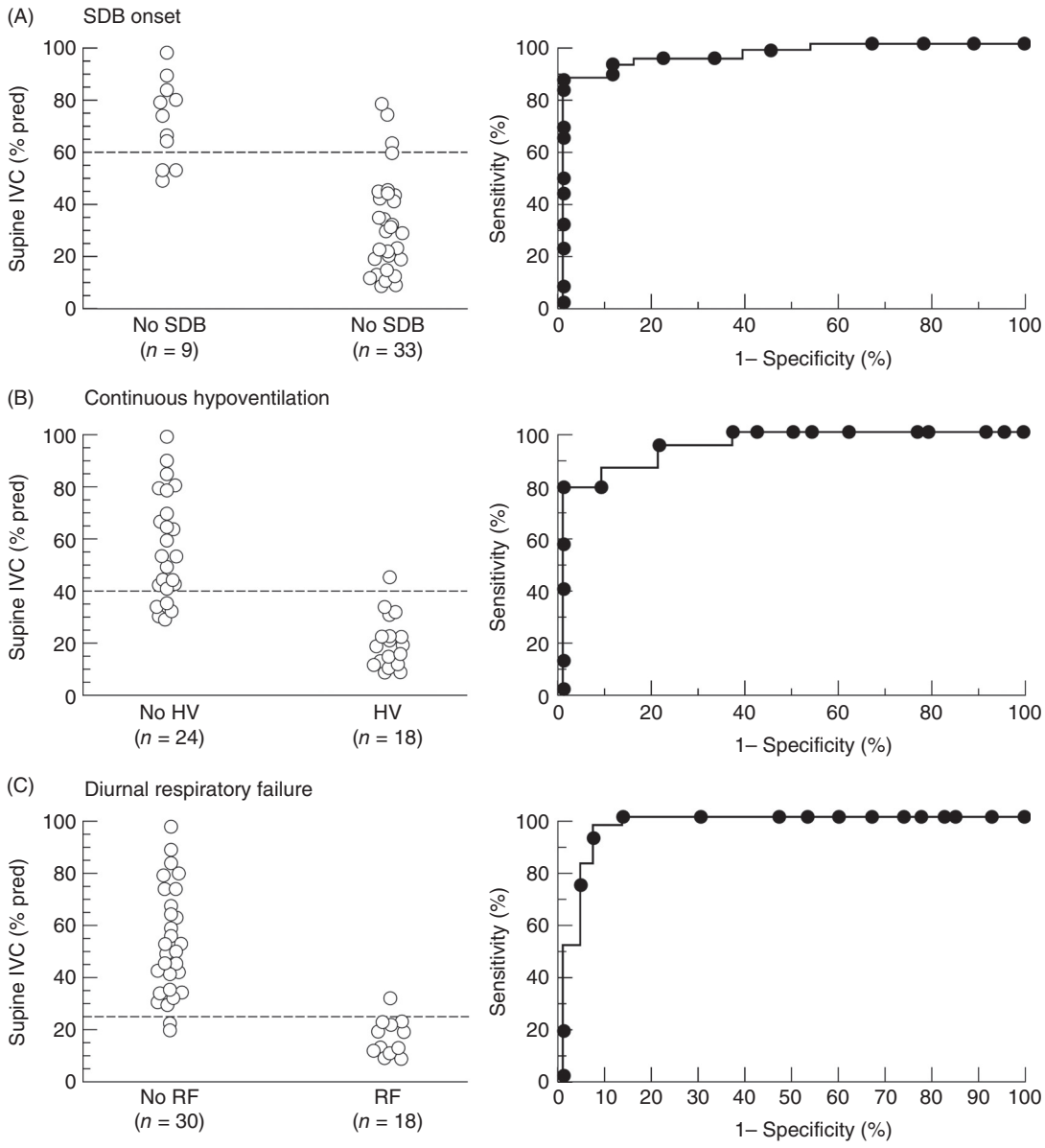

Figure 7 Scatter plots (left-hand panel) and receiver operator curves (right-hand panel) for the predictive thresholds for Inspiratory vital capacity for the (A) onset of sleep-disordered breathing (SDB), (B) continuous nocturnal hypoventilation and (C) diurnal respiratory failure. [Reproduced from Thorax, Ragette et al. 57:724-728, 2002 (327) with permission from the BMJ Publishing Group Ltd.]

change in VC from erect to supine provides a simple index of diaphragmatic weakness relative to other inspiratory muscles, with a specificity and sensitivity of a greater than 25% fall in VC for the diagnosis of diaphragmatic weakness of 90% and 79%, respectively (136). Significant negative correlations have been found between overnight oxygenation and fall in VC from erect to supine in neuromuscular patients (65,417). Simple sitting and especially supine spirometric testing at regular intervals can be a low cost and readily accessible method of identifying patients with neuromuscular and thoracic cage disorders at risk of developing nocturnal hypoventilation, in whom further investigation is warranted.

It should be borne in mind, the presence of obesity, chest wall deformity or craniofacial abnormalities may increase the likelihood of breathing abnormalities during sleep despite the relative preservation of lung function (52). VC is also a less sensitive predictor of those at risk of sleep hypoventilation in disorders such as ALS and myotonic dystrophy. In ALS oxygen desaturation and daytime symptoms attributable to hypoventilation can occur when VC is 70% or greater (173). Supine VC is a more sensitive indicator than upright VC of diaphragmatic weakness, as is accessory muscle use (216). Likewise, in a study of adult patients with myotonic dystrophy and without daytime sleepiness, 44% were found to have

sleep apnea on polysomnography (PSG) despite a normal spirometry (201). Therefore, a higher degree of suspicion and earlier nocturnal monitoring is indicated in these disorders.

In thoracic cage disorders, a VC < 1.0 to 1.5 L and a high angle of spinal curvature (>120°) should prompt further investigation as these patients have been shown to be at high risk of developing respiratory failure (361).

Measures of respiratory muscle strength are an important element of the clinical evaluation of patients with suspected nocturnal hypoventilation. While respiratory muscle weakness is common in patients with neuromuscular disorders, it may or may not be seen in patients with thoracic cage deformity depending on the strength and mechanical efficiency of the accessory respiratory muscles. Most commonly respiratory muscle strength is assessed by measuring maximal inspiratory (MIP) and expiratory (MEP) pressure generated against an occluded airway, using a simple handheld manometer and mouthpiece. Although nocturnal hypoventilation is unlikely to occur unless MIP falls below 40 cmH_2O (327), this maneuver can underestimate inspiratory muscle strength due to facial muscle weakness and difficulty maintaining a seal around the mouthpiece. Sniff nasal pressure (SNIP) is an inspiratory maneuver measured by occluding one nostril while measuring a maximal sniff through the contralateral nostril with a manometer, and has been shown to correlate well with invasive and nonvolitional tests of inspiratory muscle strength (270, 371). In patients with ALS, this maneuver has been shown to be more sensitive than VC to small changes in respiratory muscle strength, declines linearly with disease progression, and can be performed without problems late in the course of disease even when orofacial weakness is present. In addition, it has a higher prognostic value. A SNIP <40 cmH_2O correlates significantly with nocturnal hypoxia in ALS patients, and has a sensitivity of 97% and a specificity of 79% for death within 6 months in this patient group (270). However, in patients with other neuromuscular disorders and severe restriction, SNIP may actually underestimate inspiratory muscle weakness (157). This suggests MIP and SNIP should be considered as complementary tests and used alongside VC to best evaluate inspiratory muscle strength (157).

The modified Borg dyspnea scale (51) has been shown to be a good predictor of respiratory muscle weakness in patients with ALS (187). This scale asks subjects to rate their perception of dyspnea from 0 (Nothing at all) to 10 (very, very severe). A score ≥3 obtained with the patient supine is proposed to be the threshold where further investigations for hypoventilation such as blood gases or overnight monitoring should be undertaken. However, whether this scale is of similar value in other neuromuscular disorders has yet to be evaluated.

In addition to concerns about inspiratory muscle strength, weakness of the expiratory muscles is also important to identify. An inability to clear secretions effectively will promote further hypoventilation by increasing the load on the respiratory muscles and increases the susceptibility of the individual to chest infections, a major cause of morbidity and mortality in neuromuscular disorders. Peak cough flow reflects the ability of an individual to adequately clear secretions from the airways, and can be easily measured at the bedside using a standard peak flow meter. Values less than 270 L/min have been shown to identify those at high risk for developing severe chest infections (20, 104, 343), and provides a threshold where lung recruitment maneuvers and assisted cough techniques are generally introduced (190). Breath stacking using either a manual resuscitation bag or a volume preset ventilator is used to attain maximal insufflation capacity by the patient inhaling a volume of air, closing the glottis and then inhaling another volume of air on top of the first. This "stacking" continues until the patient is maximally insufflated, and then the air is suddenly released in a cough. Providing abdominal and/or thoracic compression during the attempted cough provides additional increases in peak cough flow, compared to manually assisted cough or lung recruitment maneuvers alone (75, 391).

