Long-Term Domiciliary Noninvasive Ventilation for COPD

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COPD can lead to abnormalities in oxygenation as well as ventilation. Thanks to pioneering work by Dr Thomas Petty, supplemental oxygen therapy has been shown to improve morbidity and mortality for individuals with COPD and severe daytime hypoxemia. However, efforts to augment ventilation have been less uniformly successful. Recent studies employing a so-called high-intensity noninvasive ventilation strategy, which used high inspiratory pressures and backup breathing frequency to reduce arterial carbon dioxide levels, have shown improved quality of life and reduced mortality. Thus, efforts are underway to better identify and treat patients with COPD who might benefit from noninvasive ventilation, though many practical questions remain. *Key words: COPD; noninvasive ventilation; hypercapnia; high-intensity; obstructive sleep apnea; overlap syndrome.* [Respir Care 2021;66 (7):1120–1127. © 2021 Daedalus Enterprises]

Introduction

COPD is a major cause of morbidity and mortality in the United States and around the world.[1] Although COPD is recognized to have substantial systemic effects as well, respiratory damage and symptoms predominate. The disease is often preventable, if due to cigarette smoking, but in many parts of the world the cause is more often the burning of biomass for fuel.[2] Many pharmacotherapies exist to improve symptoms, yet few interventions clearly improve survival.

Dr Thomas Petty has been called "the most important physician in the history of respiratory medicine" in part because of his work demonstrating the benefit of supplemental oxygen for individuals with COPD and severe hypoxemia.[3] His other major contribution was the description of ARDS in 1967, and his work showing that PEEP could be used to improve P_{aO_2} for individuals with ARDS.[4] Technological advances at the time made low-flow supplemental oxygen systems portable and feasible for patients. In 1967, Petty and Finigan published their case series of 20 patients with severe hypoxemia who were administered supplemental oxygen.[5] Notable at the time, the authors focused both on physiological outcomes such as P_{aO_2} and hematocrit (as many patients had polycythemia from chronic hypoxemia), as well as several patient-centric outcomes such as the number of hospitalizations and ability to work.

Over time, and with colleagues from around the world, including David Flenley, a respirologist in Edinburgh, Scotland, the groundwork was laid for 2 ground-breaking and complementary studies: the Nocturnal Oxygen Treatment

Trial (NOTT) and the Medical Research Council (MRC) study.[6-8] Petty led the NOTT study, which was published in 1980 and conclusively demonstrated the benefit of continuous versus nocturnal-only supplemental oxygen in patients with severe daytime hypoxemia.

Does Too Much Oxygen Cause Hypercapnia?

One of the major concerns about the use of supplemental oxygen was the possibility of an increase in P_{aCO_2}. Even in the initial 1967 case series, Petty argued that CO_2 retention was rare and unlikely to occur with patients who were using low-flow oxygen without exacerbation and who were initially carefully monitored. This topic was a theme throughout Petty's life, and in one of his last scientific publications he argued against treating high P_{aCO_2} in the absence of other symptoms.[9] It is worth reviewing the mechanisms by which supplemental oxygen can induce hypercapnia and recognizing that changes which have occurred over the last few decades may predispose to more oxygen-induced hypercapnia today.[10] These changes include increased prevalence of obesity and obstructive sleep apnea (OSA), the ability to provide higher amounts of oxygen, and finally the increased use of opioids and other drugs that may blunt the normal physiological response to changes in P_{aCO_2}.

Sleep and Breathing

Normal Changes in Respiration That Occur During Sleep

The respiratory system functions to provide adequate oxygen delivery and to excrete CO_2 and can do so under an incredible range of conditions, from sea level to high altitude, from rest to peak exertion. However, under nearly all conditions the major drive to breathe and the determinant of ventilation is the level of CO_2 and the resultant pH of the blood and cerebral spinal fluid. The system operates as a negative feedback loop with increases in P_{aCO_2} and drops in pH leading to increases in ventilation and vice versa.

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While awake, the linear relationship between ventilation and P_{aCO_2} usually maintains P_{aCO_2} at 40 mm Hg. However, during sleep (and with measurable changes during the different sleep stages), the slope of this relationship is decreased, ultimately leading to a slightly higher P_{aCO_2} of about 45 mm Hg and a reduction in minute ventilation of $\sim$ 15% during rapid eye movement (REM) sleep.[11] The drop in minute ventilation is due to a drop in tidal volume with the breathing frequency being about the same or even slightly increased above quiet breathing while awake.[12] Other changes that occur during sleep include the loss of muscle tone, particularly during REM sleep when only the activity of the diaphragm is preserved. The drop in muscle tone leads to a more collapsible upper airway, important for OSA.

