Impact of Sleep in COPD*

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Sleep has well-recognized effects on breathing, including changes in central respiratory control, airways resistance, and muscular contractility, which do not have an adverse effect in healthy individuals but may cause problems in patients with COPD. Sleep-related hypoxemia and hypercapnia are well recognized in COPD and are most pronounced in rapid eye movement sleep. However, sleep studies are usually only indicated in patients with COPD when there is a possibility of sleep apnea or when cor pulmonale and/or polycythemia are not explained by the awake Pa_{O_2} level. Management options for patients with sleep-related respiratory failure include general measures such as optimizing therapy of the underlying condition; physiotherapy and prompt treatment of infective exacerbations; supplemental oxygen; pharmacologic treatments such as bronchodilators, particularly ipratropium bromide, theophylline, and almitrine; and noninvasive positive pressure ventilation. ***(CHEST 2000; 117:48S–53S)***

Key words: COPD; sleep

Abbreviations: FRC = functional residual capacity; NIPPV = noninvasive positive pressure ventilation; REM = rapid eye movement sleep; Sa_{O_2} = arterial oxygen saturation; $\dot{V}/\dot{Q}$ = ventilation/perfusion

Sleep has well-recognized effects on breathing, which in normal individuals have no adverse impact. These effects include a mild degree of hypoventilation with consequent hypercapnia, and a diminished responsiveness to respiratory stimuli. However, in patients with chronic lung disease, these physiologic changes during sleep may have a profound effect on gas exchange, and episodes of profound hypoxemia may develop, particularly during rapid eye movement (REM) sleep.[1]

Effects of Sleep on Respiration

The effects of sleep on respiration include changes in central respiratory control, airways resistance, and muscular contractility. A schematic outline of the effects of sleep on respiration is given in Figure 1.

Central Respiratory Effect

Sleep is associated with a diminished responsiveness of the respiratory center to chemical, mechanical, and cortical inputs,[2,3] particularly during REM sleep. Furthermore, the responsiveness of the respiratory muscles to respiratory center outputs are also diminished during sleep, particularly during REM, although the diaphragm is less affected than the accessory muscles in this regard.[2] There is a decrease in minute ventilation during non-REM sleep and more so during REM sleep,[4–6] predominantly because of a reduction in tidal volume, which is associated with a rise in end-tidal P_{CO_2}. During REM sleep, both tidal volume and respiratory frequency are much more variable than in non-REM sleep,[4–7] particularly during phasic REM. These physiologic changes are not associated with any clinically significant deterioration in gas exchange among normal subjects, but may produce profound hypoxemia in patients with respiratory insufficiency.[1]

Airway Resistance

Most normal subjects have circadian changes in airway caliber with mild nocturnal bronchoconstriction.[8,9] Such bronchoconstriction may be exaggerated in patients with asthma, who can demonstrate falls in peak flow rate of $\geq 50\%$, compared with an average of 8% in normal subjects.[9]

Ribcage and Abdominal Contribution to Breathing

A reduction in ribcage contribution to breathing has been reported during REM sleep compared with wakefulness and non-REM sleep because of a marked reduction in intercostal muscle activity,[10]

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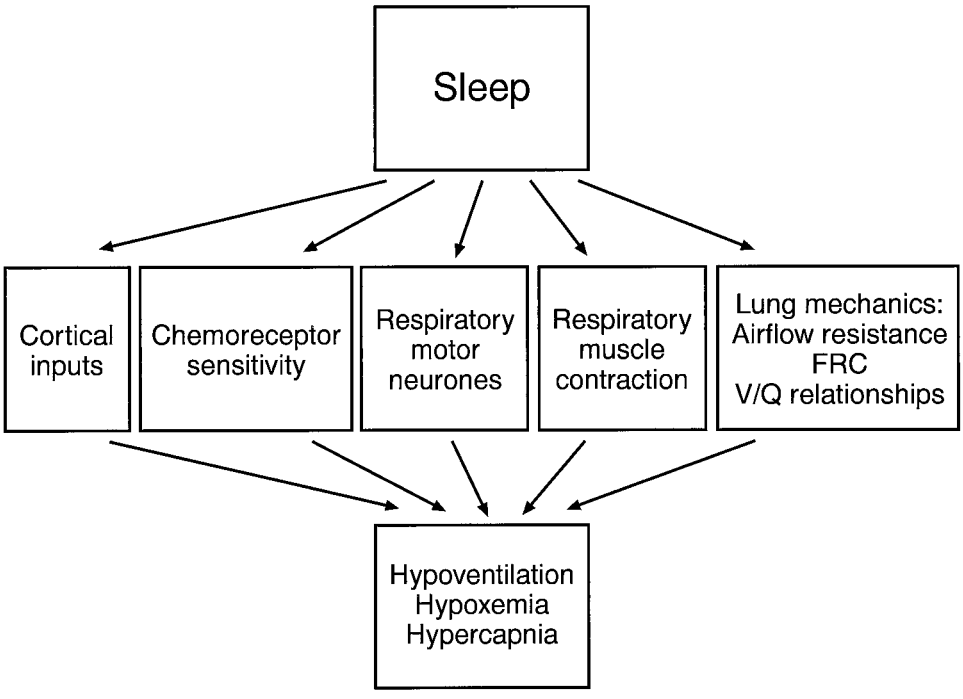

