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Impact of sleep in respiratory failure

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ABSTRACT: Sleep has a physiological influence on respiration, which can have major adverse effects on gas exchange in patients with respiratory insufficiency. These effects relate largely to a reduction in various stimulant inputs to the brainstem respiratory centre. Conditions that may be associated with sleep-related respiratory insufficiency range from pulmonary disorders (such as chronic obstructive pulmonary disease (COPD)), to central respiratory insufficiency (such as central alveolar hypoventilation), neurological and neuromuscular disorders (such as polio and muscular dystrophy), and thoracic cage disorders (such as kyphoscoliosis). All these conditions have in common the finding of hypoxaemia and hypercapnia, which become more pronounced during sleep. The relative hypoventilation, which is common to each condition, is due to varying combinations of an inadequate respiratory drive and an increase in the work of breathing.

Management of respiratory insufficiency during sleep should be directed first at optimizing the underlying disorder, then at correcting hypoxaemia with controlled low-flow supplemental oxygen. Pharmacological therapy may be effective in some instances, but the choice of agent varies with the underlying disorder.

Assisted ventilation is an important part of the management of advanced cases, and the recent development of intermittent positive pressure ventilation by nasal mask (NIPPV) has been an important advance in this area. Use of NIPPV during the night is associated with beneficial effects during the day, particularly improved awake gas exchange and respiratory muscle strength, in addition to less dyspnoea and improved quality of life. Electrophrenic pacing of the diaphragm is helpful in highly selected cases, particularly patients with central respiratory insufficiency and high quadriplegia, but is frequently complicated by the development of obstructive sleep apnoea.
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The average human spends approximately one third of life asleep, and yet, in the past, relatively little attention has been paid to physiological changes that occur during this state. Sleep involves a complex pattern of physiological processes which, though felt to be restorative and beneficial in nature, may also have potential adverse effects, particularly in subjects with underlying disease. One of the main areas of interest in sleep physiology has been the control of respiration, due largely to the discovery of a defect of respiratory control during sleep, namely sleep apnoea. This condition is now recognized to be very common, affecting 1–4% of adults [1, 2]. However, it has also long been recognized that sleep may have adverse effects on respiration and gas exchange in patients with underlying disease, and such patients may develop profound hypoxaemia during sleep [3–7], which may predispose to nocturnal death [8]. The purpose of this review is firstly, to outline the mechanisms by which sleep influences respiratory failure, secondly, to review the clinical spectrum of respiratory disorders associated with respiratory failure and how they are influenced by sleep, and, thirdly, to discuss management strategies.

Previous articles in this series: No. 1: S.K. Pingleton. Enteral nutrition in patients with respiratory disease. *Eur Respir J* 1996; 9: 364–370. **No. 2:** R. Dhand, M.J. Tobin. Bronchodilator delivery with metered-dose inhalers in mechanically-ventilated patients. *Eur Respir J* 1996; 9: 585–595. **No. 3:** N. Ambrosino. Noninvasive mechanical ventilation in acute respiratory failure. *Eur Respir J* 1996; 9: 795–807. **No. 4:** P. Pelosi, S. Crotti, L. Brazzi, L. Gattinoni. Computed tomography in adult respiratory distress syndrome: what has it taught us? *Eur Respir J* 1996; 9: 1055–1062. **No. 5:** H. Burchardi. New strategies in mechanical ventilation for acute lung injury. *Eur Respir J* 1996; 9: 1063–1072. **No. 6:** V.M. Ranieri, M. Dambrosio, N. Brienza. Intrinsic PEEP and cardiopulmonary interactions in patients with COPD and acute ventilatory failure. *Eur Respir J* 1996; 9: 1283–1292. **No. 7:** A. Corrado, M. Gorini, G. Villella, E. De Paola. Negative pressure ventilation in the treatment of acute respiratory failure: an old noninvasive technique reconsidered. *Eur Respir J* 1996; 9: 1531–1544. **No. 8:** A. Torres, M. El-Ebiary, N. Soler, C. Montón, N. Fàbregas, C. Hernández. Stomach as a source of colonization of the respiratory tract during mechanical ventilation: association with ventilator-associated pneumonia. *Eur Respir J* 1996; 9: 1729–1735. **No. 9:** J. Mancebo. Weaning from mechanical ventilation. *Eur Respir J* 1996; 9: 1923–1931. **No. 10:** D. Georgopoulos, C. Roussos. Control of breathing in mechanically ventilated patients. *Eur Respir J* 1996; 9: 2151–2160. **No. 11:** T. Vassilakopoulos, S. Zakynthinos, Ch. Roussos. Respiratory muscles and weaning failure. *Eur Respir J* 1996; 9: 2383–2400. **No. 12:** G.U. Meduri. The role of the host defence response in the progression and outcome of ARDS: pathophysiological correlations and response to glucocorticoid treatment. *Eur Respir J* 1996; 9: 2650–2670. **No. 13:** H.E. Fessler. Heart-lung interactions: applications in the critically ill. *Eur Respir J* 1997; 10: 226–237. **No. 14:** S. Singh, T.W. Evans. Nitric oxide, the biological mediator of the decade: fact or fiction. *Eur Respir J* 1997; 10: 699–707.

Effects of sleep on respiration

During wakefulness, the regulation of breathing involves the interaction of a number of inputs to the respiratory centre in the brainstem. This interaction is of critical importance, as the respiratory muscles do not have an inherent rhythmicity, and are dependent on efferent impulses transmitted from the respiratory centre *via* respiratory motor neurones. The respiratory centre is influenced by chemical inputs from chemoreceptors responding to changes in arterial oxygen tension (P_{a,O_2}), arterial carbon dioxide tension (P_{a,CO_2}) and pH, by mechanoreceptors in the airway, lungs and chest wall, and by behavioural inputs from higher cortical centres, transmitted *via* the reticular activating system [9]. Removal of these inputs can markedly reduce ventilation [10], and, in some experimental settings, can produce complete cessation of spontaneous breathing [11]. Sleep is associated with a number of effects on respiration, including changes in central respiratory control, airways resistance, and muscular contractility.

