Chronic Obstructive Pulmonary Disease and Sleep

Peter C Gay MD

The control of breathing in patients with chronic obstructive pulmonary disease (COPD) follows the same basic principles as in normal subjects, both awake and asleep, with an expected lower feedback response during sleep. This impacts nocturnal gas exchange and sleep quality most profoundly in patients with more severe COPD, as multiple factors come into play. Hypoventilation causes the most important gas-exchange alteration in COPD patients, leading to hypercapnia and hypoxemia, especially during rapid-eye-movement sleep, when marked respiratory muscle atonia occurs. The hypoxia leads to increased arousals, sleep disruption, pulmonary hypertension, and higher mortality. The primary mechanisms for this include decreased ventilatory responsiveness to hypercapnia, reduced respiratory muscle output, and marked increases in upper airway resistance. In the presence of more profound daytime hypercapnia, polysomnography should be considered (over nocturnal pulse oximetry) to rule out other co-existing sleep-related breathing disorders such as obstructive sleep apnea (overlap syndrome) and obesity hypoventilation syndrome. Present consensus guidelines provide insight into the proper use of oxygen, continuous positive airway pressure, and nocturnal noninvasive positive-pressure ventilation for those conditions, but several issues remain contentious. In order to provide optimal therapy to patients, the clinician must take into account certain reimbursement and implementation-process obstacles and the guidelines for treatment and coverage criteria. *Key words: chronic obstructive pulmonary disease, COPD, obstructive sleep apnea, continuous positive airway pressure, CPAP, oxygen, hypertension, obesity, hypoventilation, noninvasive positive-pressure ventilation, NPPV.* [Respir Care 2004;49(1):39–51.

Introduction

This discussion will begin with commentary about the ventilatory changes that normally occur in humans during sleep and will then review the gas exchange abnormalities and typical sleep characteristics of chronic obstructive pulmonary disease (COPD) patients. I will then comment on ways to evaluate COPD patients for sleep-related breathing disorders and the approach to management as it affects COPD patients during sleep. Reimbursement and implementation process issues that influence treatment decision-making will be addressed and, finally, I will discuss summary indications and recommendations for nocturnal oxygen therapy (NOT) and noninvasive positive-pressure ventilation (NPPV) to provide optimal therapy for COPD patients. Identification of gas exchange and sleep issues as well as management of sleep disorders in COPD patients will be addressed through responses to the following questions:

- How are normal control of breathing during sleep and sleep quality altered in COPD patients?
- How should we evaluate COPD patients for sleep-related breathing disorders?
- How are co-existing COPD and sleep-related breathing disorders best managed?
- How is the management of sleep-related breathing disorders in COPD complicated by process and reimbursement issues?
- What are the summary indications for supplemental oxygen and NPPV during sleep in COPD patients?

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How Are Normal Control of Breathing During Sleep and Sleep Quality Altered in COPD Patients?

Normal control of breathing and sleep physiology in adults have been reviewed elsewhere[1–3] but a brief overview of assessment techniques and findings provides a useful foundation for discussion. Breathing during sleep is typically characterized by measurement of gas exchange (via pulse oximetry) and ventilatory effort or assessment of respiratory muscle output and airflow (pneumotachography, spirometry, or electromyography), or pressure generated by respiratory muscles. Sleep quality is measured with electroencephalography, which identifies specific sleep stages, which are organized primarily as they relate to rapid-eye-movement (REM) sleep and non-REM sleep. Guidelines are available that provide consensus on the standardization for study.[4] Variables such as *sleep efficiency*, which is the total sleep time divided by total time of electroencephalographic recording, and sleep disruptions (*arousals*) can be tabulated and are useful descriptors.[5]

The normal sleep pattern follows a periodic pattern, cycling every 90–120 min, that sequences through variable stages of non-REM sleep and culminates in an episode of REM sleep. Breathing responses are distinctly different during REM and non-REM sleep. REM sleep is subdivided into 2 periods: *tonic* and *phasic*. The entire REM period is uniquely characterized by absence of electromyogram-detectable skeletal muscle tone, but the phasic period is further identified by bursts of unsynchronized rapid eye movements. Respiration becomes more irregular and autonomic tone increases during REM sleep, while thermoregulatory control changes (mammals assume a poikilothermic state).[6,7] A basic dictum is that the physiologic mechanisms that control breathing during the awake state are operative during sleep except that the response magnitudes are altered; the magnitude of response and feedback networks is usually reduced. Figure 1 shows the factors that influence control of breathing during sleep.[8]

Gas exchange is altered, with minor but significant reduction in P_{aO_2} and increase in P_{aCO_2}, most obviously during REM sleep.[9,10] The normal ventilatory response to hypercapnia and hypoxia are blunted, compared to during the awake state, most obviously during REM sleep (Figs. 2 and 3).[10] The ventilatory and arousal responses to hypercapnia are much more robust than for hypoxia, with only slight changes in P_{aCO_2} causing recognizable alterations of minute ventilation ($\dot{V}_E$).[11] Diaphragm contractility is reduced with hypercapnia and can lead to muscle fatigue and further reduction in ventilatory responsiveness.[12] Arousal responses are much more variable with hypoxia, and many subjects do not arouse even when oxygen saturation is forced to go as low as 70%. The reaction to hypoxic challenge is also distinctly affected by gender, with female subjects being more responsive.[11]

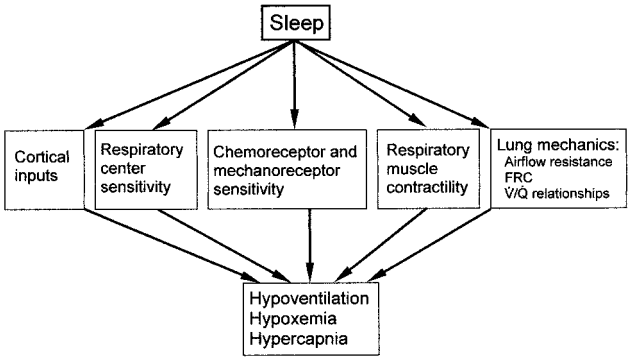

Fig. 1. The effects of sleep on respiration. In each case sleep has a negative influence, which has the overall impact of producing hypoventilation and/or hypoxemia and hypercapnia. FRC = functional residual capacity. V̇/Q̇ = ventilation-perfusion. (From Reference 8, with permission.)