FIGURE 1. Schematic diagram of the effects of sleep on respiration. In each case, sleep has a negative influence which has the overall impact of producing hypoventilation and/or hypoxemia and hypercapnia. V/Q = $\dot{V}/\dot{Q}$ ratio.

whereas diaphragmatic contraction is little affected. This 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 where lung hyperinflation reduces the efficacy of diaphragmatic contraction.[11]

Functional Residual Capacity

A modest fall in functional residual capacity (FRC) has been noted in both non-REM and REM sleep,[12,13] which does not cause significant ventilation to perfusion mismatching in healthy subjects, but can do so, with resulting hypoxemia, in patients with chronic lung disease.[12] Possible mechanisms responsible for this reduction in FRC include respiratory muscle hypotonia, cephalad displacement of the diaphragm, and a decrease in lung compliance.[4]

Sleep in COPD

Sleep-related hypoxemia and hypercapnia are well recognized in COPD, particularly during REM sleep, and may contribute to the development of cor pulmonale[14] and nocturnal death.[15] These abnormalities are most common in "blue–bloater"-type patients, who also have a greater degree of awake hypoxemia and hypercapnia than "pink–puffer"-type patients.[3,14] However, many patients with awake Pa_{O_2} levels in the mildly hypoxemic range can also develop substantial nocturnal oxygen desaturation, which appears to predispose to the development of pulmonary hypertension.[16]

Mechanisms of Nocturnal Oxygen Desaturation in COPD

1. Hypoventilation

Studies using noninvasive methods of quantifying respiration have shown clear evidence of hypoventilation, particularly during REM sleep, associated with periods of hypoxemia in patients with COPD,[17–20] but the semiquantitative nature of these measurements makes it difficult to determine if this is the sole mechanism of oxygen desaturation, or whether other factors are involved.

2. Impact of the Oxyhemoglobin Dissociation Curve

There is a close relationship between awake Pa_{O_2} and nocturnal arterial oxygen saturation (Sa_{O_2}) levels, and it has been proposed that nocturnal oxygen desaturation in patients with COPD is largely the

consequence of the combined effects of physiologic hypoventilation during sleep and the fact that hypoxemic patients show a proportionately greater fall in Sa_{O_2} with hypoventilation than normoxemic, because of the effects of the oxyhemoglobin dissociation curve.[17,18] However, Pa_{O_2} has also been shown to fall more during sleep in major desaturators as compared with minor desaturators,[19] which indicates that other factors must also play a part in nocturnal oxygen desaturation in patients with COPD.

3. Altered Ventilation/Perfusion Relationships

The reduction in accessory muscle contribution to breathing particularly during REM sleep result in a decreased FRC, and contribute to worsening ventilation/perfusion ($\dot{V}/\dot{Q}$) relationships during sleep, which also aggravate hypoxemia in COPD.[17,18] We have found that transcutaneous P_{CO_2} levels rise to a similar extent in those patients who developed major nocturnal oxygen desaturation as those who developed only a minor degree of desaturation,[19] which suggests a similar degree of hypoventilation in both groups, despite the different degrees of nocturnal oxygen desaturation. The much larger fall in Pa_{O_2} among the major desaturators as compared with the minor desaturators, in conjunction with the similar rise in transcutaneous P_{CO_2} in both patient groups, suggests that in addition to a degree of hypoventilation operating in all patients, other factors such as $\dot{V}/\dot{Q}$ mismatching must also play a part in the excess desaturation of some COPD patients.