Central respiratory effects

The onset of sleep is associated with a diminished responsiveness of the respiratory centre to chemical and mechanical inputs, and to a major reduction in the stimulant effects of cortical inputs [9, 12–14]. These effects are more pronounced as sleep deepens, particularly during rapid eye movement (REM) sleep. Ventilatory responsiveness both to hypoxia and hypercapnia is diminished. Furthermore, responsiveness of the respiratory muscles to respiratory centre outputs is also diminished during sleep, particularly REM sleep, although the diaphragm is less affected than the accessory muscles in this respect [9]. During nonrapid eye movement (NREM) sleep, breathing is remarkably regular both in amplitude and frequency. There is a decrease in minute ventilation (V'_E) during NREM sleep [15–20], predominantly due to a reduction in tidal volume (V_T), which is associated with a rise in end-tidal carbon dioxide tension P_{ET,CO_2} [13, 21]. Part of this hypoventilation during sleep is likely to be a response to the lower metabolic rate, since oxygen consumption and carbon dioxide production diminish during sleep compared to wakefulness [22, 23].

During REM sleep, both V_T and respiratory frequency (f'_R) are much more variable than in NREM sleep, [15–19, 24, 25], particularly during phasic REM, when there are bursts of rapid eye movement, as opposed to tonic REM, where eye movements tend to be absent. The first eye movement of a REM burst is associated with a sudden decrease in V_T followed by a progressive increase. V'_E is lower during phasic REM than during tonic REM sleep. These physiological changes are not associated with any clinically significant deterioration in gas exchange among normal subjects, but may produce profound hypoxaemia in patients with respiratory insufficiency [3].

Airway resistance

Upper airway resistance increases during sleep compared to wakefulness [24], which predisposes to upper airway occlusion and obstructive sleep apnoea (OSA) in susceptible individuals. In addition, lower airway patency may also be compromised during sleep. The majority of normal subjects have circadian changes in airway calibre, with mild nocturnal bronchoconstriction [26, 27]. Such bronchoconstriction may be exaggerated in patients with asthma, who can demonstrate falls in peak flow rate of up to 50% or more, compared to an average of 8% in normal subjects [27].

Ribcage and abdominal contribution to breathing

In the supine resting state, breathing is predominantly a function of diaphragmatic contraction [28]. During NREM sleep, there is an increased ribcage contribution to breathing [13, 21, 29], and an associated increase in the respiratory electromyographic (EMG) activity of intercostal muscles [17, 19], with respiratory activity of the diaphragm being little increased or unchanged. The resulting expansion of the ribcage may improve mechanical efficiency of diaphragmatic contraction by optimizing the length and/or radius of curvature of the diaphragm [30, 31]. This increased efficiency of the diaphragm is reflected in an increase in the transdiaphragmatic pressure (P_{di}) developed for a given level of diaphragmatic EMG activity.

In contrast, a reduction in ribcage contribution to breathing has been reported during REM sleep compared to wakefulness, due to a marked reduction in intercostal muscle activity [32]. Diaphragmatic EMG activity is substantially increased, while P_{di} falls significantly. which implies a decrease in diaphragmatic efficiency, a pattern opposite to that seen during NREM sleep. The fall in intercostal muscle activity assumes particular clinical significance in patients who are particularly dependent on accessory muscle activity to maintain ventilation, such as those with COPD [3, 33, 34], or with diaphragmatic weakness for traumatic or other reasons [35, 36].

Functional residual capacity

A modest, but statistically significant, fall in functional residual capacity (FRC) has been noted in healthy sleeping adults both in NREM and REM sleep [37, 38]. The fall is not considered to be sufficient to cause significant ventilation/perfusion (V'/Q') mismatching in healthy subjects, but could do so, with resulting hypoxaemia, in patients with chronic lung disease [38]. Possible mechanisms responsible for this reduction in FRC include: respiratory muscle hypotonia; cephalad displacement of the diaphragm; and a decrease in lung compliance [15].

Neuromuscular changes during sleep

The loss of stimulant input from the cerebral cortex is an important contributor to the hypoventilation of sleep described above, but in addition, during REM sleep, there is a marked loss of tonic activity in the tongue, pharyngeal, laryngeal and intercostal muscles. There appears to be supraspinal inhibition of γ-motoneurons (and to a lesser extent α-motoneurons), in addition to presynaptic inhibition of afferent terminals from muscle spindles.

The diaphragm, being driven almost entirely by α-motoneurons and with far fewer spindles than intercostal muscles, has little tonic (postural) activity and, therefore, escapes reduction of this particular drive during REM sleep [9]. This helps to explain the increase in abdominal contribution to breathing in REM sleep.

Overall effects during sleep

The above account illustrates the complex effect of sleep on respiratory function, with the overall trend being a reduction in ventilation compared to wakefulness. In normal individuals, arterial blood gas values change little from wakefulness to sleep. However, when subjects with daytime hypoxaemia, due to underlying respiratory disease, develop abnormal breathing patterns during sleep, life-threatening hypoxaemia may occur. This partly results from the fact that a similar drop in P_{a,O_2} will be associated with a much greater drop in arterial oxygen saturation (S_{a,O_2}), when the subject is already hypoxaemic and on the steep part of the oxyhaemoglobin dissociation curve. Furthermore, the changes in ribcage and abdominal contribution to breathing and the changes in FRC may result in worsening V'/Q' relationships, which will also aggravate any tendency to hypoxaemia. In addition, the reduction in ventilatory drives and changes in breathing pattern during sleep attenuate the compensatory hyperventilation seen during wakefulness in these patients. This effect on ventilation is seen, in particular, during periods of REM sleep. A schematic outline of the effects of sleep on respiration is presented in figure 1.