Obesity hypoventilation and chronic obstructive pulmonary disease

In contrast to neuromuscular and chest wall disorders, daytime lung function measures are not predictive of nocturnal hypoventilation in patients with COPD or OHS. While parameters such as VC, ERV, and MIP are typically reduced in OHS compared to eucapnic obese individuals (311), such testing is not sensitive enough to discriminate between the two groups. Similarly, in patients with COPD nocturnal desaturation has not been shown to correlate with awake pulmonary function parameters (135,387). Although one study found a correlation between MIP and nocturnal saturation in this population, the predictive value of this measurement was low, with multiple regression analysis that showing that 75% of the variance in nocturnal SpO_2 was explained by a combination of awake SpO_2 and FEV_1 (159). Consequently, daytime pulmonary function (168,241,258,327) cannot be used to predict nocturnal desaturation and hypoventilation in patients with COPD or OHS.

Daytime gas exchange

Arterial blood gases are the gold standard in identifying the presence of hypercapnia. An increase in $PaCO_2$ above 45 mmHg is generally considered to be the point at which further investigation of sleep hypoventilation or treatment for hypoventilation is undertaken. Arterial blood gases taken prior to and on awakening from sleep can provide useful information on the degree to which CO_2 is retained during sleep and the severity of the ensuing acidosis (77, 263, 287). However, performing an arterial puncture can be uncomfortable for many patients and may be difficult to obtain in some cases such as extreme obesity or in the presence of wrist and elbow contractures. As an alternative arterialized earlobe samples have been also been used (168, 241, 258, 327). However, hypercapnia is often a late feature of disease

progression especially in patients with neuromuscular and chest wall disorders, and is often only documented after the patient presents with an acute, possibly life-threatening episode of respiratory failure. In addition, blood gases even taken at two time points may severely underestimate acute rises in CO_2 especially those occurring during REM sleep. To avoid such scenarios, interest has grown in other clinical measurements that could identify possible hypoventilation at an earlier stage.

Measuring bicarbonate or base excess levels in venous blood is a useful screening procedure for patients suspected of hypoventilating during sleep. In DMD, a base excess during wakefulness of ≥ 4 mmol/L was found to be highly specific (100%) although only 55% sensitive for sleep hypoventilation (172). In patients with slowly progressive neuromuscular disorders a correlation between nadir SpO_2 and base excess has been reported (413). In a group of patients with ALS in whom daytime CO_2 and O_2 were normal, a raised bicarbonate was invariably found in those with significant nocturnal hypercapnia (241). Likewise, in OHS, only 3% of patients with a serum bicarbonate of <27 mEq/L had hypercapnia compared to 50% when serum bicarbonate was ≥ 27 mEq/L. These data demonstrate the usefulness of measuring venous blood for bicarbonate and base excess to screen for overnight hypoventilation. Both values reflect prolonged changes in CO_2 which may not be picked up on an arterial blood gas taken some hours after awakening when alterations in ventilation may have allowed $PaCO_2$ to return to within the normal range.

In patients with COPD, SpO_2 during wakefulness has not been shown to be sufficiently accurate to identify individuals likely to desaturate during sleep (222,229,252,410), although nocturnal desaturation is unlikely where awake SpO_2 is $>94\%$ (221, 229). Similarly, a $SpO_2 \leq 95\%$ in an obese individual can be useful in screening for OHS (24), but again does not predict the presence of daytime hypercapnia or the severity of sleep hypoventilation in this population.

Nocturnal monitoring

Although PSG is considered the most accurate method of identifying sleep and nocturnal breathing abnormalities during sleep, expense, limited facilities, and the difficulty of managing the physically disabled patient in a standard sleep laboratory facility often limits the routine use of this procedure (65, 172, 199, 259, 310, 327). It is also not seen as essential to the diagnosis of nocturnal hypoventilation (207), especially when daytime CO_2 is already raised. Consequently, simpler monitoring techniques to identify sleep-disordered breathing and sleep hypoventilation have been used in patients with suspected sleep hypoventilation syndromes.

Continuous overnight oximetry can be a useful screening tool to identify early in the course of a disorder the presence of nocturnal desaturation (304,308). However, overnight oximetry may be relatively insensitive to changes in oxygenation when PaO_2 is above 70 mmHg (234) or when the arousal response is brisk (201). Although nocturnal oximetry is commonly used to identify nocturnal desaturation in patients with COPD, whether an individual is classified as a desaturator or not can vary night to night depending on what metric is reported (221). Furthermore, the diagnostic usefulness of oximetry alone is severely limited if the patient is receiving supplemental oxygen (137). However, in monitoring the degree and severity of nocturnal hypoxemia, PSG does not provide any advantages over oximetry alone (57). Consequently, PSG in COPD is only recommended when symptoms and history suggestive of OSA are present, or if pulmonary hypertension or polycythemia that are out of proportion to daytime PaO_2 levels or lung function occur (207).

Portable monitoring devices which record respiratory parameters such as chest wall movement, snore, and airflow can provide additional information to oximetry alone, and have been shown to have a high level of agreement with PSG in terms of respiratory events and level of oxygen desaturation, although overscoring of respiratory events may occur (200). A number of reports have successfully identified sleep hypoventilation using such devices (200,208,304,308). However, as sleep is not recorded with these devices, a negative study cannot rule out the possibility of sleep hypoventilation. Breathing abnormalities are most likely to arise in REM sleep, and if the patient has a low proportion of this sleep state or a high REM arousal index the degree of sleep hypoventilation may be underestimated (310, 413). In a study of individuals with ALS, Arnulf and co-workers (10) found that significant diaphragm dysfunction was associated with reduced or absent REM sleep as well as poorer survival.

Continuous nocturnal monitoring of CO_2 using end-tidal ($PetCO_2$) or transcutaneous ($PtcCO_2$) measurements adds valuable additional information to sleep and respiratory recordings obtained during diagnostic studies. Where possible, the validity of these measurements should be confirmed by obtaining an arterial blood gas either at the beginning or at the conclusion of a sleep study. Although generally good, the accuracy of $PetCO_2$ monitoring is affected by ventilation perfusion inequality, mouth breathing or the use of supplemental oxygen or positive airway pressure (345). There are also recognized limitations associated with $PtcCO_2$ monitoring (179, 287, 378), including a lag time between a change in ventilation and any variation in the $PtcCO_2$ measurement. However, there is a clinically acceptable agreement between $PtcCO_2$ and $PaCO_2$ values obtained from arterial blood samples, and this technique has been widely used in monitoring trends in CO_2 during sleep in clinical and research studies of patients with potential hypoventilation syndromes (244,251,287,316,378,393,412). In a randomized trial using peak $PtcCO_2$ to identify nocturnal hypoventilation, Ward et al. (412) found that seven of the 10 patients allocated to conservative management developed symptoms or daytime hypercapnia within a 12 month period. These results suggest the value of $PtcCO_2$ in the early identification of patients hypoventilating during sleep, even in the absence of daytime respiratory failure.

Therapy for Hypoventilation

Pharmacological management of hypoventilation

Respiratory stimulants can theoretically increase respiratory drive and improve daytime hypercapnia. However, only a small number of short term studies involving small numbers of subjects have been reported, with the majority of studies being observational in nature. At present, there are few randomized trials (RCTs) on which to make evidence-based clinical decisions.

Medroxyprogesterone acts as a respiratory stimulant at the hypothalamic level (27). However, reports on the effect of progesterone on ventilatory response to CO_2, awake ventilation, and blood gases have yielded variable results. Ten males with OHS treated with oral medroxyprogesterone (60 mg/day) for one month demonstrated improvements in awake hypercapnia (382), although the impact on sleep-disordered breathing is unknown as PSG was not performed. By contrast, three OHS subjects who remained hypercapnic posttracheostomy showed no improvement in awake ventilation or hypercapnia with therapy (328). More recently, a RCT in postmenopausal women with sleep-disordered breathing in whom CPAP had been withdrawn showed significant improvements in nocturnal oxygen saturation and awake CO_2 following 6 weeks of medroxyprogesterone compared to placebo, although AHI and sleep quality did not improve (9). However, some caution with medroxyprogesterone use is needed due to an increased risk of thromboembolism, breakthrough uterine bleeding (women), and decreased libido, and erectile dysfunction in men may occur (320).