Sleep and COPD

That the normal changes in sleep might serve as a stress test for individuals with COPD has been recognized for decades. McNicholas and Fitzgerald made the observation that individuals with hypercapnic respiratory failure were more likely to die at night compared to those with stroke or nonpulmonary malignancies, whose deaths were more evenly distributed.[13] A variety of studies have shown objectively measured worse sleep compared to controls.[14] Even in the modern era, most patients with COPD have sleep complaints.[15] More recently, sleep symptoms have been shown to discriminate between those at high risk for exacerbation of COPD.[16]

Until recently, however, the most recognized sign of sleep and COPD has been nocturnal oxygen desaturation. For the reasons listed above, oxygen saturation falls slightly during the night, even in those without pulmonary disease. In those with COPD, who may rely on accessory muscle use for ventilation, the drop in both ventilation and oxygenation can be more profound (Fig. 1).[18] Even individuals with a relatively normal daytime oxygen saturation (ie, 90–95%) may have substantial nocturnal desaturation episodes.[19-21] Additionally, many patients with COPD may live on the steep part of the oxygen desaturation curve, where changes in P_{aO_2} lead to changes in S_{aO_2}.

The wide availability of pulse oximetry has focused attention on oxygen desaturation. Unfortunately, changes in P_{aCO_2} are often neglected (and much less studied) because of the difficulty in obtaining an arterial measurement or the cost of noninvasive measurements such as transcutaneous CO_2. Although not well studied, it is hypothesized that chronic hypercapnia begins with nocturnal increases in CO_2 that are not fully cleared during the day.

The Overlap Syndrome: COPD and OSA

OSA is characterized by repetitive collapse of the upper airway during sleep, resulting in intermittent hypoxemia and arousals from sleep. It results in neurocognitive (eg, daytime

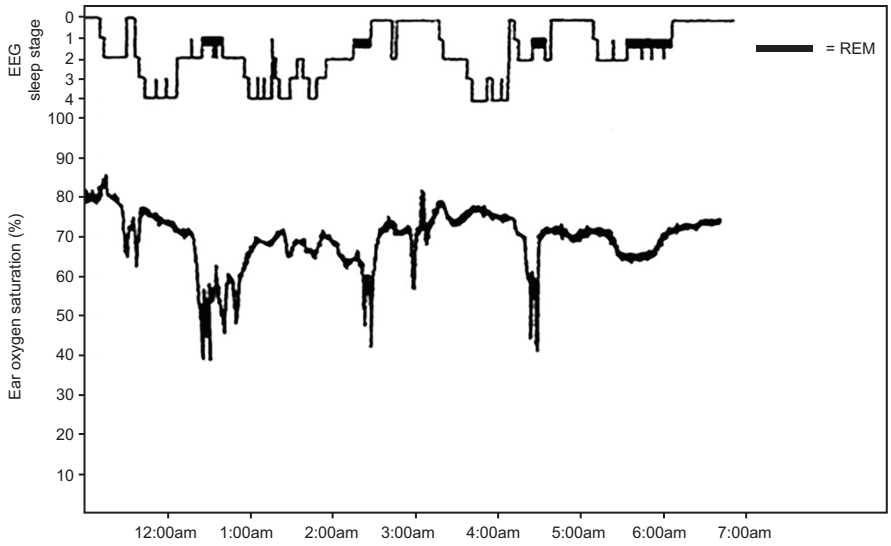

Fig. 1. Example of nocturnal oxygen desaturation. The top graph shows the electroencephalogram (EEG) sleep stages with rapid-eye movement sleep (REM) in bold. The lower graph shows transcutaneous oxygen measurements during sleep in a subject with COPD. Hypoxemia worsens during sleep, most substantially during REM sleep. From Reference 17, with permission.