Impact of sleep on patients with acute respiratory failure

There has been little research into the impact of sleep on respiratory function in patients with acute respiratory failure, who are intubated and on mechanical ventilation in the intensive care unit (ICU) setting, particularly those patients who do not have underlying chronic lung disease. Such patients would not be expected to show a significant deterioration in gas exchange during sleep, since the hypoventilation which is the principal mechanism of deteriorating gas exchange is prevented by the effects of mechanical ventilation. Changes in the ribcage contribution and in FRC may still have some adverse effects, but these have not been well-studied in mechanically-ventilated patients. Most patients who are intubated and on mechanical ventilation are also paralysed and sedated, which will further limit potential sleep-related changes in ventilation and gas exchange in such patients.

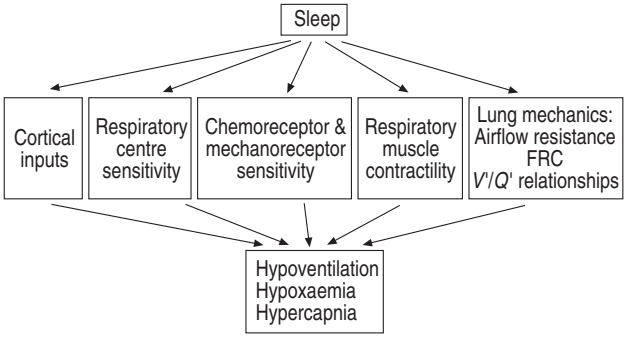

Fig. 1. – Schematic diagram of the effects of sleep on respiration. In each case, sleep has a negative influence, which has the overall impact of producing hypoventilation and/or hypoxaemia and hypercapnia. FRC: functional residual capacity; V'/Q': ventilation/perfusion.

The remainder of this review will be concerned with the impact of sleep on patients with respiratory failure due to underlying chronic disease. A variety of disorders can result in respiratory insufficiency, ranging from pulmonary disorders, such as chronic obstructive pulmonary disease (COPD), thoracic cage and neuromuscular disorders, such as kyphoscoliosis and muscular dystrophies, to disorders associated with central respiratory insufficiency. Most of these disorders are associated with relative or absolute hypoventilation, which results in hypoxaemia and hypercapnia (Type 2 respiratory failure). However, a few (particularly pulmonary) disorders, such as interstitial pulmonary fibrosis and "pink puffer" type COPD, are typically associated with hypoxaemia without hypercapnia (Type 1 respiratory failure), implying hyperventilation. A schematic outline of the various disorders associated with respiratory insufficiency, and their impact on various levels of the respiratory control system, is presented in figure 2. This figure also emphasizes the negative feedback loop mechanism, which governs the overall control of ventilation.

Chronic obstructive pulmonary disease

Sleep-related hypoxaemia and hypercapnia are well-recognized in COPD, particularly during REM sleep, and may contribute to the development of cor pulmonale [40] and nocturnal death [8]. These abnormalities are most common in "blue-bloater" type patients, who also have a greater degree of awake hypoxaemia and hypercapnia than "pink-puffer" type patients [3, 39]. However, many patients with awake P_{a,O_2} levels in the mildly

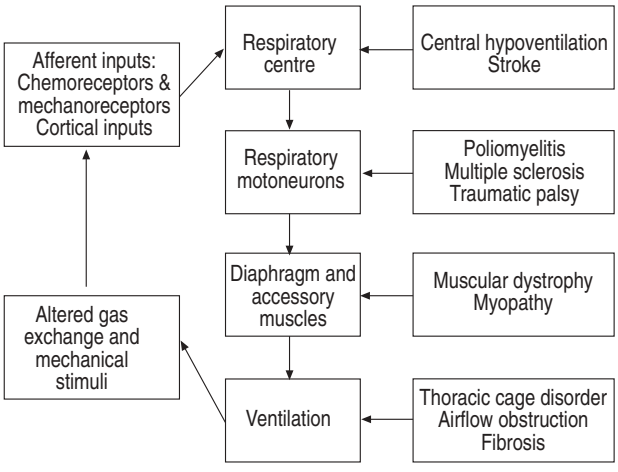

Fig. 2. – Schematic diagram of the influence of various chronic disorders on the control of breathing at various levels, ranging from the central respiratory centre to the lungs. This figure also stresses the feedback system that controls breathing through the chemoreceptors and other afferent inputs.

hypoxaemic range can also develop substantial nocturnal oxygen desaturation, which appears to predispose to the development of pulmonary hypertension [40].

Mechanisms of nocturnal oxygen desaturation in COPD

Hypoventilation. Studies using noninvasive methods of quantifying respiration have shown clear evidence of hypoventilation, particularly during REM sleep, associated with periods of hypoxaemia in patients with COPD [41–48], but the semiquantitative nature of these measurements makes it difficult to determine whether this is the sole mechanism of oxygen desaturation, or whether other factors are involved. A recent study from this department [46], in which ventilation, S_{a,O_2} and transcutaneous carbon dioxide tension (P_{tc,CO_2}) were continuously recorded during sleep in a group of patients with severe but stable COPD, demonstrated that falls in S_{a,O_2} were accompanied by a rise in P_{tc,CO_2}, and that REM sleep, in particular, was frequently characterized by irregular, low V_T respiration, and a high P_{tc,CO_2}. These observations support hypoventilation as the major cause of nocturnal desaturation in COPD, particularly during REM sleep. The loss of accessory muscle contribution to breathing, particularly from the ribcage, consequent to the generalized loss of muscle tone during REM sleep, contributes to this hypoventilation.