4. Coexisting Sleep Apnea (the Overlap Syndrome)

The incidence of sleep apnea in patients with COPD is about 10 to 15%,[21,22] which is higher than would be expected in a normal population of similar age. Factors that may predispose to sleep apnea in patients with COPD include impaired respiratory drive, particularly in blue–bloater-type COPD patients. Patients with coexisting COPD and sleep apnea typically develop more severe hypoxemia during sleep because such patients may be hypoxemic at the commencement of each apnea, whereas patients with pure sleep apnea tend to resaturate to normal Sa_{O_2} levels between apneas. Therefore, they are particularly prone to the complications of chronic hypoxemia, such as cor pulmonale and polycythemia.[21]

Investigation of Sleep-Related Breathing Disturbances in COPD

The serious and potentially life-threatening disturbances in ventilation and gas exchange that may develop during sleep in patients with COPD raise the question of appropriate investigation of these patients. However, it is widely accepted that sleep studies are not routinely indicated in patients with COPD associated with respiratory insufficiency, particularly since the awake Pa_{O_2} level provides a good indicator of the likelihood of nocturnal oxygen desaturation.[23,24] Sleep studies are only indicated when there is a clinical suspicion of an associated sleep apnea syndrome or manifestations of hypoxemia not explained by the awake Pa_{O_2} level, such as cor pulmonale or polycythemia.

Management of Respiratory Insufficiency During Sleep

A summary of management options for patients with respiratory insufficiency during sleep is given in Table 1. These options can be viewed as a stepwise 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 pharmacologic therapy, can obviate the need for assisted ventilation.

General Principles

The first principle of management of sleep-related breathing disturbance in COPD should be to optimize the underlying condition, since this will almost invariably have beneficial effects on breathing. For example, optimizing bronchodilator therapy has been shown to improve gas exchange during sleep.[25,26] Respiratory infections in these patients should be treated promptly and vigorously.

Oxygen Therapy

The most serious consequence of hypoventilation, particularly during sleep, is hypoxemia, and appropriate oxygen therapy plays an important part in the

Table 1—*Management Options for COPD Patients With Sleep-Related Respiratory Failure*

Options
General measures
Optimize therapy of underlying condition
Physiotherapy
Prompt therapy of infective exacerbations
Supplemental oxygen
Low flow to minimize risk of carbon dioxide retention
Pharmacologic therapy
Bronchodilators: anticholinergics, β_2-agonists
Theophylline
Almitrine
NIPPV

management of any disorder associated with respiratory insufficiency. Care must be taken that correction of hypoxemia 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 hypoxemia. Therefore, the concentration of added oxygen should be carefully titrated to bring the Pa_{O_2} up into the mildly hypoxemic range in order to minimize the tendency to carbon dioxide retention, particularly during sleep.[27]

However, the risk of carbon dioxide retention with supplemental oxygen therapy in such patients may have been overstated in the past, and some reports have found that carbon dioxide retention with oxygen supplementation is often modest, and usually nonprogressive.[20]

Sa_{O_2} levels do not need to be measured routinely during sleep in patients with COPD complicated by hypoxemia unless there is a concern that nocturnal ventilatory support may be required, or in patients without significant awake hypoxemia who have complications suggestive of chronic hypoxemia such as cor pulmonale or polycythemia, since unrecognized nocturnal hypoxemia may be an important factor in the pathogenesis of these complications.[28]

Pharmacologic Therapy

1. Anticholinergics

Cholinergic tone is increased at night, and it has been proposed that this contributes to airflow obstruction and deterioration in gas exchange during sleep in patients with obstructive airways disease. There is recent evidence that ipratropium improves Sa_{O_2} in addition to sleep quality in patients with COPD,[29] although other studies have shown conflicting results on the ability of ipratropium to block nocturnal bronchoconstriction in asthma.[30,31]

2. Theophylline

In addition to being a bronchodilator, theophylline has important effects on respiration that may be particularly beneficial in patients with chronic hypoventilation, including central respiratory stimulation[32] and improved diaphragmatic contractility,[33] and improves gas exchange during sleep in COPD.[25] In COPD, the benefits appear to be more likely caused by a reduction in trapped gas volume than by bronchodilation.[25] However, theophyllines have an adverse effect on sleep quality[25] in contrast with ipratropium bromide,[29] and also have a relatively high incidence of GI intolerance.

3. β_2-Agonists

There are only limited data on the efficacy of β_2-agonists on the management of sleep-related breathing abnormalities in COPD. One report found a long-acting theophylline superior to salbutamol in terms of nocturnal gas exchange and overnight fall in spirometry.[34] However, there are no studies of the impact of long-acting β_2-agonists on sleep and breathing in COPD.