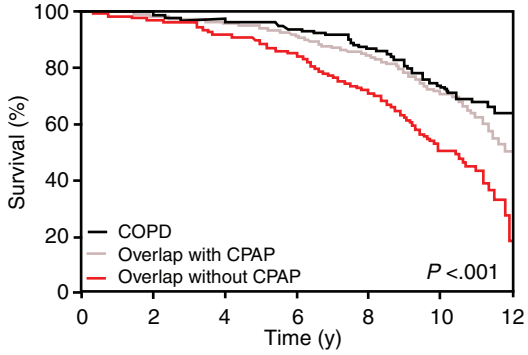

Fig. 2. Kaplan-Meier survival curves for outcomes among subjects with COPD, overlap subjects on CPAP, and overlap subjects without CPAP. CPAP treatment was not randomly assigned, which is a source of potential bias, although markers of disease severity were similar, on average, in the treated and untreated groups. Overlap = COPD and obstructive sleep apnea. From Reference 29, with permission.

tiredness, motor vehicle accidents) and cardiovascular (eg, hypertension, myocardial infarction, strokes) consequences. It is a common disease, thought to occur in 1 of 5 middle-aged men, and in 1 of 10 middle-aged women.[22] Relevant for this discussion, OSA is so prevalent that there are likely many patients with COPD who also have OSA. David Flenley coined the term "overlap syndrome" to refer to those "blue bloaters" with COPD who also had OSA.[17] He believed that such patients had a distinct clinical course compared to those without OSA.

Questions remain about the true epidemiology of overlap syndrome and whether there is any shared pathophysiology. Prevalence rates in the literature of overlap syndrome are heavily influenced by the population studied, whether a community sample or a referral population. For example, the Sleep Heart Health Study, which utilized a community-based sample, reported that there was only a 0.5% prevalence of overlap syndrome, with generally only mild obstructive lung disease.[23] In a Veterans Administration population, however, which was older and included more subjects who had previously smoked, the prevalence was 39%.[24] Finally, Soler and colleagues performed polysomnography in subjects with COPD enrolled in a pulmonary rehab program. In this cohort who had moderate to severe OSA, the prevalence of coexisting COPD was 65%.[25]

One factor in assessing OSA burden in patients with COPD is that the definition of hypopnea depends on oxygen desaturation. Thus, patients with COPD may have a greater tendency to desaturate (and meet criteria for a diagnosis of OSA) then those with a similar tendency for upper airway collapse without lung disease.[26] Alternatively, there may be mechanisms by which one disease predisposes to the other. For example, it may be that smoking (or inhaled steroid use for patients with COPD) blunts the reflexes of the upper airway, predisposing to collapse and OSA (reviewed by Owens and colleagues[27,28]).

Whatever the true prevalence and pathophysiology, data suggest that patients with overlap syndrome have worse outcomes compared to those with COPD alone. Marin et al[29] reported that, over 12 y, individuals with overlap syndrome had considerably greater mortality compared to those with COPD alone (Fig. 2). Although the data are observational and therefore subject to a number of biases, subjects who used CPAP had similar mortality compared to those with COPD alone, and this observation has been made in other cohorts.[30,31] Data also suggest that diagnosis and treatment of OSA in patients with COPD can reduce hospitalizations.[32]

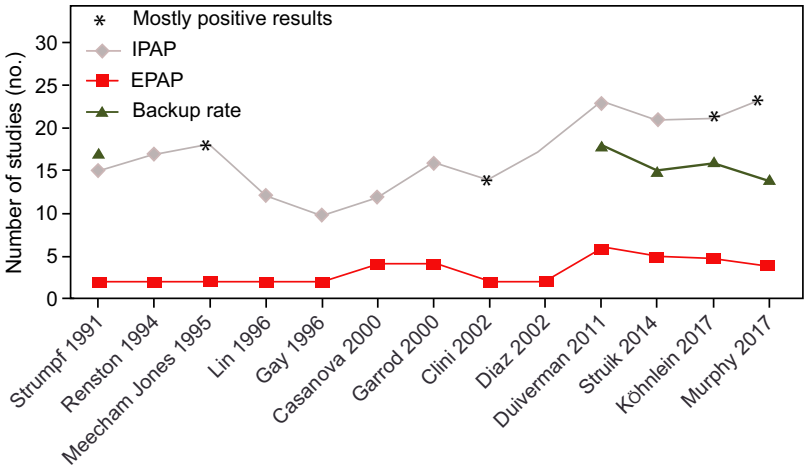

Fig. 3. Summary of ventilatory settings in many of the studies examining the use of noninvasive ventilation in stable COPD. IPAP = inspiratory positive airway pressure, EPAP = expiratory positive airway pressure. From Reference 39, with permission.