Acetazolamide is a carbonic anhydrase inhibitor and can increase minute ventilation and reduce bicarbonate levels by inducing a metabolic acidosis (388). Small studies have shown a modest reduction in AHI in patients with moderate to severe OSA (390, 420), and short term normalization of $PaCO_2$ and serum bicarbonate in one patient with OHS posttracheostomy (328). Raurich et al. (329) demonstrated that short term acetazolamide decreased plasma bicarbonate and increased hypercapnic drive response in OHS subjects who were intubated and mechanically ventilated. However, long term use of acetazolamide in subjects without positive pressure ventilation have not been studied and potential side effects such as dizziness and electrolyte imbalance have to be considered. Use may also be limited by side effects such as paresthesia.

Aminophylline is a respiratory stimulant, increasing diaphragm strength and promoting bronchodilation (210). Although older studies show improvement in hypercapnia in acute exacerbation of COPD (109), longer term use in conditions associated with hypoventilation has not been studied. Antidepressants such as Paroxetine, a selective serotonin reuptake inhibitor and Mirtazapine, a mixed 5-HT1 agonist and 5-HT2/5-HT3 antagonist, have been studied in sleep-disordered breathing. Potential mechanisms of action include increased genioglossus activity, however, clinical studies have not shown any meaningful improvements in sleep-disordered breathing (246). While respiratory depressants such as opioids may actually reduce OSA severity in some patients by reducing chemical drive/controller gain (411), in those with depressed central drive or impaired pulmonary mechanics hypoventilation can be severely worsened (76, 80).

Although respiratory stimulants maybe useful adjunct treatments for managing hypoventilation it is unclear which stimulants for different patient groups will provide the best clinical benefits. Side effects and long-term safety are also unknown. Using a respiratory stimulant in an individual who is unable to normalize their CO_2 due to ventilatory or mechanical limitations may simply make dyspnea worse. An ability to lower CO_2 during voluntary hyperventilation can assist in identifying individuals more likely to respond (365). Larger and longer term RCT studies are required before firm recommendations can made about the use of pharmacotherapy in hypoventilation syndromes.

Oxygen Therapy

Patients with hypoventilation syndromes frequently exhibit hypoxemia, either continuously or isolated to sleep. Although supplemental oxygen will improve oxygenation, its injudicious administration in patients with hypoventilation can result in significant worsening of CO_2 retention and the development of respiratory acidosis. Amongst the possible causes underlying the rise in CO_2 with oxygen administration, increased ventilation-perfusion mismatch and reduced ventilation due to a reduction in ventilatory drive are believed to be of most relevance (12, 167, 334).

Studies evaluating of hyperoxia in patients with COPD (12, 103, 334) and OHS (167, 421) have demonstrated small but clinically significant increases in CO_2 occurring following even short bouts of oxygen exposure. In both groups, lower baseline oxygen saturation was associated with larger increases in CO_2 following hyperoxia (334, 421). In patients with neuromuscular disorders, even low flow oxygen has been shown to dramatically worsen daytime CO_2 and cause narcosis particularly when daytime hypercapnia already exists (140).

Other studies have looked at the administration of oxygen during sleep to prevent nocturnal desaturation. In patients with COPD qualifying for continuous oxygen therapy, Samolski et al. (340) increased oxygen flow by 1 L/min over the daytime prescription and found that while this adequately treated nocturnal desaturation, in a significant proportion of patients it came at the expense of increasing overnight CO_2 and worsening morning acidosis. Likewise Milross and colleagues (263) demonstrated the correction of nocturnal saturation with low flow nocturnal oxygen therapy in young patients with moderate to severe cystic fibrosis lung disease, but highlighted that it had no effect on the attenuation of minute ventilation occurring during sleep and produced a mild morning respiratory acidosis. Finally, in normocapnic patients with restrictive chest wall disorders and nocturnal hypoventilation, oxygen

therapy improved nocturnal saturation but only provided minimal improvements in the symptoms of hypoventilation and in some cases even worsened them (248).

A small retrospective study found no improvements in blood gases or lung function in a group of patients with kyphoscoliosis treated with long term oxygen therapy, in contrast to a clinically similar group managed during a subsequent period with noninvasive home ventilation (64). Survival was also lower in the oxygen-treated group (64). Two large cohort studies have assessed survival of patients with chest wall deformity treated with oxygen therapy or home ventilation over a 10 year period (152, 174). In both reports, survival in those receiving oxygen therapy was almost three fold lower compared to those managed with home mechanical ventilation. Bach et al. (19) reported on 672 patients with neuromuscular disorders and found when patients were managed with oxygen therapy, significantly higher rates of pneumonia and hospitalizations for respiratory problems occurred compared to the use of home ventilation.

In patients with hypoventilation syndromes, low daytime PaO_2 or nocturnal saturation is considered to arise primarily from alveolar hypoventilation associated with pump failure. However, in a number of patients concomitant lung damage will create ventilation-perfusion inequality which requires the use of carefully controlled oxygen therapy in addition to positive pressure therapy to maintain SpO_2 above 90% (147, 256, 266, 303). As supplemental oxygen impairs the ability of oximetry to detect hypoventilation (137), additional monitoring to assess CO_2 is necessary.

Continuous Positive Airway Pressure

When hypoventilation is accompanied by significant upper airway obstruction and at least moderately preserved respiratory muscle strength, continuous positive airway pressure (CPAP) can be an effective and well tolerated therapy option. The majority of patients with OHS have at least concomitant moderate OSA (79,195,288,316), and in around 80% of cases treatment with CPAP will be effective (193, 266, 316, 339). Primarily obstructive events have also been reported in young individuals with DMD (197, 381) which has been managed initially with CPAP therapy (381). However, the short transition time from effective CPAP to the need for bilevel ventilation supports the recommendation that DMD patients with hypoventilation be commenced on bilevel support regardless of the degree of obstruction contributing to hypoventilation (381). CPAP may also have a role in the management of patients with spinal muscular atrophy, not only treating obstructive events but stabilizing respiratory complications arising from bronchitis with mucus hypersecretion and recurrent infections (191). However, unless OSA is the major contributing factor to hypoventilation and appropriate monitoring of awake and nocturnal gas exchange clearly demonstrates normalisation of breathing and CO_2, most patients with hypoventilation syndromes, particularly those with more progressive disorders, are better served by treated with noninvasive ventilation.

Noninvasive Ventilation

Domiciliary ventilation has been used for decades to reverse respiratory failure and prolong survival in patients with severe chronic alveolar hypoventilation (26, 113). Initially, this was carried out using either negative pressure devices such as tanks or cuirass ventilators or invasively with positive pressure therapy applied through a tracheostomy. In many circumstances, ventilation was offered only to the most severely affected individuals and consequently therapy was required on a continuous basis.

The widespread availability and acceptably of methods to provide noninvasive nocturnal positive pressure ventilation (NPPV) suitable for home use has had a significant impact on the management and outcomes of patients with chronic hypoventilation syndromes. In addition to improving awake blood gases, especially $PaCO_2$, the long-term use of NPPV has been linked to improvements in daytime symptoms (156,248), sleep quality (42,86,156,353), quality of life (81,156,178,396,422), reduced hospitalizations (19,36,176), increased functional capacity (161, 351, 356), and reduced mortality (53,60,251,283,364). Within this wide spectrum of reported benefits there are considerable differences in patient reported outcomes depending on the underlying diagnosis, presenting symptoms and disease progression (156). How much the patient uses therapy also impacts on the therapeutic response, with a minimum of 4 to 4.5 hours NPPV use required before a consistent change in $PaCO_2$ occurs (266,274,281) (Fig. 8). This latter point highlights the importance of maximizing patient comfort on therapy to promote use and subsequently outcome.