4. Almitrine

This agent is a powerful carotid body agonist that stimulates ventilation.[35] Almitrine also improves $\dot{V}/\dot{Q}$ relationships within the lung,[36] probably by an enhancement of hypoxic pulmonary vasoconstriction.[37] The overall effect is to lessen hypoxemia awake and asleep, and is beneficial in hypoxemic patients with COPD.[38] Important side effects include pulmonary hypertension, dyspnea, and peripheral neuropathy.[39]

5. Noninvasive Ventilation

In the past decade, increasing attention has been directed toward noninvasive methods of ventilatory support of COPD patients with chronic respiratory insufficiency, particularly during sleep.[40–42] Beneficial effects on gas exchange during wakefulness have been widely reported in patients treated with nocturnal ventilatory support in addition to improvements in respiratory muscle strength and endurance.[43–45] An example of the beneficial effect of noninvasive positive pressure ventilation (NIPPV) on oxygenation during sleep in a patient with chronic respiratory failure caused by an old thoracoplasty and COPD is given in Figure 2.

The mechanism by which NIPPV produces improvements in daytime blood gases likely involve a number of factors, including resting of the respiratory muscles[41,46,47]; resetting of respiratory drive, particularly at the chemoreceptor level; and a reduction in residual volume and in the degree of gas trapping.[45] Short-term withdrawal of NIPPV for periods of up to 2 weeks may be associated with persistence of the improvement in daytime blood gases, but not in nighttime gas exchange.[48]

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.[49] 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 very great because of the

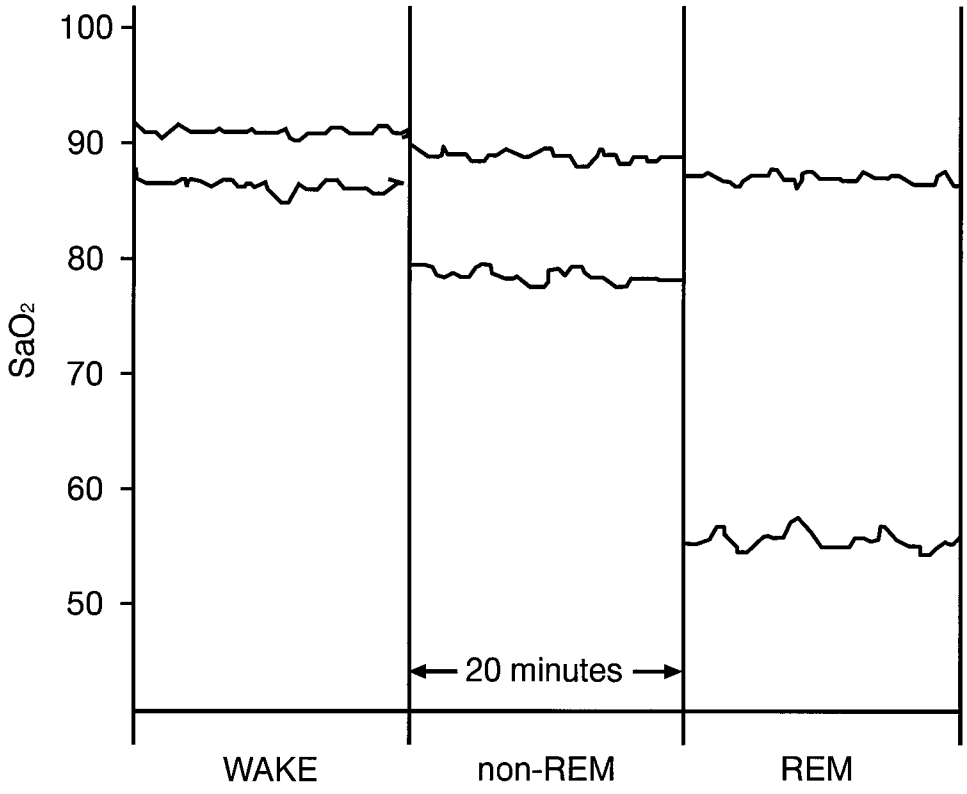

FIGURE 2. SaO_2 during sleep before and after NIPPV in a 65-year-old man with chronic respiratory failure due to COPD and an old thoracoplasty for tuberculosis. Each section represents a 20-min continuous record of SaO_2 in each of wakefulness, non-REM, and REM sleep. The lower tracings in each panel represent SaO_2 levels before NIPPV while the patient was receiving 28% supplemental oxygen by Ventimask. The upper tracings represent the values while on NIPPV in addition to 4 L/min supplemental oxygen through the nasal mask.

high prevalence of COPD. While it is clear from the literature that NIPPV will play an increasing role in the management of patients with advanced COPD over coming years, it is likely that only a subset of patients with advanced COPD will benefit from this therapy. These considerations emphasize the importance of outcome studies that evaluate the efficacy of this therapy in different patient populations.

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