Conversely, treatment of overlap syndrome with supplemental oxygen alone, at least in a one-night study, resulted in higher P_{aCO_2} and lower pH values at the end of respiratory events.[33] Clinically, the rise in nocturnal rise in P_{aCO_2} in individuals with COPD given supplemental oxygen may lead to morning headaches, a sign to consider OSA/overlap as a relevant diagnosis.[34]

Taken together, the above data suggest that clinicians who care for patients with COPD should screen their patients for OSA. Unfortunately, it is unclear how well traditional risk factors for OSA predict overlap syndrome in those with COPD.[35] Another clue to undiagnosed OSA is the development of hypercapnia or pulmonary hypertension despite relatively preserved spirometry.[36,37]

COPD and Noninvasive Ventilation

The benefits of noninvasive ventilation (NIV) for those with an exacerbation of COPD are well established. The focus of this review is the value of NIV for individuals with stable chronic hypercapnic COPD. Although not formally defined, "stable" and "chronic" suggest otherwise optimal treatment of COPD, far removed from exacerbation. Different interventional studies have used different levels of P_{aCO_2} to define hypercapnia.

A Historical Review of the Evidence

Like the use of oxygen, there is a long history for the use of NIV, even negative-pressure ventilation (eg, an iron lung) in patients with COPD.[38] However, the data have been more mixed compared to oxygen for a variety of reasons. First, as mentioned previously, the assessment of P_{aCO_2} or its surrogates is less facile than measurement of P_{aO_2} or its surrogate. Second, and related, the target for improving P_{aO_2} or S_{aO_2} is more clear than that for P_{aCO_2}. Third, devices to improve ventilation and hence P_{aCO_2} are less comfortable than oxygen. Fourth, optimum settings for such devices are still unknown. The result of these difficulties is that there have been a variety of (usually small) studies with different interventions and variable results (Fig. 3).[39] The study by McEvoy et al[40] in 2009 (not included in Fig. 3) is one of the larger ones, in which 144 subjects with stable hypercapnia (defined as $P_{aCO_2} > 46$ mm Hg) were randomized to usual care versus NIV. Here ventilation was provided in a spontaneous mode, with inspiratory pressures of $\sim$ 13 cm H_2O. Although adherence was good, there was no difference in mortality in the unadjusted analysis, and quality of life was worse.

High-Intensity NIV

Since the 2000s, some groups have advocated for the use of so-called high-intensity NIV, which refers to the use of high inspiratory pressures and a backup rate to drive down P_{aCO_2}.[41,42] In the reported studies, the typical inspiratory pressures were > 25 cm H_2O, and the backup breathing rate was > 20 breaths/min. Randomized data were lacking, however, until the publication of the landmark study by Köhnlein et al[43] in 2014. In this study, subjects with GOLD stage IV COPD with $P_{aCO_2} > 51$ mm Hg and no recent exacerbation were randomized to NIV with a high-intensity strategy. The 195 subjects had mean age of $\sim$ 63 y, body mass index $\sim$ 25 kg/m^2, FEV_1 27% of predicted, and baseline P_{aCO_2} of $\sim$ 58 mm Hg. Most were on long-term oxygen therapy. On NIV, the mean inspiratory pressure was 21.6 cm H_2O and the mean backup rate was 16 breaths/min. Adherence was quite good, with a mean use of 5.9 h/d, and ultimately P_{aCO_2} dropped to 49 mm Hg over 1 y of use (compared to a decrease to 56 mm Hg in the control

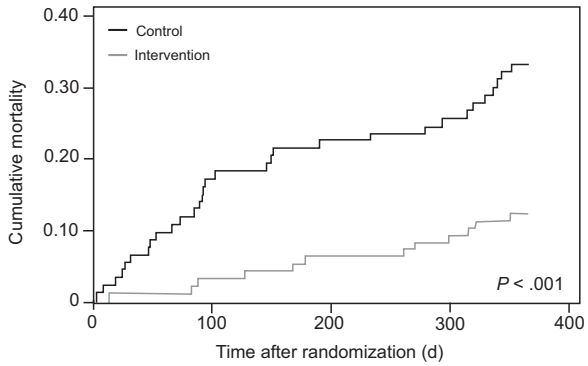

Fig. 4. Kaplan-Meier estimate of cumulative all-cause mortality during the first year after randomization. Results are from the study by Köhnlein et al,[43] a randomized controlled trial of high-intensity noninvasive ventilation for stable hypercapnic COPD. *P* value is based on log-rank test of between-group difference. From Reference 43, with permission.

group). Mortality was strikingly improved, with 12% of subjects in the NIV group dying within 1 y compared to 33% in the control group, emphasizing the severity of illness in these subjects (Fig. 4). Importantly, quality of life was improved in the intervention group.