Methods and modes of noninvasive ventilation

Nocturnal noninvasive ventilation can be delivered using different types of ventilation as well as different modes of ventilatory support. The two major types of ventilation are volume and pressure preset ventilation. With volume preset ventilation, the ventilator provides a set volume over a specific time and was the type of ventilation initially used for home care (120, 313, 315). Pressure preset ventilation in the form of bilevel devices became widely available in the 1990s, and is now the primary method of delivering NPPV (139,176,231). Volume preset ventilation provides the advantage of delivering a more stable tidal volume to the patient despite changes in sleep stage or body position, albeit with a variable peak inspiratory pressure. In contrast, pressure preset devices are more reliable for maintaining set airway pressure and compensating for some degree of leak. However, delivered tidal volume is more variable and unpredictable (425), and depends upon an interaction between the pressure set, inspiratory effort by the patient, lung and chest wall compliance, and the inspiratory time over which the inspiratory

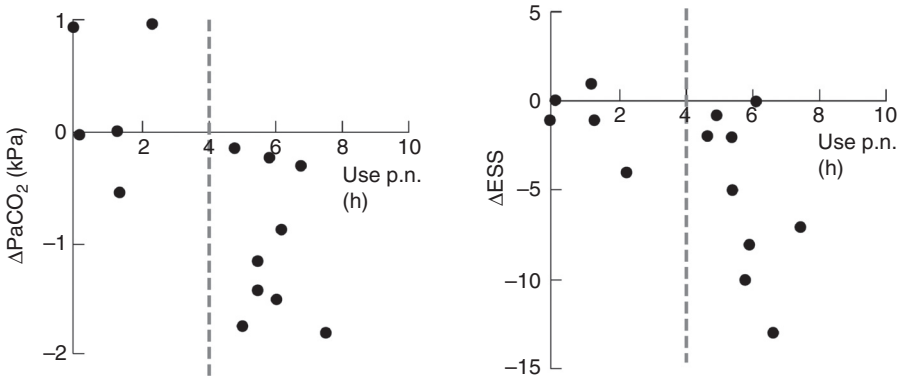

Figure 8 The "dose response" of NPPV showing the change in $PaCO_2$ (left panel) and daytime sleepiness (ESS) (right panel) in patients with neuromuscular and restrictive thoracic disorders after 3 months of therapy. The dotted line represents the threshold below which NPPV does not have a consistent effect on $PaCO_2$ or daytime sleepiness. Abbreviations: ESS—Epworth Sleepiness Scale; Use p.n.—use per night. [Reproduced from Thorax, Nickol et al. 60:754-760, 2005 (281) with permission from the BMJ Publishing Group Ltd.]

pressure is delivered (298, 324). Randomized studies comparing these two forms of ventilation have failed to find a clear advantage of one approach over the other in terms of nocturnal hypoventilation control or improvements in daytime measures (132,257,398,425). A retrospective study of over 200 patients using home ventilation found no difference in the probability of continuing NPPV or in survival between pressure and volume ventilation (176). However, uncontrolled trials suggest that patients poorly responsive to one form of ventilation may do much better when switched to the alternative method (354, 366). A recent report found that nocturnal and daytime gas exchange was better in patients with ALS using volume ventilation compared to those managed with pressure preset devices, although no difference in survival was seen (344). It should be noted however that the inspiratory pressure support delivered during pressure preset ventilation was only 8 cmH_2O, providing substantially lower tidal volumes compared to volume ventilation (415 ± 137 mL vs. 782 ± 108 mL, $P < 0.001$). A large European survey of home ventilation found that volume ventilation was more likely to be used in patients with neuromuscular disorders than in lung diseases (231). An important advantage of volume ventilation in patients with neuromuscular disorders is the capacity to provide comfortable mouth piece ventilation and breath stacking (34), essential adjunctive therapy techniques in patients with progressive neuromuscular disorders.

To achieve the more stable tidal volume delivery of volume ventilation with the greater comfort of pressure ventilation, a hybrid form of ventilation known as volume-targeted pressure support has more recently been developed for home ventilation. With this form of ventilation, the device delivers a variable level of inspiratory support breath-to-breath to meet a target volume set by the clinician. This method of ventilatory support has been compared to standard pressure support in a number of studies across a range of pathologies (7, 90, 177, 274, 291, 377). Currently, there is no strong evidence that volume targeted pressure support provides substantial improvements in sleep hypoventilation and daytime outcomes compared to more traditional pressure support ventilation in the routine management of nocturnal hypoventilation syndromes. It is possible that this technique may provide more effective sleep ventilation than standard ventilation techniques in centers relatively inexperienced with NPPV therapy or where access to nocturnal titration and monitoring of the effectiveness of therapy is limited (274). However, in a study of patients with nocturnal hypoventilation secondary to neuromuscular disease the degree of patient-ventilator asynchrony (PVA) and nocturnal oxygenation was lower during volume targeted pressure support compared to more traditional pressure controlled ventilation (90). This finding may relate to the circuit configuration used in the study, with several reports showing that the performance of volume targeted ventilation devices can be compromised by the presence of unintentional leak (129), especially if double-limb circuits (198) or active expiratory valves are used (69). Further investigation is needed to more clearly define which patient groups and under what circumstances these more sophisticated ventilation options should be used.

Modes of ventilation

In addition to the type of ventilation delivered, the mode of ventilatory support must also be considered in ensuring control of nocturnal hypoventilation is achieved. Timed (pressure ventilation) or control (volume ventilation) modes provide full ventilatory support whereby each breath is triggered only by the ventilator. Partial support occurs when the device is set so that the patient is required to trigger the device into the inspiratory phase (Spontaneous mode), while a back up rate can be provided if the patient fails to trigger the device within a set time window (Spontaneous timed or Assist control mode). Despite potential differences in triggering, residual respiratory effort and comfort, only a few studies have compared the efficacy of spontaneous/assisted (S) mode

Table 3 Types of Positive Airway Pressure Used in the Management of Hypoventilation

Mode or device	Comments
CPAP	Effective if upper airway loading or obstruction the major factor contributing to hypoventilation. Respiratory drive and muscle strength need to be sufficient to ensure adequate ventilation maintained
Pressure preset ventilation (bilevel)	
Spontaneous mode	Suitable for patients with good respiratory drive able to trigger inspiratory support consistently especially in REM sleep. Can produce central events if pressure support too high or frequent arousals.
Spontaneous-timed mode	Ensures a mandatory respiratory rate is maintained. If rate set sufficiently high can achieve passive ventilation
Timed mode	If set correctly, maximizes reductions in patient effort. Patient discomfort if poor synchrony
Volume-targeted pressure support	Autotitration of pressure support to ensure delivery of set tidal volume or minute ventilation. Maintains set volume despite changes in respiratory mechanics, sleep stage, and body position
Volume preset ventilation	Delivers a stable tidal volume to the patient with variable airway pressure, but is less effective than pressure ventilation in leak compensation
Adaptive servo ventilation	Variable inspiratory support designed for disorders characterized by central apneas and low CO_2. Adjusts support inversely to oscillations in breathing to smooth out ventilation. Not suitable for hypoventilation syndromes.

to spontaneous-timed/assist-control (ST) or timed/controlled (T) modes of ventilation in patients with nocturnal hypoventilation. Recently, published guidelines for the titration of bilevel settings during PSG recommend commencing in the spontaneous mode (43). However, in the presence of inspiratory muscle weakness or reduced drive, the patient will be unlikely to consistently trigger the device into inspiratory support during sleep. Consequently, the ST and T modes are used when there is underlying neuromuscular weakness (176, 355, 370), if the baseline respiratory rate is low or if central apneas are present during baseline studies (43) (Table 3).

One early study suggested that a T rather than S mode should be generally used for nocturnal ventilation, as effective minute ventilation was higher in the T mode for a given level of inspiratory pressure (298). Furthermore, the S mode produces greater respiratory instability with central apneas and desaturation. As this study was performed in young healthy subjects with normal awake $PaCO_2$ and without nocturnal hypoventilation, the applicability of findings to patients with hypoventilation syndromes was unclear. A randomized single night cross over study compared the effectiveness of spontaneous to the ST mode during sleep in patients with chronic respiratory failure already established on home NPPV (332). In this study, both modes of ventilation were found to be equally effective in correcting hypoxemia and reducing hypercapnia during sleep (332). However, no monitoring of sleep or breathing was undertaken, so differences in sleep architecture and residual respiratory events between the modes cannot be determined from this study. When using the spontaneous mode it is important to ensure that the patient is consistently able to trigger the device, especially in REM sleep. In some cases, failure to do so may reflect incorrectly set levels of expiratory positive airway pressure (EPAP) (4, 126) while in others the spontaneous mode is simply not appropriate due to poor respiratory drive or weak inspiratory muscles (370). Excessively high levels of inspiratory support in the Spontaneous mode can lead to "over assistance," and if CO_2 is reduced below the apneic threshold, respiratory instability and central apneas will develop (4, 126, 299) (Fig. 9).

In clinical practice, many clinicians favor the ST mode over a purely timed one (139, 176) as it provides the opportunity for the patient to initiate and terminate a breath, which may reduce PVA, while still ensuring a mandatory back up rate is delivered. Additionally, the inability to trigger additional breaths in the timed mode may mean that this mode is less tolerable and requires a longer period to achieve adaptation. Conversely, by suppressing the patient's own inspiratory efforts and achieving passive ventilation, the timed mode may produce a greater unloading of the respiratory muscles than assisted modes of ventilation (99, 132).

Using retrospective data from posttuberculosis patients, Tsuboi and colleagues (397) found that awake $PaCO_2$ was reduced to a greater extent in those using a timed mode compared to those treated with a ST mode. However, the rate and inspiratory pressure support used in the timed mode were set significantly higher than in the ST mode, favoring more effective ventilation in the timed mode. Other uncontrolled trials in patients with chest wall restriction (272) and COPD (99) reported no significant difference between timed and spontaneous timed modes in terms of time required for adaptation, tolerance, or compliance with therapy. Whether greater respiratory muscle rest was achieved in the timed mode compared to ST in these studies is unknown as nocturnal monitoring of muscle activity was not performed.