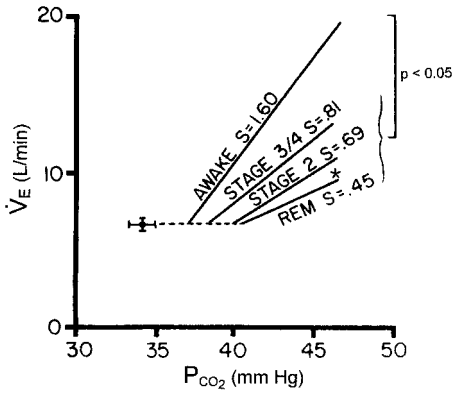

Fig. 2. Relationship of mean minute ventilation ($\dot{V}_E$) to P_{CO_2} in 12 subjects, indicating the mean ± SEM resting minute ventilation/carbon dioxide point in the awake state. The hypercapnic ventilatory response is lower in Stages 2 and 3/4 than in the awake state and is further decreased in REM sleep. V̇/Q̇ = minute ventilation. * Rapid-eye-movement (REM) sleep is statistically significantly different than Stages 2 and 3/4 sleep ($p < 0.05$). (From Reference 10, with permission.)

Major changes in upper airway resistance and tidal volume (V_T) also occur during sleep. Animal studies reveal that local lung receptor nerve traffic influences breathing pattern, which varies with sleep stage and vagal activity.[12,13] Despite a slight increase in respiratory rate, $\dot{V}_E$ in animals and normal subjects decreases, especially during REM sleep, due primarily to reduced V_T.[14,15] The lung volume and gas exchange alterations are more pronounced in COPD patients; they show modest decreases in functional residual capacity during all sleep stages and this may cause substantial ventilation-perfusion (V̇/Q̇) mismatch, leading to hypoxemia.[2,15–18] One study showed that COPD patients have similar degrees of hypoventilation regardless of whether they are major or minor sleep desaturators, which suggests that V̇/Q̇ mismatch plays an important role in nocturnal gas-exchange derangement.[19]

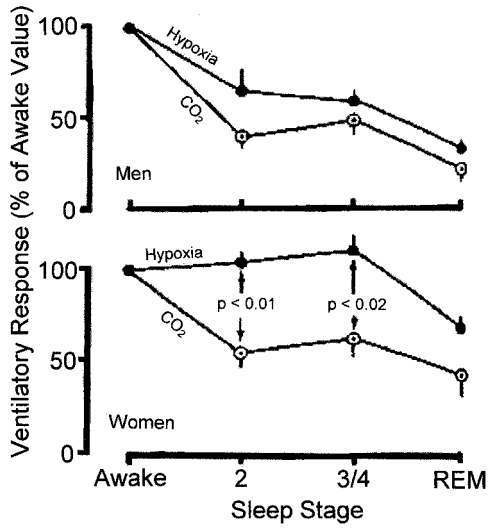

Fig. 3. Mean ± SEM decrease in hypoxic and hypercapnic response from the level in the awake state, in men ($n = 6$) and women ($n = 6$). During non-rapid-eye-movement (REM) sleep women preserve their hypoxic response significantly better than their hypercapnic response, whereas in men the decrements are similar. (From Reference 10, with permission.)

The researchers proposed that V̇/Q̇ mismatch must be influential, but the study was criticized for using end-tidal carbon dioxide measurement to assess the degree of hypoventilation; that technique may not accurately reflect P_{aCO_2} in these patients.[20] The possible mechanisms for reduced functional residual capacity include respiratory muscle hypotonia, cephalad displacement of the diaphragm with recumbency, and decrease in lung adherence.[21] Because of the REM-related atonia of the intercostal and other accessory muscles, the relative contribution of the various respiratory muscles also changes dramatically.[22,23]

The change in $\dot{V}_E$ during sleep is difficult to study accurately and most often has been described using inductance plethysmography, but recent studies with COPD patients used more elegant techniques. When $\dot{V}_E$ was measured with a pneumotachograph and arterial oxygen saturation was measured via pulse oximetry (S_{pO_2}), patients with severe COPD had nearly 20% lower oxygenation during non-REM sleep and 40% lower oxygenation during REM sleep than during the awake state, primarily due to reduced V_T.[24] An "iron lung" converted to act as a body plethysmograph was used to study 5 patients with severe COPD during sleep, and those cases indicated that neither lung volume nor lower-airway resistance changed.[25] The researchers thought that V̇/Q̇ mismatching does not play a major role in nocturnal gas-exchange derangement. They confirmed a $\dot{V}_E$ decrease, by as much as 35%, during REM sleep, due to decreased V_T. Their most impressive findings were related to the marked increase in upper airway resistance: 163% in non-REM sleep and 264% in REM sleep. In addition there was a marked decrease in

respiratory neuromuscular output during sleep, as measured via esophageal occlusion pressure, which fell 39% during REM sleep. They concluded that sleep does not seem to alter lung volume or increase lower-airway resistance dramatically, but a decrease in V_T and inspiratory flow are associated with increased upper airway resistance and reduced respiratory muscle activity. There is, however, a normal circadian rhythm to airway constriction, increasing slightly in normal subjects but much more in patients who have asthma as a component of their COPD.[26,27]

With respect to sleep quality, COPD patients are more likely to regularly use hypnotic medications and have more difficulty falling and staying asleep, and they have more daytime sleepiness. The sleep fragmentation is related to the level of nocturnal desaturation, especially during REM sleep, and the increased number of arousals correlates strongly with this.[20,28,29]

COPD patients with more severe obstruction and hypoxemia have much less total sleep time and time in REM sleep during a given sleep period, with 3 times more frequent sleep-stage changes.[20] The shorter total sleep time and numerous arousals seen in patients with milder awake hypoxemia and airway obstruction do not seem to result in objective or subjective evidence of daytime sleepiness.

Unfortunately, in the study noted above there was no improvement in the reduced sleep time and increased sleep stage changes, even when nocturnal desaturation was effectively treated, despite patients also reporting subjective improvement in sleep quality with oxygen (Fig. 4). In a smaller study, nocturnal oxygen significantly increased sleep time as well as the number and duration of REM periods in hypoxemic and hypercapnic COPD patients.[28] Other common coexisting medical problems, such as gastroesophageal reflux, could contribute to sleep disruption and should not be overlooked.[30]

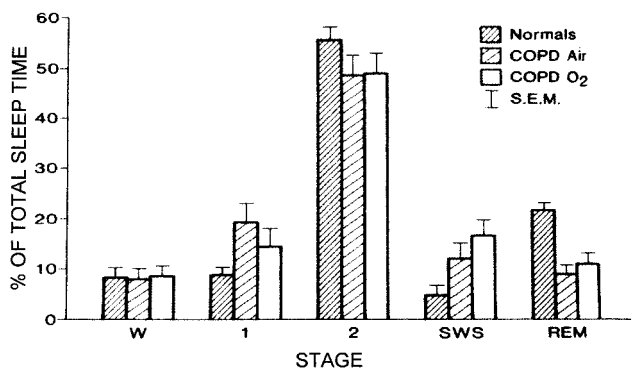

Fig. 4. Sleep stages as a percentage of total sleep time in normal subjects versus in chronic obstructive pulmonary disease (COPD) patients receiving supplemental oxygen (COPD O_2) and COPD patients not receiving supplemental oxygen (COPD Air). W = awake. 1 = sleep stage 1. 2 = sleep stage 2. The COPD patients have less rapid-eye-movement (REM) sleep and less slow-wave sleep (SWS), and this difference is not significantly increased by supplemental oxygen. (From Reference 20, with permission.)