Impact of the oxyhaemoglobin dissociation curve. Numerous reports have demonstrated a close relationship between awake P_{a,O_2} and nocturnal S_{a,O_2} levels [43, 46, 47]. It has been proposed that, in patients with COPD, nocturnal S_{a,O_2} is largely the consequence of the combined effects of physiological hypoventilation during sleep and the fact that hypoxaemic patients show a proportionately greater fall in S_{a,O_2} with hypoventilation than normoxaemic, because of the effects of the oxyhaemoglobin dissociation curve. However, recent work from this department [46] has shown that P_{a,O_2} falls to a greater degree during sleep among patients who show a major degree of nocturnal oxygen desaturation, when compared to the fall in P_{a,O_2} during sleep among minor desaturators. This indicates that the greater fall in S_{a,O_2} during sleep among more severely hypoxaemic COPD patients is not simply a consequence of their being on the steep portion of the oxyhaemoglobin dissociation curve, and that other factors must play a part in the blood gas changes observed in these patients during sleep.

Altered ventilation/perfusion relationships. The changes in respiratory muscle function during sleep, particularly the loss of accessory muscle contribution to breathing also result in a decreased FRC, and contribute to worsening V'/Q' relationships during sleep, which also aggravate hypoxaemia in COPD [34, 42–48].

We found that levels of carbon dioxide tension rose to a similar extent in those patients who developed major nocturnal oxygen desaturation and those who developed only a minor degree of desaturation [46], which suggests a similar degree of hypoventilation in both groups, despite the different degrees of nocturnal oxygen desaturation. The much larger fall in P_{a,O_2} among the major desaturators as compared to the minor desaturators, in conjunction with the similar rise in P_{tc,CO_2} in both patient groups, suggests that, in addition to a degree of hypoventilation operating in all patients, other factors such as V'/Q' mismatching must also play a part in the excess desaturation of some COPD patients. Nonetheless, awake P_{a,O_2} remains the factor which best predicts a likelihood of nocturnal oxygen desaturation.

Coexisting sleep apnoea (the overlap syndrome). An early study on the mechanisms of nocturnal oxygen desaturation in COPD proposed that nocturnal oxygen desaturation was due to the presence of coexisting obstructive sleep apnoea [49]. However, this report was flawed by the fact that patients included in that study had been referred because of a clinical suspicion of sleep apnoea, and later reports have found sleep apnoea in only a minority of patients with COPD, who show evidence of nocturnal oxygen desaturation [50]. Various reports suggest an incidence of sleep apnoea in patients with COPD of about 10–15% [51, 52], which is a higher incidence than would be expected in a normal population of similar age. Factors that may predispose to sleep apnoea in patients with COPD include impaired respiratory drive, particularly in "blue-bloater" type COPD patients. Patients with coexisting COPD and sleep apnoea are prone to develop episodic profound hypoxaemia during sleep because of the fact that such patients may be hypoxaemic at the commencement of each apnoea, whereas patients with isolated sleep apnoea tend to resaturate to normal S_{a,O_2} levels between apnoeas. Therefore, they are particularly prone to the complications of chronic hypoxaemia, such as cor pulmonale and polycythaemia [51].

Contrasts with exercise

The mechanisms of hypoxaemia during sleep contrast with those during exercise, where the normal physiological increase in ventilation and in lung volumes during exercise are limited in COPD, because of the effects of increased airflow resistance, inadequate ventilatory response, and lack of reduction in dead space. These factors combine to cause relative hypoventilation and V'/Q' disturbances, leading to hypoxaemia in some patients [53, 54].

We have found that patients with COPD desaturate more than twice as much during sleep than during maximal exercise [46, 55], which contrasts with the findings in patients with interstitial lung disease, who develop greater desaturation during exercise than sleep [56]. This greater oxygen desaturation during sleep supports the finding [57] that, in patients with COPD, the demand for coronary blood flow during episodes of nocturnal hypoxaemia can be transiently as great as during maximal exercise. This increased myocardial oxygen demand may be a factor in the nocturnal arrhythmias [58] and the higher nocturnal death rate among patients with COPD [8], particularly since the level of exercise achieved during these studies was much greater than patients would normally reach during daily activities. Nocturnal oxygen desaturation also appears to be important in the development of pulmonary hypertension, even in the absence of significant awake hypoxaemia [59].

Nocturnal asthma

Nocturnal worsening of pulmonary function in patients with asthma is common and frequently underdiagnosed [60], and is particularly important in patients with acute severe asthma. Patients with asthma may develop progressive bronchoconstriction and hypoxaemia while asleep [61], and there is evidence that deaths from asthma are more prevalent at night [62].

Both large and small airways appear to be involved in nocturnal asthma [63, 64], and the daytime improvement in airflow is due to an increase in calibre of the large airways, with persistence of some narrowing of the small airways. Nocturnal asthma is characterized by an increase in airway smooth muscle responsiveness to histamine during the night compared to the daytime [65], which suggests that airway smooth muscle may be more sensitive to constrictor influences at night.

The events contributing to the development of bronchial obstruction may also result in V'/Q' mismatching in patients with asthma, and it has been speculated that the accentuation of an existing mismatch can result in increased hypoxia during sleep [66].

Factors contributing to nocturnal asthma

Circadian influences. There appears to be a circadian rhythm in peak expiratory flow rate (PEFR) that is often in phase with the timing of sleep, regardless of whether sleep is during daytime or night-time [67]. There is some evidence to suggest that pulmonary function is worst during REM sleep [68], but other reports have indicated that airway resistance rises progressively throughout the night, irrespective of sleep stage [69, 70].

There is also a circadian rhythm in circulating hormones and inflammatory mediators, that predisposes to nocturnal bronchoconstriction. Serum cortisol and catecholamine levels are lowest, and plasma histamine levels are highest, during the night-time [71, 72].

Cholinergic tone increases at night, which may also contribute to the pathogenesis of nocturnal bronchoconstriction [73–75]. This rise in cholinergic tone may be further increased by the action of inflammatory mediators, such as histamine, by gastro-oesophageal reflux, cold air, snoring, or by a fall in plasma adrenaline.