Another important recent study was the HOT-HMV study published in 2017.[44] Similar to the work by Köhnlein et al,[43] the subjects included in this study were quite ill: potential subjects had had a recent exacerbation of COPD, yet P_{aCO_2} remained > 53 mm Hg, and they required long-term oxygen therapy. Again, a high-intensity strategy resulted in a statistically and clinically important reduction in the combined end point of admission-free survival.

There are several important caveats for these studies. First, subjects were enrolled at least 2 weeks after any recent exacerbation. That is, they were not sent home from the hospital with NIV following an exacerbation. Second, both studies excluded patients with known OSA or those with a body mass index > 35 kg/m^2. Third, initiation of NIV often took place in hospital.

Struik and colleagues[45] examined the possibility of initiation of NIV at the time of exacerbation of COPD with hypercapnia. Patients with COPD are at risk for readmission, and each COPD exacerbation contributes to worse outcomes.[46-48] Thus, the so-called Rescue Trial enrolled 201 subjects during hospital admission and randomized them to high-intensity NIV versus usual care. Perhaps surprisingly, there was no difference in mortality at 1 y. One interpretation of these results is that many of the subjects in the Rescue Trial would not have had persistent hypercapnia. Indeed, in the HOT-HMV trial, about 20% of potential enrollees no longer met criteria for hypercapnia when they were re-evaluated 2–4 weeks after discharge from their recent exacerbation. These findings have practical implications about the timing and location of delivery of NIV therapy.

2020 Guidelines for NIV in Stable Hypercapnic COPD

As a result of the research discussed here, both the European Respiratory Society (ERS) and the American Thoracic Society (ATS) produced updated clinical practice guidelines in 2020 for NIV in individuals with COPD.[49,50] These separate efforts both used the GRADE methodology, and both addressed similar questions (with some other questions unique to each group).[51] In the GRADE context, a strong recommendation suggests that most patients should receive the intervention, and that adherence to this recommendation could be used as a quality criterion. Weak or conditional recommendations suggest that most patients and providers should consider the intervention, but implementation may be motivated by individual concerns.

First, both societies recommended the use of NIV for individuals with stable hypercapnic COPD, although the recommendations were both considered weak rather than strong. The recommendation was weak in that the data are not conclusive, although the data suggest trends toward reduced mortality, hospitalization, and improved quality of life. Certainly, real-world considerations about implementation such as adherence and cost are important areas for further research.

Second, both societies recommended the use of a high-intensity, P_{aCO_2}-targeted approach. Even considering only studies using a high-intensity approach, the aggregated data do not clearly show benefit in terms of mortality and other outcomes for those with COPD. In addition, there are no studies directly comparing a low-intensity approach versus a high-intensity approach. However, the additional resources needed to implement this strategy are relatively limited.

Third, both societies addressed timing for initiation of NIV for hypercapnic COPD. Consistent with the studies presented here, the ATS guideline[50] recommended against initiation of NIV immediately following an exacerbation, instead favoring reassessment for hypercapnia 2–4 weeks after resolution, unless patients are persistently hypercapnic and cannot be weaned from NIV while in the hospital. The ERS guideline[49] suggests that such a reassessment could be considered but was not necessary (ie, NIV treatment could begin or extend after an exacerbation). As reflected in these slightly different recommendations, there are no studies examining which hospitalized patients will have resolution of hypercapnia versus those who will not; further, the improvement in P_{aCO_2} after COPD exacerbation has not been examined rigorously. Thus, the 2–4 week reassessment of the need for NIV reflects a single well-done study, but this may not be the optimal time frame.

Practical Questions for Initiation of NIV

While there is broad agreement based on the current literature that NIV should be provided, major questions remain.

How Well Is High-Intensity NIV Tolerated? Most clinicians in the United States have little experience with such high inspiratory pressures or backup rates. Most studies of high-intensity NIV are based in Europe and rely on in-hospital acclimatization and titration, which might not be possible in the United States. However, there are several studies to suggest that high-intensity NIV is better tolerated then low-intensity NIV.[52] Dreher and colleagues[53] used both high-intensity and low-intensity NIV, in random order, for 6 weeks. Interestingly, subjects who started on high-intensity settings had better adherence (as hours/night) compared to those who started on low-intensity settings, and then when transitioned from high to low settings usage dropped. Conversely, hours of use per night increased when going from low to high settings. Thus, while adherence is important, the high-intensity pressure settings themselves might not be expected to reduce adherence. Of note, the high-intensity strategy is associated with reduced respiratory muscle activity (measured with electromyogram), suggesting more offloading of intrinsic work, although the mechanism by which lower P_{aCO_2} might lead to improved outcomes is not known.[52]