How Should We Evaluate COPD Patients for Sleep-Related Breathing Disorders?

Nocturnal oxygen desaturation (NOD) has long been recognized in COPD patients,[21,24,31–33] who may spend $>$ 30% of sleep time with oxygen saturation $<$ 90% or $>$ 5% of sleep time below awake S_{pO_2}, mostly during REM sleep (Figure 5). The degree of nocturnal desaturation differs markedly among COPD patients and is often difficult to predict. Pulmonary function testing correlates poorly with nocturnal hypoxemia.[19] Nocturnal hypoxemia is affected by co-morbidities such as heart failure and obstructive sleep apnea (OSA), which were not always excluded in studies.[29] Patients with more chronic bronchitis ("blue bloaters") show the best correlation between awake oxygen saturation and lowest saturation, when cardiac arrhythmia are also likely to occur.[28,29,34] The maximum change in nocturnal oxygen saturation has been negatively correlated with the awake ventilatory response to hypercapnia and awake oxygen saturation.[33] The hypoxic ventilatory response during the awake state is not useful in predicting nocturnal oxygen saturation change, but moderate desaturation during exercise does have some predictive value for reduced nocturnal mean and nadir saturation.[19,31]

There is no universal agreement as to how and when COPD patients should be evaluated for nocturnal hypoxemia, because it is controversial what level of nocturnal hypoxemia merits treatment, who should be treated, and how aggressively to follow it. Both the Report of the Medical Research Council Working Party and the Nocturnal Oxygen Therapy Trial demonstrated improved survival with the continuous use of long-term oxygen therapy (LTOT) when including the hours of sleep.[35,36] In the Nocturnal Oxygen Therapy Trial, the survival advantage also paralleled a reduced rate of progression for pulmonary hypertension.[37] A joint effort by the American Thoracic Society and the European Respiratory Society is underway to revise the standards for evaluation and treatment of COPD patients. The standards will include those patients with NOD who do not meet current recommended criteria for treatment with continuous oxygen therapy. It is not expected that there will be major changes for this category, compared to the 1995 guidelines.[38]

- Nocturnal oxygen should be prescribed to patients who suffer substantial desaturation ($\leq$ 88%) during sleep. This can generally be predicted from daytime hypoxia ($P_{aO_2} < 55$ mm Hg), and the goal is to maintain arterial oxygen saturation (S_{aO_2}) $>$ 90% for 70% of the time.

- Measuring nocturnal oxygen saturation in COPD patients who have daytime P_{aO_2} of 55–59 mm Hg is not

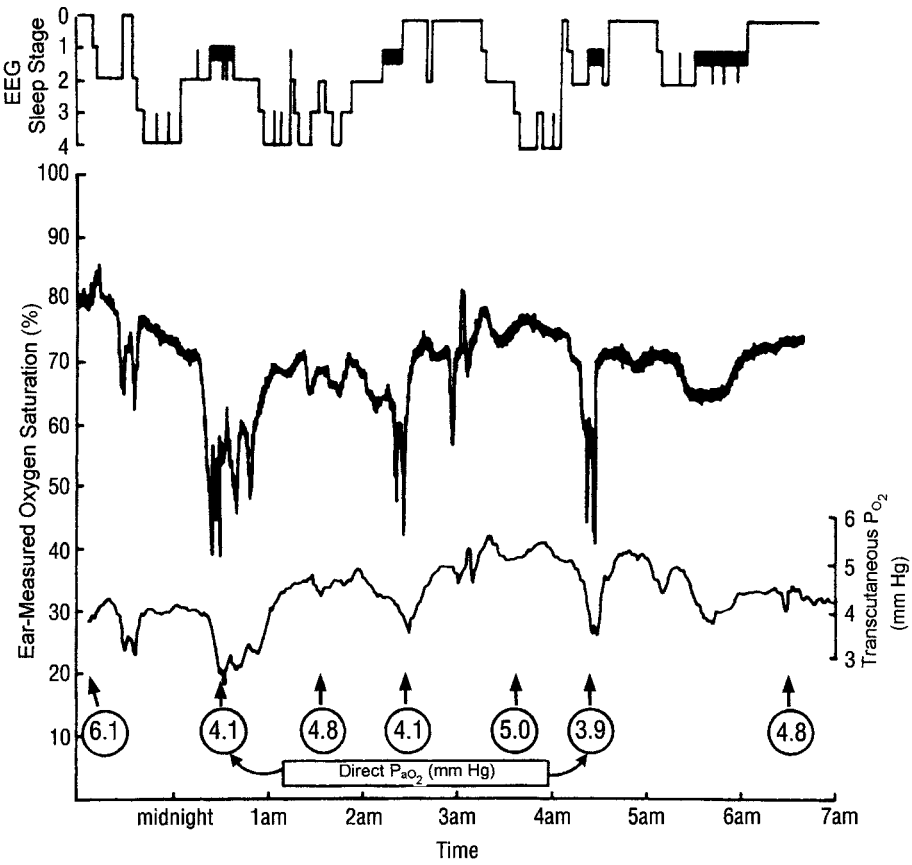

Fig. 5. Overnight recordings of: (top curve) electroencephalographically-measured sleep stage (in which the shaded areas represent rapid-eye-movement sleep); (middle curve) ear-measured oxygen saturation; (bottom curve) transcutaneously-measured P_{O_2}; and (circled values) intermittently measured P_{aO_2} in a 55-year-old male patient with chronic obstructive pulmonary disease. (From Reference 33, with permission.)

recommended, except in patients with unexplained polycythemia or cor pulmonale, in which case oxygen flow should be titrated to maintain $P_{aO_2} > 60$ mm Hg. Full polysomnography should be performed with COPD patients whose symptoms suggest coexistent OSA.