When using the ST mode, whether the patient is "passively" ventilated or receives partial ventilatory support will depend largely on the back up rate set by the clinician. Back up rates on pressure preset devices have often been set relatively low (i.e., 10-12 breaths/min), primarily with the aim

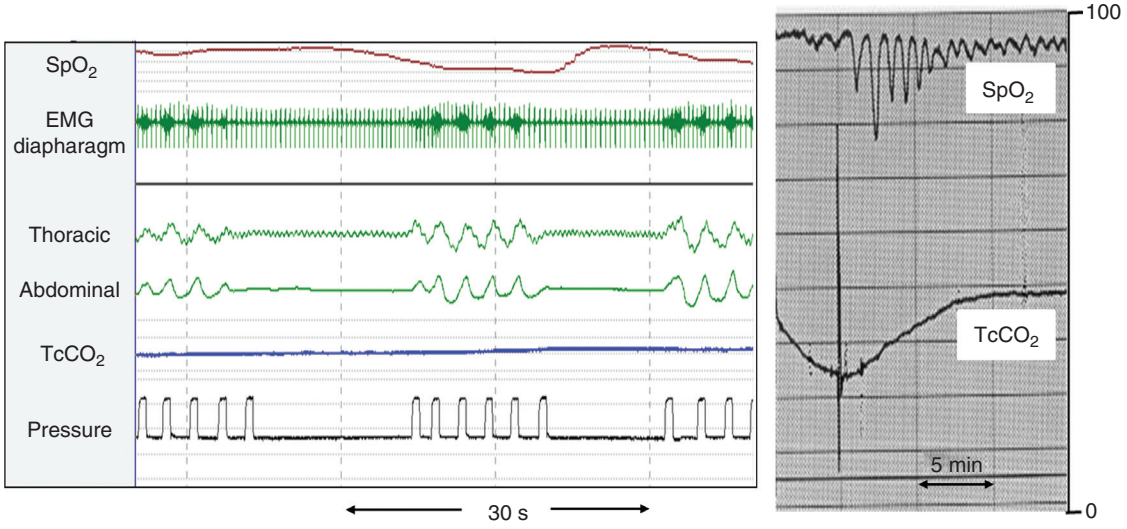

Figure 9 Illustration of overventilation during the spontaneous mode of bilevel ventilation. Note the markedly reduced $TcCO_2$ (right panel). Reducing CO_2 below the apneic threshold will create central events which are associated with significant oxygen desaturation. Note the loss of diaphragm EMG activity along with absence of respiratory efforts on the thoracic and abdominal bands. This breathing abnormality occurs commonly at sleep onset or following arousal if excessive levels of pressure support are used in the spontaneous mode.

of preventing apneic periods (127, 132, 176). Setting higher back up rates (close to or slightly above the patient's own spontaneous rate) is likely to reduce patient triggering and achieve more passive ventilation (84, 424). In young stable patients with cystic fibrosis, higher back up rates produced larger reductions in respiratory effort and greater increases in ventilation compared to the use of lower rates (130). In patients with OHS, higher back up rates in the ST mode are associated with reduced patient triggering (i.e., more passive ventilation) (84, 274), a more stable pattern of breathing (84), better nocturnal control of nocturnal $PtcCO_2$ and greater improvements in daytime CO_2 (274). High back up rates along with high inspiratory pressures have also been advocated by a number of groups to improve nocturnal ventilation and daytime outcomes in patients with COPD—termed "high-intensity" NPPV (112, 424). However, results from a small randomized crossover study have challenged this approach, suggesting that the improvements seen in blood gases may arise primarily from the high inflation pressures used rather than the high machine rate (273). In this study, compliance, awake blood gases, or sleep quality did not differ between the two approaches. These findings need to be viewed with caution given the small sample size, high dropout rate, and limited overnight monitoring that was undertaken in this study. Furthermore, the "high" back up rate was set at 16 breaths per minute, significantly lower than the 19 to 21 breaths per minute usually used in similar studies of high intensity NPPV (62, 112, 423, 424). Consequently, reported outcomes with the ST mode vary between studies depending on whether the machine back up rate used was set high enough to achieve passive ventilation producing results similar to a timed mode, or a comparatively low back up rate in comparison to the patient's own spontaneous breathing rate, such that a more assisted mode of support is provided. To maximize the efficacy of NPPV, further work is needed to determine how best to set the back up rate in patients in whom respiratory drive and triggering are maintained during sleep.

Setting pressure support and end expiratory pressures

As volume preset ventilation does not compensate for leak, tidal volumes of 10 to 15 mL/kg are generally used to achieve adequate nocturnal ventilation with NPPV (44, 131, 220, 398). In contrast, lower target tidal volumes of 7 to 10 mL/kg of ideal body weight are generally effective with pressure ventilation, with optimal volumes varying according to the underlying disorder and respiratory rate (44). With these latter devices increasing the inspiratory positive airway pressure (IPAP) augments inspiratory effort, which increases tidal volume while decreasing the work of breathing. Patients with reduced thoracic or lung compliance may require more substantial IPAP levels to achieve effective ventilation compared to those with normal or high respiratory system compliance. Most of these home devices also provide an EPAP which is used to stabilize the upper airway (43, 273, 316), to offset intrinsic PEEP and improve inspiratory triggering (126, 409), to improve CO_2 washout from the mask (337), or recruit alveoli to improve gas exchange (116, 324). With some home ventilators, altering EPAP impacts on the level of ventilatory assistance provided as the device will not automatically adjust the inspiratory pressure to ensure the same level of pressure support is provided. Reducing the IPAP-EPAP difference (or pressure support) can adversely impact on improvements in CO_2 (58). Excessive levels of EPAP may also increase the effort to exhale, and in those with lung disease this can

increase end expiratory lung volumes, thereby contributing to patient discomfort and intolerance of therapy. In patients with neuromuscular and skeletal disorders, low level EPAP (5 cmH_2O) has been shown to improve nocturnal gas exchange and sleep quality (116). In patients with OHS where upper airway obstruction is common, failure to provide adequate EPAP to control upper airway patency results in the persistence of oxygen desaturation and sleep disturbance irrespective of the mode of ventilation used (84, 377).

Pressure levels used during NPPV will be influenced by the goals of therapy and the nature of the baseline sleep breathing disorder. Where the aim of therapy is to unload the inspiratory muscles, Tuggey and Elliott (399) demonstrated that there was little benefit in increasing the inspiratory pressure above 20 cmH_2O in patients with chest wall restriction and COPD. In contrast, if higher minute ventilation is required this can be achieved in both groups by increasing the levels of pressure or volume ventilation, despite parallel increases in mask leak (399). Increasing pressure support also reduces inspiratory muscle activity in patients with OHS, although much lower maximum inspiratory pressures have been evaluated (296). Therefore, the IPAP level is usually increased as high as the patient comfortably tolerates. In patients with thoracic cage abnormalities and chronic hypoventilation, a correlation between absolute IPAP levels and improvement in VC has been reported, while the degree of pressure support (i.e., IPAP-EPAP difference) is related to the change in awake $PaCO_2$ achieved with NPPV (58). There has been some concern that higher inspiratory pressure levels with corresponding increases in leak may interfere with sleep quality and affect patient tolerance to therapy, although a small study of patients with COPD did not find this to be the case. Using a high-pressure (mean 29 $\pm$ 4 cmH_2O) or low-pressure (mean 14 cmH2O) ventilation strategy, Dreher and colleagues (110) found sleep quality was similar. Moreover, higher IPAP levels produced significantly better control of nocturnal hypoventilation with a mean difference in overnight $PaCO_2$ of 6.4 mmHg (95% CI, -10.9 to -1.8; $P < 0.01$).

Low levels of inspiratory support, rather than being more comfortable for the patient, may contribute to poor tolerance of therapy and less favorable outcomes if sufficient levels of pressure support to control hypoventilation and hence symptoms are not provided. In patients with chest wall disease, failure to reduce awake $PaCO_2$ below 50 mmHg after a month of therapy was related to a threefold increase in the probability of death, highlighting the importance of CO_2 control (247). On the other hand, higher inspiratory pressures may initially be difficult for the patient to tolerate (101, 408), requiring a more prolonged period of adaptation (240, 399, 424). Care needs to be taken if the high levels of inspiratory support are delivered using the Spontaneous mode as asynchronies, especially ineffective efforts and central events, are common and have been associated with poorer tolerance to therapy (68).