Where, When, and How Should Therapy Be Initiated? Most studies of NIV have initiated and titrated therapy while in hospital. Another alternative might be to have patients undergo titration in the sleep laboratory, where they could be introduced to equipment by a registered polysomnographic technologist (RPSGT) or CPAP technician. However, it is important to consider that the goal of P_{aCO_2} reduction is best accomplished over days to weeks, not in a single night, which might cause harm.[54] An alternative approach then would be to start NIV in the home and adjust settings over time, which is feasible with modern machines that have wireless capability for adjustment as well as advanced monitoring capabilities. Duiverman and colleagues[55] recently demonstrated the noninferiority (and lower cost) of this approach compared to hospital initiation of therapy. Of note, in this study the mean time in hospital for acclimatization was 7 d. The ATS guideline[50] suggests against in-laboratory initiation of NIV for similar reasons.

There are a number of ventilation modes that could be used for individuals with COPD and hypoventilation. In particular, volume-assured pressure support (VAPS) modes could be used to automatically titrate inspiratory pressure and then backup breathing frequency to achieve a specified minute ventilation.[56] While theoretically attractive, few data exist regarding the long-term use of these modes in patients with hypercapnic COPD, and nearly all of the prior research has been performed with fixed pressure modes. Thus, the ERS guideline recommends the use of fixed pressure settings.

A related issue, at least in the United States, is how a clinician is able to order devices that provide a backup rate. Currently, Medicare guidelines (often followed by other payers) allow for provision of bi-level positive airway pressure without a backup breathing frequency after a variety of criteria are met. Specifically, daytime hypercapnia ($P_{aCO_2} > 52$ mm Hg) must be documented with arterial blood gas analysis; there must be at least 5 min of oxygen desaturation $\leq 88\%$ despite supplemental oxygen therapy; and OSA and CPAP treatment must be considered (sleep study not required). Only after initial therapy with this basic device and again with a variety of diagnostic procedures can a device with a backup rate be ordered. Perhaps in part because of these requirements, it may be easier to prescribe and receive a home mechanical ventilator than a less costly bi-level device with a backup rate.[57,58] The current guidelines for NIV provision in those with COPD are from 1998, and an update incorporating new science and technology is clearly required.

Consideration of OSA. As mentioned above, overlap syndrome is a common disorder, yet most of the studies of NIV in subjects with COPD above excluded those with OSA or those at risk of OSA from obesity. There may be advantage to correctly diagnosing OSA in a patient with COPD and hypercapnia before the start of NIV. OSA may contribute to obesity hypoventilation as another cause for elevated P_{aCO_2}.[59] The diagnosis of obesity hypoventilation is often delayed, and misdiagnosis, especially with obstructive lung disease, is common.[60] Additionally, patients with COPD and OSA might be treated effectively with CPAP, similar to some patients with obesity hypoventilation who do not require NIV.[61] There is also the theoretical concern that NIV may be less effective if the expiratory positive airway pressure is set too low to keep the upper airway open. For these reasons, the ATS guideline[50] recommends screening for OSA before initiation of NIV but does not recommend consideration of OSA before initiation of NIV and does not require polysomnography at all, which might delay care.

Unanswered Questions and Summary

There are many questions and areas for research in this arena. Identifying the patients most likely to benefit from NIV is a priority. Other than invasive arterial blood gas measurements, are proxy measures such as transcutaneous estimates adequate? Will nocturnal changes in P_{aCO_2} be more useful than daytime values in determining those likely to benefit from nocturnal NIV? Although patient selection is likely very important for improved outcomes with NIV, difficulty in obtaining arterial blood gas measurements in

the out-patient setting might mean that many patients with COPD are not recognized as appropriate candidates. Whether the drop in P_{aCO_2} is the cause of improved outcomes, a marker for sufficient ventilation, or unrelated to the improved outcomes observed is also unclear. The optimal modes and settings for NIV are also unknown. Finally, many of the seminal studies discussed above provided additional support for patients in addition to NIV; these additional resources are likely unavailable in the United States when starting on NIV.

Despite these questions, the use of NIV is on substantially firmer footing than any time in the last 40 years. There are few interventions for patients with COPD shown to improve both quality of life and mortality. Dr Petty recommended that we not treat an elevated P_{aCO_2} of 70 mm Hg in the absence of other symptoms. However, the data presented here suggest that it is increasingly clear that we can and should do so to improve patient-centric outcomes. Many barriers remain to implement current practice guidelines, and advocacy efforts from patients and their physicians are needed.

REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1736-1788.
2. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017;389(10082):1931-1940.
3. Pierson DJ. Thomas L Petty's lessons for the respiratory care clinician of today. Respir Care 2014;59(8):1287-1301.
4. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319-323.
5. Petty TL, Finigan MM. Clinical evaluation of prolonged ambulatory oxygen therapy in chronic airway obstruction. Am J Med 1968;45 (2):242-252.
6. Petty TL. Studies of domiciliary oxygen in a common cause. Thorax 1989;44(7):588-590.
7. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93(3):391-398.
8. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981;1(8222):681-686.
9. Petty TL. CO2 can be good for you! Chest 2006;129(2):494.
10. Malhotra A, Schwartz DR, Ayas N, Stanchina M, White DP. Treatment of oxygen-induced hypercapnia. Lancet 2001;357(9259):884-885.
11. Douglas NJ, White DP, Weil JV, Pickett CK, Zwillich CW. Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 1982;126(5):758-762.
12. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. Thorax 1982;37(11):840-844.
13. McNicholas WT, Fitzgerald MX. Nocturnal deaths among patients with chronic bronchitis and emphysema. Br Med J (Clin Res Ed) 1984;289(6449):878.
14. Krachman SL, Chatila W, Martin UJ, Nugent T, Crocetti J, Gaughan J, et al. Effects of lung volume reduction surgery on sleep quality and nocturnal gas exchange in patients with severe emphysema. Chest 2005;128(5):3221-3228.
15. Price D, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of night-time symptoms in COPD: a real-world study in five European countries. Int J Chron Obstruct Pulmon Dis 2013;8:595-603.
16. Geiger-Brown J, Lindberg S, Krachman S, McEvoy CE, Criner GJ, Connett JE, et al. Self-reported sleep quality and acute exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:389-397.
17. Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985;6(4):651-661.
18. O'Donoghue FJ, Catcheside PG, Eckert DJ, McEvoy RD. Changes in respiration in NREM sleep in hypercapnic chronic obstructive pulmonary disease. J Physiol 2004;559(Pt 2):663-673.
19. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, Levi-Valensi P, et al. Sleep-related O2 desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. Eur Respir J 1997;10(8):1730-1735.
20. Fletcher EC, Miller J, Divine GW, Fletcher JG, Miller T. Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tensions above 60 mm Hg. Chest 1987;92(4):604-608.
21. Lewis CA, Fergusson W, Eaton T, Zeng I, Kolbe J. Isolated nocturnal desaturation in COPD: prevalence and impact on quality of life and sleep. Thorax 2009;64(2):133-138.
22. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177(9):1006-1014.
23. Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003;167(1):7-14.
24. López-Acevedo MN, Torres-Palacios A, Elena Ocasio-Tascón M, Campos-Santiago Z, Rodríguez-Cintrón W. Overlap syndrome: an indication for sleep studies? A pilot study. Sleep Breath 2009;13(4):409-413.
25. Soler X, Gaio E, Powell FL, Ramsdell JW, Loredo JS, Malhotra A, et al. High prevalence of obstructive sleep apnea in patients with moderate to severe chronic obstructive pulmonary disease. Ann Am Thorac Soc 2015;12(8):1219-1225.
26. Malhotra A, Schwartz AR, Schneider H, Owens RL, DeYoung P, Han MK, et al. Research priorities in pathophysiology for sleep-disordered breathing in patients with chronic obstructive pulmonary disease. An official American Thoracic Society research statement. Am J Respir Crit Care Med 2018;197(3):289-299.
27. Owens RL, Macrea MM, Teodorescu M. The overlaps of asthma or COPD with OSA: a focused review. Respirology 2017;22(6):1073-1083.
28. Owens RL, Malhotra A. Sleep-disordered breathing and COPD: the overlap syndrome. Respir Care 2010;55(10):1333-1344.
29. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med 2010;182(3):325-331.
30. Stanchina ML, Welicky LM, Donat W, Lee D, Corrao W, Malhotra A. Impact of CPAP use and age on mortality in patients with combined COPD and obstructive sleep apnea: the overlap syndrome. J Clin Sleep Med 2013;9(8):767-772.
31. Jaoude P, Kufel T, El-Solh AA. Survival benefit of CPAP favors hypercapnic patients with the overlap syndrome. Lung 2014;192(2):251-258.
32. Konikkara J, Tavella R, Willes L, Kavuru M, Sharma S. Early recognition of obstructive sleep apnea in patients hospitalized with COPD exacerbation is associated with reduced readmission. Hosp Pract (1995) 2016;44(1):41-47.