There is evidence to support a more aggressive stance with NOD than the ATS guidelines suggest. In a large registry of patients who died with severe COPD after being treated with LTOT, death during sleep occurred in 20% and unexpectedly in 26% of those deaths.[39] One large study examined the relationship between NOD and mortality in 169 COPD patients with daytime $P_{aO_2} > 60$ mm Hg, using 2 definitions.[40] Definition 1 included patients with $S_{pO_2} < 90\%$ for 5 min to a nadir of at least 85%, to focus on episodic desaturation associated mainly with REM sleep. Definition 2 enrolled patients who had > 30% of the time-in-bed with S_{pO_2} below 90%. Patients with NOD spent a mean ± SD 134 ± 111 min below 90% S_{pO_2}, such that around 20 min reduction below that level included 90% of patients. The non-NOD subjects' survival (corrected for age) was significantly better, but when NOD subjects were stratified for supplemental oxygen use, survival remained better only in subjects separated by definition 1, with a nonsignificant trend toward better survival among the 35 oxygen-treated subjects, compared to the 38 non-oxygen-treated subjects.

The development of increased pulmonary vascular resistance and poorer survival has been correlated with more pronounced NOD, especially during REM sleep.[41] Pulmonary artery pressure is less pronounced in patients who have NOD than in those who do not, and oxygen has a protective effect on supporting better nocturnal pulmonary hemodynamics.[42,43] Mean pulmonary artery pressure actually fell in NOD patients who received (for 36 months) oxygen during sleep, compared to patients given sham treatment (defective oxygen concentrator).[44] Another study assessed whether COPD patients with NOD by definition 2 above develop increased pulmonary artery pressure.[45] NOD occurred in 82% of patients and was predicted by both forced expiratory volume in the first second (FEV_1) and P_{aCO_2} level. Mean nocturnal S_{pO_2} correlated with body

mass index and P_{aCO_2} but not with P_{aO_2}. On the other hand, not even multi-variate analyses were capable of predicting the presence of pulmonary hypertension.

In a randomized trial, 135 consecutive stable COPD patients with definition 2 NOD were evaluated after an average of 40 months of oxygen use (12–14 h/d); oxygen failed to show survival benefit, despite nearly 30% mortality in the first 3 years.[46]

A 2-year, randomized trial in Europe studied 66 COPD patients who had mean daytime P_{aO_2} of 56–69 mm Hg and NOD but no OSA (measured via polysomnography). Forty-one patients received NOT with a goal of $S_{pO_2} > 90\%$ all night, and 35 patients received no NOT.[47] The measured variables included pulmonary hemodynamic effects, survival, and requirement for LTOT. The 2 groups were well matched, with identical baseline mean ± SD daytime P_{aO_2} (63 ± 3 mm Hg). Twenty-two patients (12 in the NOT group and 10 in the control group) required LTOT ($p = 0/98$) and 16 patients died (9 in the NOT group and 7 in the control group, $p = 0.84$). Forty-six patients showed slight increase (< 2 mm Hg) in mean resting pulmonary artery pressure, which settled near 20 mm Hg and did not differ between the groups. Use of NOT also did not delay the prescription of LTOT and had no effect on survival. The study can be criticized for having a small number of patients and there were very few deaths, which precludes firm conclusions about survival. Nevertheless, the researchers concluded that use of NOT for this group of COPD patients is probably not justified.

With the ready availability and low cost of nocturnal oxygen saturation studies, it seems prudent to also be more attentive to saturation measurement in patients who have moderate COPD and possible NOD. As noted above, there is guarded consensus on the use of alternative predictors of NOD. Awake S_{pO_2} and lowest exercise S_{pO_2} during a 6-min walk test are the standard methods of determining a patient's need for LTOT, but those measures correlated poorly with oxygenation measures during sleep or activities of daily living in a prospective, cohort study of 20 stable COPD patients.[48]

The ATS guidelines encourage increasing oxygen flow by 1 L/min during sleep in COPD patients receiving LTOT, but a study of 82 consecutive severe-COPD patients (mean ± SD FEV_1 0.87 ± 0.33 L, P_{aO_2} 51.6 ± 5 mm Hg, and P_{aCO_2} 47 ± 8 mm Hg) suggested otherwise.[38,49] Thirty-nine patients (47.6%) spent > 30% of the night with $S_{pO_2} < 90\%$ while breathing supplemental oxygen. Their mean ± SD overnight S_{pO_2} while breathing oxygen was 87.1 ± 4.5%, and the percentage of the recording time spent with $S_{pO_2} < 90\%$ was 66.1 ± 24.7%. Comparison of ventilatory variables and daytime blood gases between both groups revealed statistically significantly higher P_{aCO_2} on air ($p < 0.001$) or on oxygen ($p < 0.05$) and lower P_{aO_2} on oxygen ($p < 0.05$) in the group of patients demonstrating this substantial nocturnal desaturation. The researchers concluded that about half of COPD patients receiving LTOT need oxygen flow increases > 1 L/min during sleep, especially those with both $P_{aCO_2} \geq 45$ mm Hg and $P_{aO_2} < 65$ mm Hg while breathing oxygen.

Polysomnography is generally not recommended for COPD patients except in a subset population.[50] The term "overlap syndrome" was introduced by David Flenley to describe OSA in association with COPD, in which gas exchange and symptoms seemed out of proportion to the degree of airway obstruction.[51] Clinicians were cautioned to suspect COPD patients who are hypercapnic but have only moderately severe reduction in FEV_1, who are obese snorers, or who get headache after NOT. Daytime hypercapnia in COPD patients, then, may also be associated with OSA or other types of sleep-related breathing disorders, such as obesity hypoventilation syndrome, and require further evaluation and treatment.[52]

The prevalence of hypercapnia was investigated in a review of 219 consecutive patients evaluated in a sleep center.[53] Overall, only 17% had hypercapnia ($P_{aCO_2} > 45$ mm Hg), with 3 distinct groups having some distinguishing features. As expected, the overlap patients (10%) had more airway obstruction, and the degree of hypercapnia was correlated with the obstruction. The obesity hypoventilation syndrome patients (13%) were younger, heavier, and the most hypercapnic, with P_{aCO_2} related to the degree of restrictive lung disease. The remaining patients (77%) had more "pure" OSA, but the apnea-hypopnea index did not help distinguish the degree of hypercapnia. Awake hypercapnia worsens during sleep in patients with chronic bronchitis, obesity hypoventilation syndrome, and overlap syndrome, such that these patients are more prone to develop cor pulmonale or congestive heart failure and have a poorer prognosis.[54,55] When P_{aCO_2} increases in a COPD patient during the first 6–18 months of LTOT, this also portends a higher mortality rate.[56] The arterial blood gas values may serve as a useful warning sign for patients prone to exaggerated daytime, and especially nocturnal, hypoventilation with LTOT.