While high intensity NPPV in patients with COPD has been associated with improved nocturnal and awake gas exchange compared to low-pressure support approaches (110, 112, 225, 251, 423), this strategy may also reduce cardiac output and other measures of cardiac performance (239). The impact of this on patients' pre-existing cardiac disease is unclear at present, and as pointed out by the investigators, requires further evaluation. Furthermore, this was an acute physiological study, so whether the degree of change in cardiac performance occurs if inspiratory pressures are titrated upward over a more prolonged period of time is unknown (240). Another important consideration when using high pressure support levels is the increased tidal volumes this can generate, carrying with it the potential to overventilate some patients, especially if a spontaneous mode of ventilation is used or high leaks are present (4, 126, 298).

Other ventilator settings

There are a number of ancillary ventilator parameters that also need to be set by the clinician, designed to optimize patient-ventilator interactions or improve patient comfort. An inspiratory time needs to be set for machine delivered breaths, bearing in mind the respiratory rate and hence the inspiratory to total respiratory cycle time. It is recommended this be set at 30% to 40%, with shorter inspiratory ratios usually used in patients with lung disease to maximize exhalation time and promote lung deflation (4, 99, 273, 423), while longer inspiratory ratios are used in those with restrictive thoracic disorders (43, 397). Some devices permit the clinician to set a minimum and maximum time window for inspiration even with patient triggered breaths, which can be valuable in preventing premature or prolonged cycling. With many home ventilators, both the inspiratory trigger and expiratory cycling sensitivities can be altered to better match the delivery of airflow from the device to the patient's own respiratory pattern. Pressurization slope or rise time refers to time taken for the device to reach the target pressure (324). A fast rise time is often more comfortable and provides greater patient-ventilator synchrony in patients with a high respiratory drive, whereas those with a lower drive may be more synchronous and comfortable with a slower rise time (163). In patients with COPD, a faster rise time during NPPV has been reported to provide better unloading of the respiratory muscles, although this may come at the expense of greater air leaks and poorer tolerance (322). Consequently, the rise time is adjusted to maximize patient comfort. While each of these parameters are set with the goal of improving patient comfort and ventilation, delivery of the target inspiratory support can be reduced if the interaction between these additional settings is not fully appreciated (146).

Implementing and monitoring nocturnal ventilation

The type of monitoring regularly used to determine the efficacy of ventilation during sleep varies considerably between regions and centers (139), ranging from simple oximetry with or without transcutaneous carbon dioxide monitoring

performed in the home through to attended PSG in a sleep laboratory (43, 139, 233, 234, 333). Many see the latter as a difficult undertaking especially for patients with significant physical disability and high care needs, and with limited resources available to conduct PSG, the majority of reports evaluating NPPV have used more simplified methods to assess the efficacy of therapy and adjust settings during sleep.

Nocturnal oximetry is the primary method of monitoring NPPV. A normal nocturnal oximetry trace in conjunction with improvements in awake $PaCO_2$ and symptoms is often considered sufficient to ascertain if a patient is doing well on therapy (118). However, if abnormalities are seen, the clinical response to NPPV is suboptimal or the patient is using nocturnal oxygen in conjunction with NPPV more detailed monitoring is necessary (118, 175). Although daytime arterial blood gases are frequently used to assess the efficacy of therapy, they may not accurately capture the persistence in hypoventilation during NPPV even when used in conjunction with nocturnal oximetry (219, 276, 294). An arterial blood gas taken on awakening may show changes in night to morning CO_2 levels, but a delay in sampling or changes in ventilation with wakefulness will readily alter this measurement (175, 276). Attention to the morning bicarbonate is probably a better guide to possible overnight hypoventilation than the arterial CO_2 (276). Consequently, to more confidently identify whether NPPV is adequately controlling nocturnal hypoventilation, some assessment of nocturnal CO_2 is necessary.

Earlobe capillary gases can be performed during sleep and have been used to monitor ventilation and guide the adjustment of ventilator settings in some centers (58, 99, 112). Although capillary gases provide a good estimate of $PaCO_2$ and pH (428), like arterial blood sampling this technique is limited by the intermittent nature of the procedure and the likelihood of waking the patient and altering ventilation while obtaining the sample. The two techniques available for providing continuous noninvasive monitoring of carbon dioxide are end-tidal ($EtCO_2$) and transcutaneous ($PtcCO_2$) carbon dioxide monitoring. However, end-tidal CO_2 does not reliably reflect $PaCO_2$ in patients with chronic respiratory failure undergoing NPPV and therefore is not recommended (175). Transcutaneous carbon dioxide monitoring has been shown to have good agreement with arterial measurements (378) and while time lag and calibration drift can impact on accuracy (92), this method is more accurate than $EtCO_2$ (164). Ongoing technical improvements in $PtcCO_2$ sensors have led to greater stability and reliability of these devices in recent years, rendering them even better suited to monitoring alveolar ventilation during nocturnal ventilation (376) and facilitating the appropriate adjustment of ventilator settings.

Although changes in gas exchange can be identified using either nocturnal oximetry or transcutaneous carbon dioxide, simultaneous monitoring using both techniques is clinically more informative. In a study of overnight ventilation in patients with DMD, Nardi and colleagues (276) found changes in $PtcCO_2$ were more sensitive than changes in SpO_2 for detecting moderate prolonged leak, while SpO_2 was more sensitive in detecting transient severe leak. However, in most situations even a combination of $PtcCO_2$ and SpO_2 monitoring, while identifying the presence of suboptimal ventilation, cannot distinguish the cause of the problem (175). In recent years, more extensive nocturnal monitoring has demonstrated how common abnormal nocturnal breathing during NPPV is and the impact this has not only on gas exchange (127), but sleep quality (126, 151) and other patient reported outcomes (4). Importantly, these events are often "silent," with neither the patient being aware of a problem nor daytime clinical review easily uncovering these nocturnal abnormalities (89, 127). Consequently, there is now growing awareness of the importance of more extensive nocturnal monitoring to identify and correct more subtle problems arising during NPPV.

PSG and cardiorespiratory polygraphy (PG) provide clinically relevant information regarding sleep quality and/or patient-ventilator interactions that cannot be identified with SpO_2/$PtcCO_2$ monitoring alone. Recent guidelines from the American Academy of Sleep Medicine recommend the use of PSG for the titration of NPPV, especially in patients where OSA in conjunction with sleep hypoventilation is present (43). In some centers, PSG is routinely used to adjust ventilator settings at the completion of the implementation process (86, 125, 139, 233, 316, 333), ensuring sleep has not been adversely affected by NPPV through leak, PVA or residual respiratory events. Adler and colleagues (4) identified eight of 32 patients with severe COPD treated at their center with NPPV who were experiencing severe morning dyspnea when removing ventilatory support. Using PSG, patients underwent two overnight studies: the first on their usual settings followed by a second study where the ventilator settings were adjusted to reduce breathing abnormalities and PVA. While the changes in settings had no impact on sleep quality or arousal index (though the latter was in the normal range in both studies), PVA index was reduced significantly from 40.5 ± 32 to $6.7 \pm 7.3\%$. Furthermore, there was a marked reduction in morning dyspnea as measured by the modified Borg scale, a measure of a subject's perceived breathlessness ranging from 0 (Nothing at all) to 10 (Very, very Severe). Slight reductions in nocturnal and morning CO_2 levels were also seen. Attended PSG can also confirm the patient has attained REM sleep, the period where sleep hypoventilation is generally at its worst, permitting the adjustment of settings to ensure sufficient pressure support is being provided during this sleep stage. However, PSG is costly, disruptive for the disabled patient and generally resources available to perform these studies are limited.

PG provides the same detailed information on cardiorespiratory parameters as PSG, at lower cost and, paradoxically, with less interference to sleep quality (89). Regardless of whether or not sleep is measured, monitoring leak and patient-ventilatory synchrony are key aspects of implementing and reviewing the effectiveness of nocturnal NPPV.