33. Alford NJ, Fletcher EC, Nickeson D. Acute oxygen in patients with sleep apnea and COPD. Chest 1986;89(1):30-38.
34. Goldstein RS, Ramcharan V, Bowes G, McNicholas WT, Bradley D, Phillipson EA. Effect of supplemental nocturnal oxygen on gas exchange in patients with severe obstructive lung disease. N Engl J Med 1984;310(7):425-429.
35. Soler X, Liao SY, Marin JM, Lorenzi-Filho G, Jen R, DeYoung P, et al. Age, gender, neck circumference, and Epworth sleepiness scale do not predict obstructive sleep apnea (OSA) in moderate to severe chronic obstructive pulmonary disease (COPD): the challenge to predict OSA in advanced COPD. PloS One 2017;12(5):e0177289.
36. Resta O, Foschino Barbaro MP, Brindicci C, Nocerino MC, Caratozzolo G, Carbonara M. Hypercapnia in overlap syndrome: possible determinant factors. Sleep Breath 2002;6(1):11-18.
37. Kessler R, Chaouat A, Weitzenblum E, Oswald M, Ehrhart M, Apprill M, et al. Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. Eur Respir J 1996;9(4):787-794.
38. Shapiro SH, Ernst P, Gray-Donald K, Martin JG, Wood-Dauphinee S, Beaupré A, et al. Effect of negative pressure ventilation in severe chronic obstructive pulmonary disease. Lancet 1992;340(8833):1425-1429.
39. Duiverman ML. Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? ERJ Open Res 2018;4(2):00012-2018
40. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax 2009;64(7):561-566.
41. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity noninvasive positive pressure ventilation for stable hypercapnic COPD. Int J Med Sci 2009;6(2):72-76.
42. Windisch W, Storre JH, Köhnlein T. Nocturnal non-invasive positive pressure ventilation for COPD. Expert Rev Respir Med 2015;9(3):295-308.
43. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2014;2(9):698-705.
44. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA 2017;317(21):2177-2186.
45. Struik FM, Sprooten RT, Kerstjens HA, Bladder G, Zijnen M, Asin J, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax 2014;69(9):826-834.
46. Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. Thorax 2004;59(12):1020-1025.
47. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57(10):847-852.
48. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60(11):925-931.
49. Ergan B, Oczkowski S, Rochwerg B, Carlucci A, Chatwin M, Clini E, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. Eur Respir J 2019;54(3):1901003.
50. Macrea M, Oczkowski S, Rochwerg B, Branson RD, Celli B, Coleman JM 3rd, et al. Long-term noninvasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020;202(4):e74-e87.
51. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ 2008;336(7652):1049-1051.
52. Duiverman ML, Maagh P, Magnet FS, Schmoor C, Arellano-Maric MP, Meissner A, et al. Impact of high-intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study. Respir Res 2017;18(1):76.
53. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax 2010;65(4):303-308.
54. Parreira VF, Jounieaux V, Aubert G, Dury M, Delguste PE, Rodenstein DO. Nasal two-level positive-pressure ventilation in normal subjects. Effects of the glottis and ventilation. Am J Respir Crit Care Med 1996;153(5):1616-1623.
55. Duiverman ML, Vonk JM, Bladder G, van Melle JP, Nieuwenhuis J, Hazenberg A, et al. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. Thorax 2020;75(3):244-252.
56. Arellano-Maric MP, Gregoretti C, Duiverman M, Windisch W. Long-term volume-targeted pressure-controlled ventilation: sense or nonsense? Eur Respir J 2017;49(6):1602193
57. Coleman JM 3rd, Wolfe LF, Kalhan R. Noninvasive ventilation in chronic obstructive pulmonary disease. Ann Am Thorac Soc 2019;16(9):1091-1098.
58. U.S. Department of Health and Human Services, Office of the Inspector General. Escalating Medicare billing for ventilators raises concerns. Available at: https://oig.hhs.gov/oei/reports/oei-12-15-00370.asp. *Accessed April 6, 2021.*
59. Masa JF, Pépin JL, Borel JC, Mokhlesi B, Murphy PB, Sánchez-Quiroga MA. Obesity hypoventilation syndrome. Eur Respir Rev 2019;28(151):180097
60. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. J Intensive Care Med 2013;28(2):124-130.
61. Masa JF, Mokhlesi B, Benítez I, Gomez de Terreros FJ, Sánchez-Quiroga MA, Romero A, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. Lancet 2019;393(10182):1721-1732.