Patients with milder COPD were recently the subject of a large study done in conjunction with the Sleep Heart Health Study group.[57] The Sleep Heart Health Study enrolled 5,954 patients who underwent unattended home polysomnography and spirometry, with a total of 1,132 participants who had predominantly mild COPD (mean ± SD ratio of FEV_1 to forced vital capacity [FVC] 63.81 ± 6.56%). The prevalence of sleep apnea-hypopnea was not greater when using a respiratory disturbance index threshold of > 10 events per hour with, versus without, mild COPD (22.3% vs 28.9%, respectively). Participants with both COPD and sleep apnea-hypopnea had greater sleep disruption and desaturation than those with either disorder alone, but generally mild COPD alone was associated with

minimally altered sleep quality. In the absence of sleep apnea-hypopnea but with $FEV_1/FVC < 65\%$, the adjusted odds ratio for sleep desaturation (> 5% total sleep time with $S_{pO_2} < 90\%$) was > 1.9. The researchers concluded that there is no relationship between generally mild COPD and sleep apnea-hypopnea, but an $FEV_1/FVC < 65\%$ is associated with higher risk of sleep desaturation and is greater with both COPD and sleep apnea-hypopnea than with either of those alone.

How Are Co-existing COPD and Sleep-Related Breathing Disorders Best Managed?

The treatment for patients with overlap syndrome should generally start with continuous positive airway pressure (CPAP), as guided by findings from full polysomnography, using current recommendations outlined for patients with OSA.[58] Supplemental oxygen may be necessary in addition to CPAP for those overlap patients with more severe COPD and cor pulmonale, and the continued need for LTOT can be re-evaluated later.[59–61] Optimizing other co-morbid conditions such as left-ventricular dysfunction and other cardiovascular complications should also be addressed in these patients.[55,62]

Patients with obesity hypoventilation syndrome may develop hypoventilation insidiously as weight gain advances and other organ system dysfunction occurs. As daytime gas exchange abnormalities develop, and especially with the development of cor pulmonale, associated sleep deterioration is often observed.[63] Polysomnography is often indicated to rule out an OSA component, but a trial of NPPV can also be initiated at this time; NPPV is efficacious in patients with obesity hypoventilation syndrome.[64] NPPV may be especially useful with patients who require frequent hospitalization and who do not respond to or are intolerant of CPAP.[65,66] A recent consensus conference suggested that polysomnography should be performed to rule out OSA before considering NPPV for a patient with nocturnal hypoventilation due to causes other than COPD or neuromuscular disease. A CPAP trial is recommended if OSA is predominant, unless CPAP has previously failed or it is unlikely that the hypoventilation will respond to CPAP.[67]

Nicholas Hill discusses NPPV treatment of COPD patients in more detail in another report in this Journal Conference,[68] so the present report will concentrate primarily on the issues that pertain to sleep and nocturnal gas exchange. Since little has been published on sleep quality with negative-pressure ventilatory support or mechanical ventilation through a tracheostomy, my remarks will be confined to NPPV treatment alone. The results of studies with patients suffering severe COPD and hypercapnia have been discrepant with respect to both gas exchange and sleep quality, which may relate to both patient selection issues and methodology, particularly choice of ventilator settings.[69–73] Given that the issues of optimal ventilator mode, support level, and interface choice remain unresolved, the true effect of NPPV on sleep architecture is also controversial. Most ventilator adjustments in these studies were guided by forcing the patient to maximum tolerance levels of pressure support with mean inspiratory positive assist pressure of 10–22 cm H_2O. Only in the study with the highest mean inspiratory positive assist pressure ($\geq$ 18 cm H_2O) did patients with severe COPD show significant but small increases in sleep efficiency and total sleep time.[70] Another unique aspect in this study was the increased nocturnal P_{aCO_2} when NOT was given alone, compared to with NPPV, and there was a correlation between rising nocturnal versus diurnal P_{aCO_2} (Fig. 6). Those researchers also enrolled patients with the highest apnea-hypopnea threshold, 10 events per hour, as opposed to a cutoff of 5 events per hour in all the other unsuccessful studies noted above. This again supports the concept that those severe-COPD patients who show worsening hypercapnia with LTOT are probably having worsening hypoventilation with LTOT at night and may be the best candidates for a trial of NPPV (Fig. 7). Sleep architecture and the number of arousals is usually unchanged before and after NPPV, but REM sleep percentage remains reduced, compared to normal older adults (Table 1).[71,73,74] This can relate to the fact that patients may be aroused due to discoordination of the upper airway/glottic opening with the timing of inhalation, and special attention should also be given to mouth leak and poor mask fit.[75–77] Optimizing coordination between patient and ventilator may be key to reducing the more-frequent sleep-stage changes frequently seen with NPPV.[78,79]

How Is the Management of Sleep-Related Breathing Disorders in COPD Patients Complicated by Process and Reimbursement Issues?

The major *process* barriers encountered by the clinician during the management of sleep-related breathing disorders in COPD patients can best be discussed first in terms of deciding about specific treatment *goals* or targets. The *implementation* of treatment must also be carefully thought out to avoid additional difficulties for delivery of optimal care. The therapies under consideration here involve oxygen therapy and NPPV. Although the comments that follow regarding *reimbursement* will soon be outdated because of the frequent reappraisals, the necessity for the clinician to keep in touch with current coverage criteria can easily be appreciated.

Oxygen

The questions when determining the goals of NOT are: What is the threshold saturation level for treatment, and

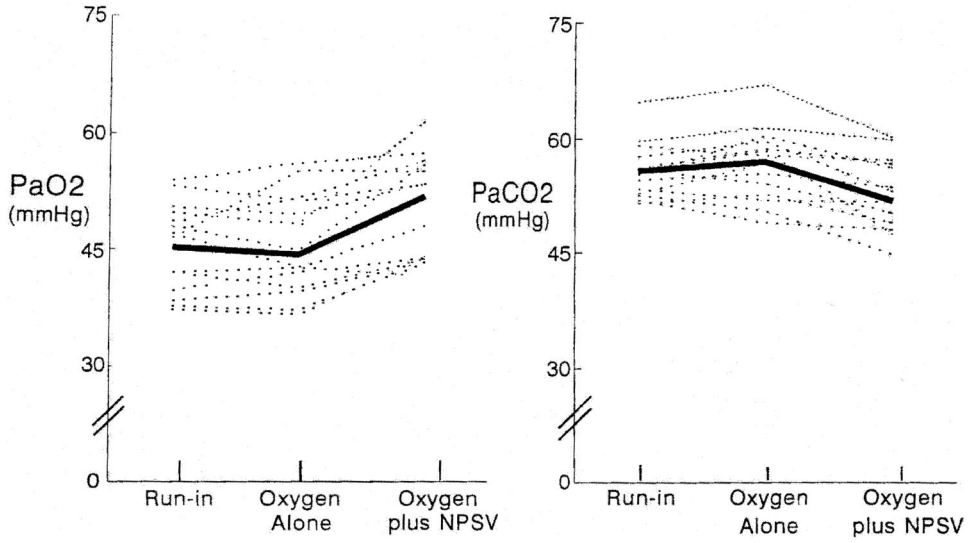

Fig. 6. Individual (dashed lines) and mean (solids line) daytime P_{aO_2} and P_{aCO_2} at run-in and after 3 months of oxygen alone and after 3 months of oxygen plus nasal pressure-support ventilation (NPSV) (n = 14). (From Reference 70, with permission.)