Other factors. Other factors, which do not relate to circadian influences, have also been proposed to play a role in the development of nocturnal asthma. These include gastro-oesophageal reflux [76], although the evidence is conflicting in this regard [77]. Airway cooling [78], snoring and sleep apnoea [79], and allergens in the bedding [80], have also been proposed as significant factors which contribute to the development of nocturnal asthma.

Central hyperventilation syndromes

These very rare syndromes relate to a defect in central respiratory centre drive, which results in chronic alveolar hypoventilation, often without any mechanical ventilatory defects [81, 82]. Patients demonstrate both hypoxaemia and hypercapnia on arterial blood gas analysis, but can usually normalize the blood gas values by voluntary hyperventilation [81]. These syndromes are often referred to as "Ondine's curse", from a character in Greek mythology who was cursed with having to voluntarily control his automatic body functions, including respiration [82]. Patients typically present with recurring episodes of severe respiratory failure, often in association with respiratory infection, since the defective respiratory drive is insufficient to cope with the increased work of breathing associated with respiratory infection [83].

Patients with central hypoventilation frequently develop severe respiratory insufficiency during sleep [84–86], as a consequence of the "normal" reduction in respiratory drive during sleep [9]. Minute ventilation falls during sleep, and central sleep apnoea is a common finding.

The precise pathophysiological basis of the syndrome is unclear, but could involve abnormalities in the brainstem and peripheral chemoreceptors [87], resulting in an inadequate afferent input to the brainstem respiratory centre. Patients with central alveolar hypoventilation have been shown to have an impaired ventilatory responsiveness to hypoxia and hypercapnia [87]. A deficiency in the respiratory centre itself could also account for the syndrome, and isolated cases have been reported of the syndrome complicating acoustic neuroma [88], neurofibromatosis [89], and stroke [90], which support this possibility, since the hypoventilation in these cases has been shown to be associated with involvement of the brainstem respiratory centre in the disease process.

Neurological and neuromuscular disorders

A variety of neurological disorders have been associated with respiratory insufficiency, particularly during sleep. These disorders can affect the brainstem respiratory centre, as outlined above, or alternatively could affect the peripheral nervous system, resulting in impaired transmission of the respiratory centre output to the muscles of respiration, particularly the diaphragm. Neurological disorders that can affect the brainstem include stroke [90], and those involving the peripheral nervous system include multiple sclerosis [91], polio [92], traumatic paralysis, such as cervical spine fracture [35, 93], and motor neurone disease [94]. Each condition is associated with a variable degree of hypoventilation, which is exacerbated by sleep because of the physiological effects of sleep on ventilation, as outlined above [9].

Neuromuscular disorders, particularly Duchenne's and other forms of muscular dystrophy [6, 7, 95–102], are also typically associated with hypoventilation, which becomes more severe as the disease progresses [101, 102], particularly during sleep. Muscular dystrophy produces respiratory insufficiency because of progressive degeneration of the muscles of respiration, and respiratory failure is the major cause of death in this condition, although cardiomyopathy due to degeneration of cardiac muscle is also a common finding [103]. The deterioration in awake blood gas values has been found in several reports to parallel the decline in lung function as measured by spirometry and maximum inspiratory pressures [7, 102, 104], although other reports have not shown such a relationship [100, 105]. Although Duchenne's

muscular dystrophy is a progressive and ultimately fatal condition, patients with the disease can be kept alive for many years by appropriate modalities of assisted ventilation, once respiratory failure has developed [104].

Sleep-related hypoxaemia in muscular dystrophy is predominantly found in REM sleep [100], because of the loss of accessory muscle contribution to breathing in the setting of diaphragmatic weakness. REM-related desaturation is also frequently associated with recurring apnoea and hypopnoea. These apnoeas are most commonly central in nature, but obstructive apnoea could develop if upper airway muscle contraction was impaired. Traditional noninvasive methods of distinguishing obstructive from central apnoeas in this condition may be inadequate because of the reduced respiratory effort associated with muscle weakness, and it is possible that some apparently central apnoeas are obstructive in origin, but appear central because of poor respiratory effort [100]. Coexisting sleep apnoea is particularly likely in obese patients [7, 100], and diagnostic sleep studies may be necessary to characterize the aetiology of sleep-related hypoxaemia, depending on the clinical features.

Thoracic cage disorders

The maintenance of effective ventilation is dependent on adequate lung expansion in response to diaphragmatic contraction. Disorders of the thoracic cage may interfere with this process, resulting in hypoventilation, particularly during sleep. Thoracic cage disorders which have been associated with respiratory insufficiency include kyphoscoliosis [5, 106–108], and thoracoplasty [109]. Oxygen desaturation is most pronounced during REM sleep, because of the marked reduction of accessory muscle contribution to breathing, and night-time saturation levels closely parallel the awake levels, similar to COPD [3, 46]. Sleep apnoea is an uncommon cause of hypoxaemia during sleep in these patients [106].

Factors that contribute to respiratory insufficiency in kyphoscoliosis include: V'/Q' inequality; alveolar hypoventilation; increased work of breathing; and reduced surface area for gas diffusion. Thoracoplasty causes an additional restrictive ventilatory defect as a consequence of pleural thickening and thoracic cage deformity, and is associated with a variable degree of scoliosis. Furthermore, airflow obstruction has been reported as a common long-term consequence of thoracoplasty, which does not appear to be related to smoking history [110]. The mechanism of this airflow obstruction is uncertain, but may relate to diffuse bronchial wall fibrosis and/or emphysema.

Thoracic cage disorders also appear to have an adverse effect on respiratory muscle contractility, since effective therapy of the hypoventilation and associated respiratory insufficiency have been shown to improve respiratory muscle strength [111]. However, this phenomenon may be a consequence of chronic hypoxaemia and hypercapnia, rather than a primary feature of the condition.