Simultaneous monitoring of patient respiratory outputs (flow, chest wall movement, SpO_2) and device outputs (mask

pressure, leak) allows the clinician to identify any mismatching between the patient and the ventilator. These asynchronies can be categorized as affecting EPAP to IPAP transitions (ineffective triggering, double triggering or autotriggering) or IPAP to EPAP transitions (premature or prolonged cycling) (406) (Fig. 10). Recent studies have highlighted how common such events can be during nocturnal NPPV across all patient categories (11, 126, 127, 151), and PG like more complex PSG can readily identify the presence of these abnormalities. However, until recently a systematic approach to identifying and defining these abnormal respiratory events on PG or PSG has been lacking. Two consensus papers from the SomnoNIV working group published in 2011 and 2012 have outlined proposals for identifying and classifying these events, as well as providing hypotheses regarding potential causes of these events and suitable approaches to correcting the problem (145, 324). One of the conclusions of this group was the issue related to nomenclature defining abnormal respiratory events in sleep during spontaneous breathing not being applicable to PG and PSG tracings during NPPV. Indeed, it can be difficult to distinguish between central and obstructive events occurring with NPPV (85). Not all studies have demonstrated an improvement in the apnea-hypopnea index following NPPV despite improved symptoms (84, 147, 377), likely arising from failure to recognize and adequately control upper airway obstruction. Pulse transit time has been shown to be a surrogate marker of inspiratory effort during NPPV, although the technique has a number of limitations and has only been studied during NPPV in patients with OHS (85). However, a simple noninvasive tool to determine if an event is obstructive or central is clinically relevant as the change in ventilator settings needed to correct the problem differs.

Unintentional leaks out the mouth or around the mask are inevitably present during NPPV, as well as during tracheostomy ventilation when uncuffed tubes are used (89). Although pressure preset devices are better able to compensate for leak than volume preset machines, a substantial proportion of additional flow simply contributes to increased leakage and may only marginally increase tidal volume (375). Increasing leak can increase PVA (66, 89). Furthermore, even with pressure preset devices, if leaks are large the set pressure support and EPAP levels may not be maintained (400), effective ventilation can be reduced and overnight $PtcCO_2$ increased (277, 389). In bench studies, even alterations in intentional leak (i.e. leakage from ports placed near on in the mask designed to vent exhaled air from the circuit) can impair the performance of pressure preset devices (49). High intentional leak potentially affect the maintenance of inspiratory pressure (49), while low intentional leak can create CO_2 rebreathing (237). Therefore, any monitoring of nocturnal NPPV should include leak monitoring.

A drawback of PG is the inability to quantify sleep disturbances such as microarousals which could be a significant factor in poor patient response to NPPV. However, this limitation may be overcome. Recent work suggests that pulse wave amplitude reduction could be used as a surrogate marker of microarousals related to respiratory events during NPPV (3). However, this is preliminary work carried out in patients with OHS only, so it is not clear if the findings will be applicable to other patient groups, or in circumstances of high leak or PVA. Nevertheless, the data illustrate the potential for the development of simpler, less expensive techniques for identifying and monitoring aspects of sleep without the need for more time consuming EEG measurements. Importantly, such techniques could be performed in the home and as part of routine monitoring, with little disturbance of the patient.

An important development over the past few years has been the technical improvements in home ventilator design which have incorporated monitoring software and expanded data storage capacity into these devices. In addition to recording usage and compliance of therapy, home ventilators now have inbuilt flow and pressure sensors capable of monitoring and storing breath by breath data over several days, and providing compressed data from multiple ventilation parameters acquired over many months. In addition to flow and pressure signals, information about tidal volume, leak, respiratory rate, patient triggering and residual obstructive/central events are recorded by these devices. These data can be viewed in real time or downloaded and reviewed later to assess the efficacy of nocturnal ventilation and make appropriate adjustments (175, 323). Following bench testing to confirm the accuracy of leak and minute ventilation provided by one home bilevel ventilator, Rabec et al. (323) assessed the efficacy of ventilation in 169 patients using these machine-derived outputs in conjunction with oximetry. They found this approach provided a good estimation of the global efficacy of ventilation, identifying abnormalities and enabling modification of settings to the extent that the need for PG/PSG was only necessary in 16% of cases. However, only one brand of device was tested. In another study of patients with ALS, remote monitoring of ventilator data permitted frequent modifications of settings to improve patient comfort and machine synchrony (307). Although remotely monitored patients only showed a trend towards better compliance and survival compared to those allocated to usual hospital/office adaptations of NPPV, they did not fare worse and required significantly fewer hospital and emergency room admissions. However, there is substantial variability in both the performance of ventilators and the reliability of ventilator-derived parameters (129,175,237,368). The way in which leaks are estimated and the precision of leak estimation varies significantly between devices (87), while tidal volume is frequently underestimated by the device (87, 129). Consequently, clinicians need to use caution when interpreting data obtained from device software (175), especially when comparing values generated from different devices or when there is a switch of masks with different intentional leaks (237). While some work has been undertaken validating leak and tidal volume measured by device software, other machine-derived parameters have not yet been independently tested (175). Moreover, there is currently no consensus on which parameters reported by ventilator software are the most clinically relevant to monitor (175, 238, 300), and if

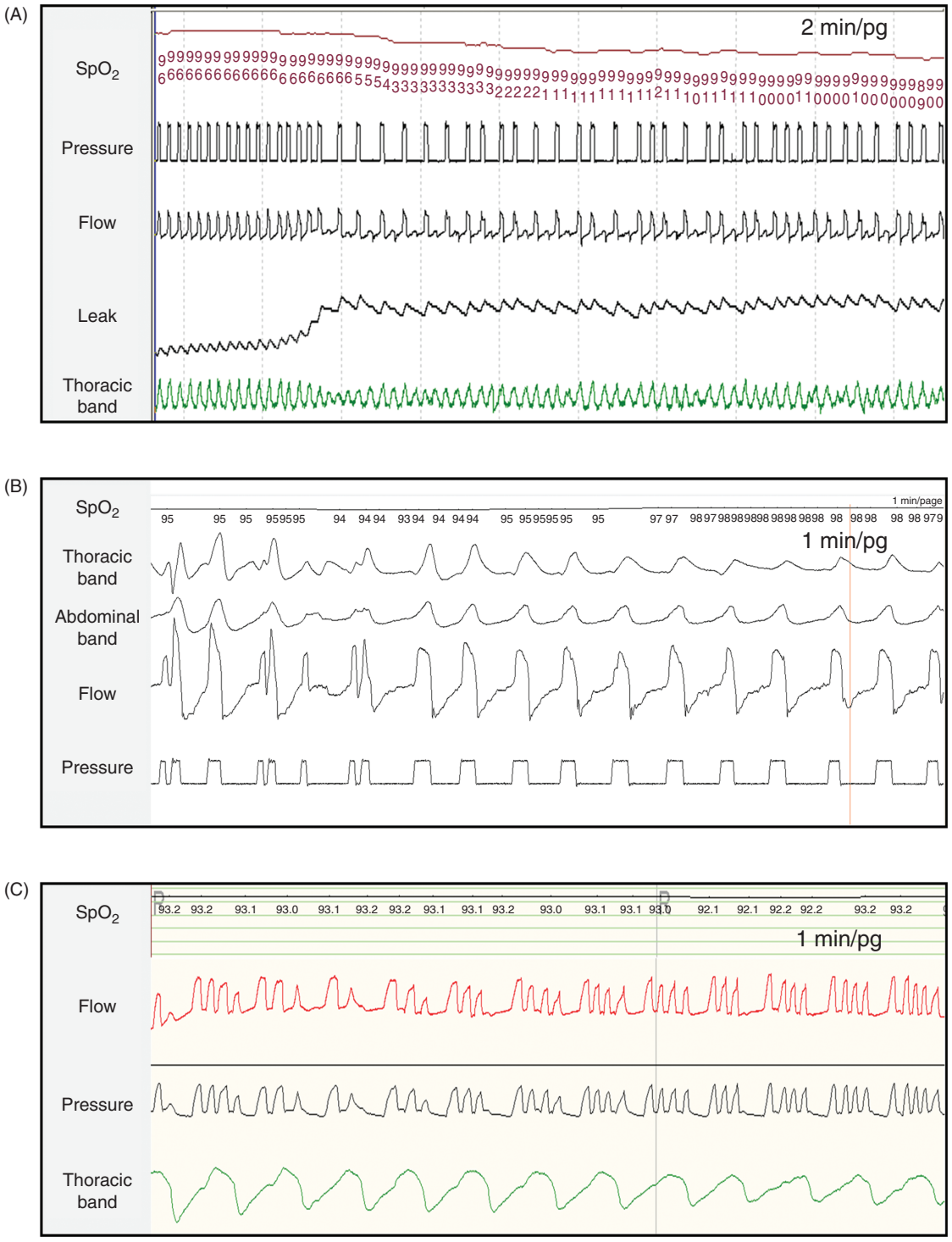

Figure 10 Examples of the more common asynchronies that can occur during NPPV therapy. Such events may not be apparent during wakefulness but can impact on the quality of ventilation during sleep. Panel A illustrates ineffective efforts caused by high leak. Small upward deflections can be seen in the airflow channel without a corresponding EPAP to IPAP transition on the pressure trace. Inspiratory efforts go unrewarded. Note also the generalized reduction in thoracic band movement during the leak period and a gradual fall in SpO_2. The first, third, and fifth breaths on the airflow and pressure channels in Panel B show the machine has cycled twice with a very short expiratory period between the two during a single inspiratory effort (Thoracic and Abdominal bands). This can indicate pressurization is too short compared to inspiratory demand or the level of inspiratory support is too low (406). Panel C illustrates autotriggering—a rapid succession of multiple machine pressurizations clearly above the patient's native respiratory rate (151). This can occur if the inspiratory trigger has been set too low, especially in the presence of leak (406).

abnormalities are detected and corrected, what if any impact this has on clinical outcomes. Nevertheless, combining clinically relevant machine-derived data such as tidal volume and leak with physiological measures such as SpO_2, $PtcCO_2$, and arterial blood gases can substantially improve our basic monitoring of nocturnal NPPV (175, 300).