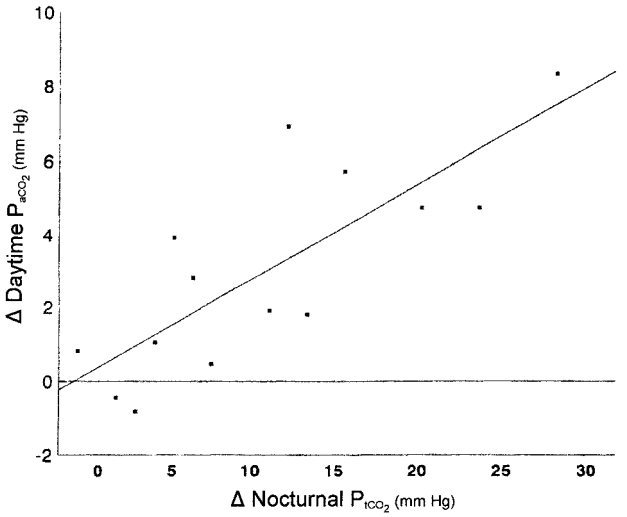

Fig. 7. Correlation between change in daytime P_{aCO_2} and change in mean overnight transcutaneously-measured P_{CO_2} (P_{tCO_2}) for individual patients: n = 14, r = 0.69, p = 0.1. (From Reference 70, with permission.)

what is the necessary vigor of maintenance above an oxygen desaturation limit? Although sleep quality is another consideration and may be subjectively improved with oxygen therapy, there is little objective evidence that sleep quality should be used as a treatment goal.[20] *How* to determine the threshold saturation and vigor of saturation maintenance may be influenced by the presence and degree of pulmonary hypertension, especially in patients with more severe COPD and NOD. *Where* to make the decisions is usually a practical concern, but oxygen therapy is typically determined during an office visit when continuous LTOT is needed. Home overnight oximetry before and after selection of nocturnal oxygen flow rates should usually be done for optimal management. Given the paucity of data to enlighten practitioners in either regard, however, it is understandable that both targets are not clear-cut. Each of these decisions is probably best individualized by the treating caregiver, but some more specific guidelines are offered below.

The current Centers for Medicare and Medicaid Services coverage criteria are relatively liberal and allow ready access according to most of the evidence reviewed above. The criteria most pertinent for this discussion deal with NOT, which is permitted when the threshold is met for 24-hour LTOT, but there are also specific requirements for patients who have nocturnal hypoxemia alone that are less stringent in the presence of other medical problems such as cor pulmonale. There is some concern about the present language, and one of the revisions proposed in the draft policy that was released for comment in July 2001 was to change the coverage criterion for oxygen when it is based solely on a nocturnal oximetry study, as explained below.

Current and Draft Oxygen Coverage Criteria. Home oxygen therapy is currently covered only if all of the following conditions are met:[80]

- Group I criteria include either (1) awake $P_{aO_2} \leq 55$ mm Hg or $S_{aO_2} \leq 88\%$ or (2) asleep $S_{aO_2} \leq 89\%$ for at least 5 continuous minutes, with a nadir of $\leq 85\%$.
- Group II criteria include the presence of criterion A or B (below) plus criterion 1, 2, or 3 (below).

  A: Awake (at-rest or during exercise) P_{aO_2} of 56–59 mm Hg or $S_{aO_2} \leq 89\%$

  or

  B: S_{aO_2} decrease of $>$ 5% for at least 5 continuous minutes, with a nadir of $\leq$ 85% during sleep

Table 1. Summary of Sleep Data from Chronic Obstructive Pulmonary Disease Patients Who Received Noninvasive Positive-Pressure Ventilation

Authors	*n*	Disease	TST	Efficiency	% REM	Arousals
Strumpf et al[69]	7	COPD	NC	NC	NC	U
Meecham-Jones et al[70]	18	COPD	↑ ↑	↑ ↑	NC	U
Gay et al[71]	4	COPD	NC	NC	↓ ↓	U
Lin[72]	12	COPD	U	↓	NC	U
Krachman et al[73]	6	COPD	↑ ↑	↑ ↑	NC	NC

TST = total sleep time
% REM = percent of time in rapid-eye-movement (REM) sleep
↑ ↑ = significantly improved
NC = no change
↓ = worse
↓ ↓ = significantly worse
U = data unavailable

1. Dependent edema due to congestive heart failure, *or*
2. Pulmonary hypertension or cor pulmonale, determined by measurement of pulmonary artery pressure, gated blood pool scan, echocardiogram, or "P pulmonale" on electrocardiogram, *or*
3. Erythrocythemia with hematocrit $>$ 56%

The draft policy initially proposed qualification criteria similar to the above but included a clause to consider mandating recertification for LTOT. Under scrutiny are patients who were given LTOT during recovery from a COPD exacerbation and who may not need continued LTOT yet keep it for "convenience" and subjective benefit, which further increases the high costs of LTOT delivery and should probably be curtailed. Although recertification is proposed in the draft policy, it is unlikely this will be acceptable, given that oximetry reimbursement is limited at best and would pose an additional cost and inconvenience. Another alternative would be to consider attaching more specific payment methods to the various oxygen delivery systems (liquid oxygen, compressed gas, and oxygen concentrator).

Noninvasive Positive-Pressure Ventilation

The treatment goals of NPPV are primarily determined by what must be done to address individual patient complaints or requests for symptom relief. Since evidence does exist for improved sleep quality, especially for those with OSA, but also for those with COPD alone, this goal may be reasonable and achievable in patients with severe sleep disruption.[58,70] How this is best accomplished with NPPV is more problematic, as questions remain regarding whether ventilator settings that achieve maximum $\dot{V}_E$ also optimize sleep quality. Where to initiate and assess optimal NPPV settings is easily determined when more obvious overlap and obesity hypoventilation clinical features are present. There is a clear need to achieve upper-airway patency and increased inspiratory flow for hypoventilation in this subset of COPD patients. A recent intriguing finding is that patients who demonstrate improved sleep quality on initial use of CPAP have much better long-term CPAP-therapy adherence, so clinicians should strive to create an optimal initial CPAP experience.[81] The use of hypnotic medications to facilitate the adjustment to NPPV has not been formally studied but should be.