Management of respiratory insufficiency during sleep

A summary of management options for patients with respiratory insufficiency during sleep is presented in table 1. These options can be viewed as a step-wise approach, and, in many instances, careful attention to detail with the earlier options, such as optimizing the patient's general condition, in addition to appropriate use of supplemental oxygen and pharmacological therapy, can obviate the need for assisted ventilation.

Table 1. – Management options for patients in respiratory failure

General measures
Optimize therapy of underlying conditions
Physiotherapy
Prompt therapy of infective exacerbations
Supplemental oxygen
Low-flow to minimize risk of CO_2 retention
Pharmacological therapy
Theophyllines
Almitrine
Progesterone
Protriptyline
Assisted ventilation
Intermittent negative pressure ventilation
Intermittent positive pressure ventilation
via tracheostomy
Noninvasive by nasal mask
Diaphragmatic pacing
Frequently complicated by obstructive sleep apnoea

General principles

Whatever the primary cause of hypoventilation, the first principle of management should be to optimize the underlying condition, since this will almost invariably have beneficial effects on breathing. For example, in the case of obstructive airway diseases, such as COPD and asthma, optimizing bronchodilator therapy has been shown to improve gas exchange during sleep [112, 113].

Respiratory insufficiency in conditions associated with hypoventilation due to impaired respiratory drive or to impaired neuromechanical coupling will be adversely affected by any factor which increases the work of breathing [83], particularly respiratory infection, and such infections in these patients should be treated promptly and vigorously. The respiratory muscle weakness associated with these disorders may also result in impaired clearance of bronchial secretions, and physiotherapy and postural drainage play an important part in management, particularly during exacerbations.

Oxygen therapy

The most serious consequence of hypoventilation, particularly during sleep, is hypoxaemia, and appropriate oxygen therapy plays an important part in the management of any disorder associated with respiratory insufficiency. Care must be taken that correction of hypoxaemia is not complicated by hypercapnia in patients with respiratory insufficiency due to hypoventilation from any cause, since respiratory drive in such patients is partly dependent on the stimulant effect of hypoxaemia. Therefore, the concentration of added oxygen should be carefully titrated to bring the P_{a,O_2} up into the mildly hypoxaemic range, in order to minimize the tendency to carbon dioxide retention, particularly during sleep [114].

However, the risk of carbon dioxide retention with supplemental oxygen therapy in such patients may have been overstated in the past, and more recent reports have suggested that carbon dioxide retention with oxygen supplementation is often modest, and usually nonprogressive [48]. Indeed, some reports have suggested that supplemental oxygen may have beneficial effects on ventilation in some patients with central hypoventilation [84], possibly by removal of a depressant effect of hypoxaemia on the brainstem respiratory centre.

The need for monitoring oxygen levels during sleep in patients with respiratory insufficiency is debatable [115]. While S_{a,O_2} almost invariably falls during sleep in patients with respiratory insufficiency, the degree of fall is most closely related to the awake S_{a,O_2} levels [46, 115, 116]. This indicates that a knowledge of the awake P_{a,O_2} is the most important variable needed to predict the likelihood of nocturnal oxygen desaturation, and it is not usually necessary to record S_{a,O_2} during sleep, unless there is a perceived requirement for nocturnal ventilatory support. However, the relationship of awake to sleep S_{a,O_2} is variable, and previous reports have described patients who demonstrate nocturnal oxygen desaturation without significant awake hypoxaemia [40]. Therefore, it would be appropriate to monitor nocturnal S_{a,O_2} in patients without significant awake hypoxaemia who have complications suggestive of chronic hypoxaemia, such as cor pulmonale or polycythaemia, since unrecognized nocturnal hypoxaemia may be an important factor in the pathogenesis of these complications [40].

Pharmacological therapy

Theophylline. In addition to being a bronchodilator, theophylline has important effects on respiration, which may be particularly beneficial in patients with chronic hypoventilation, including central respiratory stimulation [117] and improved diaphragmatic contractility [118]. This agent has been demonstrated to have beneficial effects in several respiratory disorders associated with nocturnal hypoxaemia, including COPD [112] and sleep apnoea [119]. The beneficial effect in COPD does not appear to be due to bronchodilation, but a reduction in trapped gas volume appears to play an important role in ameliorating hypoxaemia [112]. However, the principal limiting effect of theophyllines in this context is an adverse effect on sleep quality [112], which appears to differ from the effects on sleep quality of normal subjects [120], and also the relatively high incidence of gastrointestinal intolerance.

Almitrine. This agent is a powerful carotid body agonist, which stimulates ventilation [121]. Almitrine also improves V'/Q' relationships within the lung [122–124], probably by an enhancement of hypoxic pulmonary vasoconstriction [125]. The overall effect is to lessen hypoxaemia [126], and the agent is a useful addition in the management of conditions associated with hypoxaemia, particularly in COPD patients with type 2 respiratory failure. Almitrine is not helpful in most patients with central respiratory insufficiency, since such patients usually have defective carotid body responses to hypoxaemia, which is the most important site of action of this drug. Important side-effects include: pulmonary hypertension; dyspnoea (presumably due to the respiratory stimulant effect in patients with chronic airflow limitation); and peripheral neuropathy [127]. The latter complication can be minimized by giving the drug on an intermittent basis, with a 1 month holiday after each 2 months of active therapy.

Progesterone. This agent, which is a female hormone, has long been recognized to have respiratory stimulant effects [128, 129], and an illustration of this effect is that women in the later stages of pregnancy tend to become hypocapnic because of the high levels of circulating hormone. The effect appears to be centrally mediated, and persists even when peripheral chemoreceptor activity is abolished [130]. Progesterone has been used therapeutically in conditions associated with central respiratory insufficiency [131], but is not effective in patients with COPD, particularly if unable to lower their P_{a,CO_2} levels by voluntary hyperventilation [132]. Progesterone has also been used in the treatment of sleep apnoea syndrome, with variable results [133, 134], although benefit is most likely to be seen in those patients whose ventilatory responsiveness to hypercapnia is increased by progesterone [134].