Mechanisms underlying improved daytime breathing

Understanding how NPPV improves ventilation and gas exchange when the patient is actually on therapy is straightforward. However, how such improvements extend to spontaneous daytime breathing is less obvious and has been the subject of some speculation. Since maintaining an appropriate level of spontaneous ventilation depends on the interplay between load, capacity, and drive, each mechanism has been proposed to underlie the improvements seen in awake CO_2 following the commencement of NPPV.

Improvements in respiratory muscle strength and endurance (capacity) (58, 147, 153, 312, 350) and pulmonary mechanics (load) (58, 59, 160, 424) following the commencement of NPPV have been reported in some, but not all, studies (203, 256, 380, 426). However, even when present these changes are often small and therefore unlikely to have a major impact on spontaneous ventilation (8, 101, 281). In contrast, numerous studies have shown improvements in the ventilatory response to CO_2 following the use of NPPV (8, 79, 93, 281, 330), with significant correlations found between changes in daytime CO_2 and changes in CO_2 chemosensitivity (93, 98). Hence, a change in ventilatory responsiveness to CO_2 appears to be the principle mechanism by which NPPV reverses daytime respiratory failure in patients with neuromuscular weakness and chest wall deformity (281), as well as those with obesity hypoventilation (93, 330). Reducing CO_2 sufficiently during sleep through ventilatory support permits a lowering of previously elevated bicarbonate and improved CO_2 chemosensitivity (144), allowing a more appropriate change in ventilation to occur in response to an alteration in $PaCO_2$. By this downward resetting of respiratory sensitivity to CO_2 an improvement in awake ventilation would be achieved.

In addition to improved drive, changes in respiratory load through improvements in pulmonary mechanics appear to be an additional major mechanism contributing to improvements in awake CO_2 in patients with COPD. Several studies have demonstrated a correlation between the reduction in CO_2 following NPPV and a decrease in gas trapping (119, 280). Nocturnal ventilatory support in patients with COPD can induce significant changes in spontaneous breathing pattern, increasing tidal volume and reducing respiratory rate (101, 102, 278). A slower deeper pattern of breathing allows more time for lung emptying during expiration with the effect of promoting lung deflation (102). Reductions in lung hyperinflation following NPPV in stable COPD patients have been shown to have significant positive effects not only on awake CO_2, but also exercise capacity (101), breathlessness (101) and survival (59).

Understanding the mechanisms by which NPPV achieves improvements in awake spontaneous breathing in different patient groups is relevant to clinical practice. It provides some guidance as to which patients may gain the greatest benefits from therapy and provides a physiologic target on which to base ventilator settings (58, 117). In all patient groups, a key goal of NPPV is to optimize control of nocturnal CO_2 to produce significant improvements in awake CO_2 levels (256, 280, 423, 424). Despite the lack randomized trials evaluating NIV in patients with neuromuscular and skeletal chest wall disorders, the clinical evidence overwhelmingly demonstrates significant improvements in daytime CO_2 and health outcomes are achieved when effective nocturnal ventilation is used. In contrast, the role of NIV in reversing respiratory failure in patients with stable COPD has remained controversial due to inconsistencies in reported benefits (81, 112, 203, 225, 251, 380, 423). It has been argued that many previously conducted randomized trials failed to show significant reductions in awake CO_2 values because sufficiently high inflation pressures to effectively reduce CO_2 during sleep were not employed (112, 117, 203, 256, 349). For instance, McEvoy and colleagues (251) used a mean pressure swing of around 8 cmH_2O, reducing the overnight rise in $PtcCO_2$ by 4 mmHg, with changes in awake $PaCO_2$ of approximately 2 mmHg. In contrast, studies using inflation pressures of 18 to 30 cmH_2O have reported falls in overnight CO_2 of around 9 to 12 mmHg and changes in awake $PaCO_2$ ranging from 4 to 12 mmHg (59, 112, 256, 423). High inflation pressures also appear necessary to induce persisting changes in breathing pattern when the patient is off ventilatory support (101, 102, 278). However, care needs to be taken to ensure the expiratory period is sufficiently long to allow lung emptying otherwise this strategy could increase PEEPi and worsen the load placed on the respiratory system (280). Not only would this impact on the effectiveness of ventilatory support, the resulting PVA can increase daytime breathlessness and worsen sleep quality (4).

Since chronic hypoventilation generally manifests first during sleep and is worse compared to awake breathing, ventilatory support for these individuals is usually prescribed for use during sleep. Sleep fragmentation and loss have been associated with attenuations in ventilatory responsiveness to CO_2 (88, 230, 416), and it is plausible that improvements in awake CO_2 following NPPV could arise from better sleep quality. However, studies in both restrictive chest wall disorders (352) and lung disease (101, 102) have clearly demonstrated that NPPV applied during wakefulness alone can lead to significant improvements in spontaneous CO_2 levels, despite the persistence of significantly abnormal nocturnal breathing (352). These studies provide evidence of the importance of providing sufficient ventilation, irrespective of sleep state, over a sufficiently long time period to effectively reduce CO_2 and consequently bicarbonate concentrations to effectively manage hypoventilation.

Intermittent daytime and continuous ventilation

Despite sufficient regular nocturnal use and well-controlled nocturnal ventilation during NPPV, hypercapnia can persist during periods off ventilatory support. Most commonly this occurs in patients with progressive neuromuscular disorders and to a lesser extent those with very severe lung disease (16,26,34,253,392). In patients with DMD, the need to extend ventilation into daytime periods to manage hypercapnia and symptoms is likely to occur 4 to 5 years after commencing NPPV (18,394), usually coinciding with a fall in tidal volume to around 400 mL or less (18, 154, 394).

While historically tracheostomy ventilation, and to a more limited extent negative pressure devices such as cuirass and iron lungs, were used when more continuous ventilatory support was required, NPPV has been shown to be both a feasible and safe alternative for many patients (18, 34, 253). Soudon and colleagues (369) followed 42 patients with DMD requiring at least 15 h per day over a 5 year period. Sixteen were ventilated via tracheostomy and 26 used noninvasive ventilation. Rates of tracheal injury, mucus hypersecretion and chest infection were substantially greater in those receiving tracheal ventilation, although weight loss and enteral feeding were slightly more frequent in the NPPV group.

Although nasal mask or nasal pillows can be used for daytime ventilation, they are better suited to nocturnal use and where possible mouthpiece ventilation preferred, providing the patient with greater autonomy as to how much ventilation they receive and the way in which they receive it (394). Many newer high-end home ventilators provide mouthpiece ventilation as a separate ventilation mode, greatly simplifying the process of introducing and using this technique. Twenty four hour ventilatory support using noninvasive ventilation strategies is now considered a realistic alternative to tracheostomy (18, 253). Nevertheless, centers embarking on continuous noninvasive ventilation need to have extensive skills in NPPV as well as access to noninvasive airway clearance techniques (14, 17, 34). Tracheostomy ventilation is a consideration where NPPV becomes inadequate, for those with impaired glottic function or where effective clearance of airway secretions cannot be achieved. Clinicians and patients also need to be aware of the high burden that is imposed on caregivers by continuous ventilation especially when delivered by tracheostomy (123, 134). Decisions regarding treatment options for individuals requiring extended periods of ventilation to adequately control hypoventilation will also be influenced by the available health care resources, cultural difference and national laws (162, 325).

Conclusion

Sleep hypoventilation is a common occurrence in a range of disorders characterized by impaired respiratory muscle function, thoracic wall dysfunction or altered pulmonary mechanics, and usually occurs prior to the development of diurnal hypoventilation. Correction of sleep breathing abnormalities can significantly delay or even reverse chronic hypoventilation. Nocturnal noninvasive ventilation is the most widely used and reliable strategy currently available to manage chronic hypercapnic respiratory failure. However, the most effective modes and methods of providing ventilatory support for the various conditions associated with hypoventilation have yet to be determined. Evolving technology for both monitoring and treating hypoventilation will aid in maximizing the clinical benefits received from therapy and may provide insights into alternative or complementary management strategies.

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