With respect to reimbursement, certain patients must undergo polysomnography to qualify for reimbursement. Presently there are only 3 categories in which to qualify patients with COPD and sleep-related breathing disorders for NPPV, and they fall under the primary diagnoses of either severe COPD, central sleep apnea, or intolerance of CPAP for OSA.[80] The major reimbursement issue that complicates NPPV treatment pertains to the prescription of a backup rate, which is very difficult in coverage category II and III and not allowed at all in category IV (see below). The consensus guideline recommendations noted above and those in the Summary (below) leave much of this decision-making to the discretion of the treating physician.

The current (as of December 1999) NPPV coverage categories (I–IV) and criteria are:

I Restrictive lung disease. This category is not applicable to COPD.

II Severe COPD:

A1: $P_{aCO_2} \geq 52$ mm Hg while the patient is awake and breathing his or her usual fraction of inspired oxygen (F_{IO_2}), *and*

A2: $S_{pO_2} < 88\%$ for at least 5 continuous minutes while the patient is asleep and receiving oxygen at 2 L/min or his or her usual F_{IO_2}, whichever is higher, *and*

A3: Prior to initiating therapy, OSA and CPAP have been considered and ruled out.

B1: A K0532 device (without a backup rate) will be covered for the first 3 months, but the patient

must be reassessed (61–90 days after the initiation of therapy) for adequate therapy-adherence, to ensure continued coverage.

B2: A K0533 device (with a backup rate) will not be covered until after the first 2 months and only when the patient has been compliant with a K0532 device and has not improved.

III Central sleep apnea (ie, apnea not due to airway obstruction):

A: The diagnosis of central sleep apnea, based on complete facility-based, attended polysomnography, *and*

B: OSA is excluded as the predominant cause of sleep-associated hypoventilation, *and*

C: The ruling out of CPAP as effective therapy if OSA is a component of the sleep-associated hypoventilation, *and*

D: Oxygen saturation $<$ 88% for at least 5 continuous minutes, measured while the patient is breathing his or her usual F_{IO_2}, *and*

E: Substantial improvement of the sleep-associated hypoventilation with the use of a K0532 or K0533 device on the settings that will be prescribed for initial use at home, measured while the patient is breathing his or her usual F_{IO_2}.

IV Obstructive sleep apnea:

A: A complete facility-based, attended polysomnography has established the diagnosis of OSA *and*

B: A single-level (E0601) CPAP device has been tried and proven ineffective.

A looming concern relates to the category of payment that the K0533 backup rate device falls under, which is one requiring "frequent servicing" with indefinite coverage, as opposed to the "capped rental" with fixed payment duration, like CPAP. It is very likely there will be a policy change, to switch the K0533 to the "capped rental" coverage category and thereby reduce reimbursement and patient services to an indeterminate but concerning level.

What Are the Summary Indications for Supplemental Oxygen and NPPV During Sleep in COPD Patients?

Summarizing the information above, it is assumed that the normal mechanisms that control breathing during sleep are intact for COPD patients but the responses are blunted, generally leading to hypoventilation and gas exchange abnormalities, particularly in REM sleep. This is most profound for severe-COPD patients, especially those showing worsening hypercapnia with LTOT. Patients who suffer worsening hypoventilation with LTOT at night would probably be the best to consider for a trial of NPPV, presuming that concerns about OSA have been appropriately addressed. Sleep architecture and the number of arousals, however, may not be greatly improved by NPPV, compared to normal older adults. Nevertheless, I believe the following recommendations are reasonable regarding NPPV for patients with severe COPD.

Oxygen

The effects on survival and pulmonary hemodynamics clearly support oxygen therapy for COPD patients. The most contentious issue regards the need for oxygen in COPD patients with NOD (with no universally accepted level) in the absence of current indications for 24-hour oxygen therapy. Although current ATS guidelines recommend treatment only for more extreme desaturation (nocturnal $S_{aO_2} \leq 90\% > 30\%$ of the time), the Centers for Medicare and Medicaid Services coverage criteria are much more liberal ($S_{aO_2} < 89\%$ for 5 continuous minutes). There is nevertheless persuasive evidence of worse survival in patients who have $S_{aO_2} \leq 90\%$ for 5 min and nadir saturation $\leq 85\%$. Both the ATS and ERS updated guidelines and the revised Centers for Medicare and Medicaid Services coverage criteria for oxygen therapy are pending but, based on the available data, as stated above, it seems prudent to recommend that:

1. Continuous oxygen therapy is justified in patients with awake $P_{aO_2} \leq 55$ mm Hg or $S_{aO_2} \leq 89\%$. Oxygen flow should be controlled to maintain a target S_{aO_2} of $\geq 90\%$, with increased oxygen flow as needed, and with special efforts to assess this via additional monitoring during the hours of sleep.

2. With patients who do not meet criteria 1, NOT should be considered for patients with $S_{aO_2} \leq 90\%$ for 20 min, with a targeted attempt to maintain $S_{aO_2} \geq 90\%$.

3. Although evidence is limited, oxygen therapy may be considered for less total time (5 min) with $S_{aO_2} \leq 90\%$, at the discretion of the treating clinician, in the presence of other cardiopulmonary or cerebrovascular disorders such as pulmonary hypertension, arrhythmia, left ventricular dysfunction, angina, or stroke.

Noninvasive Positive-Pressure Ventilation

These recommendations regarding NPPV for COPD patients are confined to effects on improvement in sleep quality and nocturnal gas exchange. Based on guidelines from the NPPV consensus conference and other evidence described above, it seems prudent to recommend that:

1. Patients with COPD and awake chronic $P_{aCO_2} \geq 55$ mm Hg, and who are receiving otherwise optimal therapy, should be considered for nocturnal NPPV without a backup rate; therapy may be guided by empirical ventilator settings, overnight oximetry, and awake blood gas values.

2. Patients with P_{aCO_2} of 50–55 mm Hg who have obesity or worsening hypercapnia on LTOT or NOT alone

should be considered for complete polysomnography. In the presence of OSA, CPAP could be tried and should be proven ineffective before introducing NPPV, unless the patient's severity of disease is unlikely to respond to CPAP.

3. In all cases, aggressive continued monitoring of blood gas values or nocturnal S_{pO_2} and optimization of alternative therapies should take place as indicated. Further observation in the laboratory with full polysomnography should be considered for patients who are not improving, with attempts to observe REM sleep state to best decide on the need for a backup rate or additional oxygen.