Protriptyline. This drug is a tricyclic antidepressant, which has a number of other effects that may be beneficial in some patients with sleep-related respiratory insufficiency. The most important of these effects is a fragmentation of REM sleep, since sleep-related breathing abnormalities tend to be most severe in this sleep stage [3, 100, 106]. A preferential increase in upper airway muscle, as opposed to diaphragmatic contractility, has also been described [135], which could be beneficial in obstructive sleep apnoea. Indeed, protriptyline has been shown to decrease the severity of sleep apnoea in some studies [136], although other reports have failed to show a consistent benefit [137]. Those patients who do show a benefit tend to report a lessening of daytime hypersomnolence [136]. Several short-term studies have shown a benefit both in awake and asleep blood gas levels in patients with COPD [138, 139], although this benefit may not persist with long-term use of the drug [140]. Furthermore, long-term use is significantly limited by side-effects, particularly anticholinergic.

Assisted ventilation

Patients with respiratory insufficiency, who fail to respond to the above measures, should be considered for some form of assisted ventilation. In an acute setting, this may require intubation and ventilation, but, in the past decade, increasing attention has been directed towards noninvasive methods of ventilatory support, particularly during sleep [141–143]. In patients with chronic respiratory failure, noninvasive assisted ventilation has been an established form of therapy for many decades, dating back to the "iron lung" used in the management of patients with respiratory failure due to polio [92]. Noninvasive ventilation is particularly beneficial in patients with respiratory insufficiency due to hypoventilation, and has been reported to be effective in neurological [143–145], neuromuscular [146, 147], and thoracic cage disorders [148–150]. Assisted ventilation is usually confined

to sleep, if possible, for obvious practical reasons, but beneficial effects on gas exchange during wakefulness have been widely-reported in patients treated with nocturnal ventilatory support [149, 151], in addition to improvements in respiratory muscle strength and endurance [111, 152]. An example of the beneficial effect of noninvasive ventilation by nasal intermittent positive pressure (NIPPV) on oxygenation during sleep in a patient with chronic respiratory failure due to an old thoracoplasty and COPD is given in figure 3.

Negative pressure ventilation. The earliest form of noninvasive ventilation was the "iron lung", which saved many lives during the polio epidemics of the first half of this century. Various forms of noninvasive ventilation have been used over the years, including the rocking bed [153] and, more recently, the abdominal cuirass [142, 154]. While generally effective, negative pressure ventilation can be complicated by the development of upper airway obstruction and obstructive sleep apnoea [155, 156]. This complication develops because of the loss of the normal timing relationship between the phasic contraction of the upper airway dilating muscles, which normally contract in association with diaphragmatic contraction in order to ensure oropharyngeal patency during inspiration [157].

Negative pressure ventilation has been found to be particularly effective in patients with hypoventilation and/or thoracic cage disorders, but studies of its effects in patients with COPD have produced conflicting results [158, 159], and this form of ventilation appears to be inferior to positive pressure ventilation in these types of patients [160].

Nasal intermittent positive pressure ventilation. The past decade has seen the widespread introduction of noninvasive intermittent positive pressure ventilation by nasal mask (NIPPV), and this technique has now largely replaced other forms of noninvasive ventilation during sleep [161–165]. Nasal IPPV is dependent on the patient maintaining exclusive nasal breathing for efficacy, but is helped by the fact that humans are semi-obligate nose-breathers, particularly during sleep. However, some patients do breathe through the mouth while on NIPPV, but this problem can usually be overcome by wearing a chin-strap. The mask is usually well-tolerated, although some patients with respiratory failure find the nasal mask uncomfortable and/or claustrophobic, in which case negative pressure ventilation is usually preferred. Some patients who require assisted ventilation both day and night are better managed by intermittent positive pressure ventilation (IPPV) *via* mouthpiece, and this method provides a suitable alternative to tracheostomy [144].

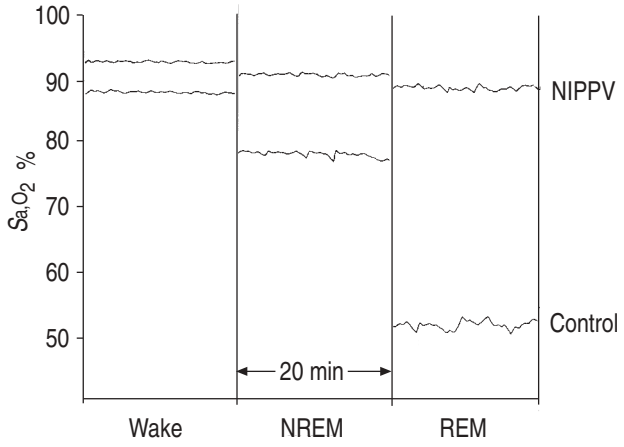

Fig. 3. – Levels of arterial oxygen saturation (Sa,O_2) during sleep before and after nasal intermittent positive pressure ventilation (NIPPV) in a 65 year old male with chronic respiratory failure due to chronic obstructive pulmonary disease (COPD) and an old thoracoplasty for tuberculosis. Each section represents 20 min continuous record of Sa,O_2 in each of wakefulness, nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. The lower tracings in each panel represent Sa,O_2 levels before NIPPV, while the patient was receiving 28% supplemental oxygen by ventimask (control). The upper tracings represent the values while receiving NIPPV in addition to 4 $L \cdot min^{-1}$ supplemental oxygen through the nasal mask.