Studies clearly need to be continued to further explain the true effect of NPPV on sleep quality and control of breathing, both on an immediate and sustained basis. Until the mechanisms to explain the benefit of NPPV for COPD and other sleep-related breathing disorders are better known, the indications, ideal ventilator settings, and expected response will remain unclear.

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Discussion

Enright: Are you treating the physician, or are you treating the patient? Improving physiologic variables doesn't always result in improved quality of life for the patient. I don't understand which goals of the therapy help the patient. Are you trying to make them live longer? I didn't see any data that suggested that.

Gay: Dr Nick Hill will talk about mortality issues in his presentation to this Journal Conference.[1]

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Enright: With regard to sleep apnea, what you're trying to treat, and what happens—amazingly—just by the next day, is reduced daytime sleepiness. I didn't see any data suggesting that. You talk about improving sleep variables such as reducing nocturnal desaturation, but maybe people sleep better and get more restful sleep if they have lower oxygen levels? Maybe you're just messing with Mother Nature and not achieving any positive outcomes.

Gay: I'm not sure I understand your question—whether you're talking about supplemental oxygen or NPPV?

Enright: Both. What is the therapeutic goal? Are you trying to increase the duration of life? Increase the quality of life? Or are you just trying to bring physiologic measurements into the normal range of a healthy person without COPD?

Gay: I think for supplemental oxygen the arguments are a lot more difficult and it's not easy to be precise about the targets, but for NPPV I emphasize the fact that COPD and OSA are often co-existing disorders. I think these people have OSA problems such as sleepiness, and they are better when you treat that, as opposed to what I think you're saying, which is that in the patient with pure COPD you're maybe just treating the gas-exchange abnormality without substantial symptomatic benefit, and I actually agree with you.

But for the patients who are symptomatic with sleep disruption and you put them in the laboratory and they get better, everyone would agree that that's of value to the patient. The data from randomized, controlled trials (both short-term in Gerry Criner's group,[1] and in the other long-term 3 studies[2–4]) showed some benefit with sleep, certainly in the largest group of patients in the Meecham-Jones study, who had more than just COPD. They had a disorder of ventilation during sleep, and they became more hypercapnic with supplemental oxygen. Perhaps I can accept some of your argument focusing on pulmonary hypertension and on improvement in daytime gas exchange alone as somewhat ignoring patient symptom-relief. In my study the placebo group was the most compliant.[3] The other patients would send the box back. So I think it's important to recognize that it's the *combined* disorders that are most likely to benefit from NPPV. Recognition of an additional hypoventilation component in those patients will, I think, dramatically improve this subset of COPD patients.

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Enright: So it's the daytime sleepiness I should be aware of with any patient, regardless of whether they

have COPD? Is that what I'm looking for that would tell me to look at their nocturnal oxygen saturation or even do a full polysomnogram, because that's what I'm trying to fix?

Gay: That with other features that suggest worsening hypoventilation. I'm amazed at how infrequently even some of my own colleagues take a sleep history, when they're so focused on COPD. Daytime sleepiness is not a very good marker. These are patients who are miserable. They're just trying to get through the day, and they just think daytime sleepiness and fatigue is what they're going to have. So thinking, "Oh, I'll find a symptom, and now I'll find a reason to treat it with NPPV," is naïve. I don't think that's going to get all the answers and pick out those people who will benefit.

MacIntyre: What about patients in a pulmonary rehabilitation group who come with baseline P_{O_2} in the mid-60s or 70s [mm Hg], but who desaturate quite a bit during exercise on stationary bike or walking? We put them on oxygen during their exercise periods. Is there any correlation between exercise desaturation and sleep desaturation?

Gay: There is some, but it's a weak correlation. It's difficult to predict nocturnal desaturation from other studies. I think the take-home lesson is that just about nothing during the daytime, except significant hypoxemia that qualifies for continuous oxygen, tells you, "Aha, this patient should get nocturnal oxygen."

Giordano:* Regarding your description of the "capped rental," you were accurate as far as you went, but there is another piece to it, which is that after 15 months of rental the home medical equipment supplier will be paid the equivalent of 1 month's rent every 6 months to maintain the equipment. So there is a bit of a tail on the payments, and I just want to make sure we describe the entire process.

Fahy: I discuss sleep with my patients during the initial assessment and they often say, "I sleep as well as I should be sleeping, I guess." But then I get them into an education class and, though I'm pretty loud when I lecture, they're *sleeping* through my lecture. I call the referring doctor and say maybe that patient should get a sleep study, and we've identified quite few patients who require CPAP or nocturnal ventilation of some sort.

Gay: These patients have so many obstacles in front of them; trying to convince them that improving their sleep should be a priority can be difficult and often doesn't come up.

Hill: One of the things that struck me about sleep-disordered breathing in patients with severe COPD is the remarkable individual variability. In the noninvasive ventilation study we did with David Strumpf, we excluded patients who had more than 5 apneas or hypopneas per hour, and those people maintained essentially normal oxygen saturation all night without oxygen supplementation.[1] Those patients had severe airway obstruction with FEV_1 averaging about 500 mL, but patients with much less obstruction may have far worse nocturnal oxygenation and frequent desaturations. Physiologically, what do you think explains that kind of variability? Is it central drive? Is it that the patients who have less desaturation have less REM-sleep? What's going on there?

Gay: I've got to be honest and say I really don't know. Obviously, there are multiple mechanisms, and how they interact ultimately determines gas exchange. It's pretty clear that those single items—the severity of FEV_1 abnormality and the apnea-hypopnea index in the overlap patients—do not predict the combination result that you see at night in these patients. I think that's why a lot of these where the oximetry studies that are simple and available really should be used more frequently in these patients. You can't predict very well from the history alone.

Wedzicha: Something that confuses me is increasing oxygen flow at night. Some physicians advocate increasing the oxygen flow rate at night in patients who desaturate but I would argue that these are the patients with whom you do not want to increase the oxygen flow. My practice is to keep oxygen at the same level, 2 L/min, overnight. What do you do in practice, and what do you believe we should all do?

Gay: That's an excellent question. I really appreciate your bringing that up, because the focus is on gas exchange there. In essence, if I turn the oxygen up to improve the oxygenation, I may overlook the fact that the carbon dioxide has been chasing that through the night and blood gas values are worse during the day. The focus should be not only on maintaining oxygenation, but also asking whether hypercapnia is getting worse. I think those are the patients you want to consider for NPPV. That's overlooked when you're wearing your "oxygenation hat." Sure, I can make oxygenation look better, but that may not be better for the patient.

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REFERENCE

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