Many studies have reported an improvement in daytime blood gas values and respiratory muscle strength with NIPPV [111, 166, 167]. The mechanism by which NIPPV produces improvements in daytime blood gas values probably involve a number of factors, which include resting of the respiratory muscles [160, 166–169]. This resting does not appear to occur with nocturnal negative pressure ventilation in COPD [160]. Respiratory muscle fatigue appears to be an important factor in the development of hypercapnia among patients with COPD [170, 171]. Other factors that may be important include resetting of respiratory drive, particularly at the chemoreceptor level, and an improved ventilatory responsiveness to hypercapnia has been demonstrated in COPD following NIPPV [151]. A reduction in residual volume and in the degree of gas-trapping has also been demonstrated with NIPPV, implying a reduction in respiratory load [151]. In some cases, where the Pa,CO_2 fails to fall during NIPPV, this failure is due to carbon dioxide rebreathing through the standard exhalation device, and use of an appropriate alternative exhalation device can eliminate the problem [172]. Short-term withdrawal of NIPPV for periods of up to 2 weeks may be associated with persistence of the improvement in daytime blood gas values, but not in night-time gas exchange [173].

Extensive experience has now been gained with NIPPV in adults with a variety of different disorders associated with respiratory failure, including a variety of neuromuscular and thoracic cage disorders, in addition to cystic fibrosis [162]. Similar improvements have been documented in children with NIPPV [165], although the experience is more limited in this group. Recently, NIPPV has been successfully used in the management of acute exacerbations of COPD associated with respiratory failure, and has been shown to reduce the need for intubation and mechanical ventilation in such patients [174]. There is also considerable evidence that NIPPV may help patients with COPD who are in chronic respiratory failure [163, 168, 175]. Sleep quality and diurnal Pa,O_2 and Pa,CO_2 levels are better with NIPPV plus supplemental oxygen than with supplemental oxygen alone [168]. Early studies of NIPPV in stable COPD [175] indicated that the treatment was poorly tolerated, but a more recent report in patients with more severe derangement of awake blood gas values found that NIPPV was well-tolerated by the vast majority of patients [168]. One factor that may influence patient acceptance of NIPPV is the length of time spent initiating therapy, and compliance may be improved if therapy is commenced as an in-patient [168].

The reported benefits of NIPPV in severe COPD contrast with the findings from several studies of negative pressure ventilation [176–178] in COPD, which have failed to show improvements in daytime blood gas values, exercise performance or quality of life, although other studies have shown benefit [152].

The findings from studies of NIPPV in COPD offer exciting new prospects for the management of patients with advanced disease, who are in chronic respiratory failure. However, the health care resource implications of this therapy are potentially enormous.

Electrophrenic pacing

Electrical stimulation of the diaphragm has been used in selected patients with central respiratory insufficiency over the past two decades [179–181]. This procedure is highly specialized, and involves implanting a pacing electrode around the phrenic nerve, either in the cervical or, more commonly, the high thoracic region. The criteria for successful diaphragm pacing include the need for long-term mechanical ventilatory assistance, a functionally intact phrenic nerve-diaphragm axis, and chest wall stability. The technique has been reported to be effective, particularly in patients with central alveolar hypoventilation [182, 183], and those with a high quadriplegia [181, 184, 185]. Care must be taken in the latter group, however, to ensure that the phrenic nerve has remained viable, and adequate testing of phrenic nerve function and diaphragmatic contractility should be performed in all patients before deciding on this procedure. The phrenic nerve is usually tested by means of an external stimulator applied percutaneously in the neck over the nerve pathway. Diaphragmatic contractility in response to phrenic nerve stimulation can be tested either by recording EMG activity from surface electrodes or by recording P_{di} changes with oesophageal and gastric balloons [181]. The function of the phrenic nerve-diaphragm axis can more easily be tested in patients with central alveolar hypoventilation, by recording the response to voluntary hyperventilation.

Adults with hypoventilation due to either central respiratory centre insufficiency or high quadriplegia can often be successfully managed with a unilateral phrenic nerve pacemaker, but children generally require bilateral pacemakers because the chest wall is more compliant than in adults, and therefore, a unilateral pacemaker will result in paradoxical movement of the contralateral diaphragm and chest wall with consequent reduction in efficacy.

Approximately 50% of patients develop OSA as a complication [181], for the same reason as occurs in patients treated with negative pressure ventilation, namely the loss of the normal timing relationships between upper airway and diaphragmatic contraction, which splints the upper airway open in advance of the onset of inspiration [157]. Such patients may require nasal continuous positive airway pressure (CPAP) or tracheostomy, in addition to pacing of the diaphragm. Obstructive sleep apnoea is more likely in those patients with central alveolar hypoventilation, because these patients have a reduced upper airway muscle tone and contractility as part of their reduced respiratory drive, whereas patients with high quadriplegia should have a normal respiratory drive, and, therefore, the tone of the upper airway muscles should be higher, and thus less likely to obstruct in response to phrenic nerve stimulation. Attempts have been made to develop pacemakers which synchronize the contraction of upper airway muscles and diaphragm, which would remove the likelihood of upper airway obstruction, but so far without success.

Summary

The impact of sleep on ventilation and gas exchange in patients with chronic respiratory failure can be dramatic and potentially life-threatening. These effects often go unrecognised, either due to lack of facilities for sleep monitoring, or to a failure by the attending clinician to appreciate the potential impact of sleep on ventilation in these patients. However, appropriate management of the sleep-related deterioration in gas exchange can greatly improve life expectancy, in addition to producing improvements in daytime gas exchange and quality of life. Optimum management requires a careful attention to detail, and such an approach, by optimising the underlying condition, in addition to appropriate oxygen and drug therapy, can avoid the need for assisted ventilation in many cases. The recent development of intermittent positive pressure ventilation by nasal mask has been a major development in this area, and has opened up exciting new possibilities for improving the management of patients with chronic respiratory failure.

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