Chronic Obstructive Pulmonary Disease and Breathing during Sleep: A Strain in the Neck

Although sleep is often considered a time of rest and recuperation, in many ways, sleep presents a challenge for patients with chronic lung disease (1). Although data are relatively sparse, disrupted sleep in individuals with chronic obstructive pulmonary disease (COPD) is both a common complaint and an objective finding (2, 3). In addition, normal physiological changes during sleep such as increased upper airway resistance, decreased lung volumes, ventilation-perfusion mismatching, and decreased respiratory drive may result in substantially worsened breathing during sleep among patients with COPD (4). Importantly, it is increasingly appreciated that these issues with sleep and breathing may have far-reaching effects: poor sleep has been linked to an increased risk for exacerbations (5), and sleep-disordered breathing (both sleep apnea and hypoventilation) has been convincingly shown to lead to rehospitalizations and mortality, although mechanisms remain unclear (6–9).

In this innovative study published in this issue of the *Journal*, Redolfi and colleagues (pp. 414–422) examined whether respiratory accessory muscle use quantified as neck inspiratory muscle (NIM) activity was present during sleep among patients with a recent severe COPD exacerbation, whether its presence was associated with signs of sleep disruption, and whether it could predict recurrent exacerbation requiring hospitalization (10). They found that many patients had evidence of NIM during sleep, and there were no observed differences in demographics, lung function, or hypoventilation/hypercapnia between those with and without NIM, although awake oxygenation was worse in those with NIM activity. Second, those with NIM had more disrupted sleep, quantified by EEG changes (i.e., persistent high-frequency activity during sleep). Third, those with NIM activity were more likely to be rehospitalized. The effect was most pronounced in those with “permanent” NIM activity, meaning they had NIM all throughout sleep, including during REM sleep. Such unusual physiology has also been noted in those with neuromuscular disease (11), highlighting that in the setting of disease, respiratory muscle activity patterns may differ substantially from normal physiology.

What are the potential explanations for these findings? Perhaps NIM activity is indeed causative and does lead to sleep disruption as hypothesized, which leads to a risk for severe exacerbation via mechanisms yet unknown. However, another possibility is that the finding of poor sleep in those with NIM activity and a higher risk for readmission is correlative. With respect to NIM activity, this activation of accessory muscles presumably serves to compensate for inadequate ventilation relative to respiratory drive, which may reflect diaphragm dysfunction as well as poor respiratory mechanics and high intrinsic drive to breathe. Given similar levels of lung function and gas exchange between groups, another explanation is that those with NIM activity have unrecognized severe respiratory muscle (i.e., diaphragm) dysfunction, and that NIM activity is indeed compensatory, but simply insufficient to stabilize breathing long-term. Finally, NIM activity may be a marker of individuals who are “sicker” in some way that we are not capturing with our usual measures of COPD severity. Indeed, those with NIM had lower PaO₂ during wakefulness.

Importantly, those with NIM activity might represent a group that would benefit from nocturnal noninvasive ventilation (NIV). Conventional criteria for NIV has required the presence of daytime hypercapnia (i.e., development of chronic respiratory failure). Indeed, reduction in PaCO₂ has been linked to usefulness of NIV (6, 7), whereas those without daytime hypercapnia have not had clear benefit (12). However, breathing strategies vary across patients with COPD, classically conceptualized as the blue bloater versus pink puffer. Might patients with NIM activity be those who benefit from nocturnal NIV to offload overtaxed respiratory muscles, potentially reducing their risk for adverse outcomes? Even in those with hypercapnia, optimal targets for NIV titration are not known, and perhaps elimination of NIM activity might represent a rational goal.

What are the barriers to implementing NIM measurement? A noninvasive measure to identify a previously unrecognized high-risk group certainly has appeal. However, obtaining polysomnography after each COPD exacerbation may not be feasible in many centers. Similarly, there are a lack of standards for measurement of NIM in the clinical setting. Technician training would be needed, along with software packages capable of quantifying NIM activity and removing artifacts such as electrocardiogram signals. Limited channel polygraphy recordings incorporating an EMG channel might be sufficient. In addition, Redolfi’s study did find differences in NIM activity during wake, although outcomes were not assessed on the basis of awake activity. Finally, until high-quality trials of NIV (and perhaps other therapeutic strategies) are available, it is not exactly clear whether we can prevent poor outcomes in this nonhypercapnic group. Nonetheless, this study provides additional evidence that sleep and breathing at the same time are difficult in some patients with advanced COPD and should encourage additional investigation toward diagnostic and therapeutic strategies.
We commend Zampieri and colleagues (pp. 423–429) for their study presented in this issue of the Journal (1), in which they conducted a thoughtful Bayesian reanalysis of results from a trial conducted within a developing research network to assess an intervention with broad applications (2). The premise of the ANDROMEDA-SHOCK trial was to compare a novel peripheral perfusion–based resuscitation approach using capillary refill time with a more conventional lactate-based approach to guide resuscitation (2). The trial reported an 8.5% reduction in absolute mortality but failed to reject the null hypothesis, motivating Zampieri and colleagues to repeat the analysis from a Bayesian perspective, which showed a consistently high probability that the intervention improved mortality across a range of prior beliefs. This reanalysis gives us an opportunity to consider the usefulness of a Bayesian approach in critical care medicine.

Bayesian analysis can be intimidating for many clinicians because it uses unfamiliar terms and takes a fundamentally different approach to drawing statistical conclusions from data as compared with frequentist analysis. However, any increased familiarity that clinicians feel toward conventional (frequentist) statistics is likely a false comfort, given the well-documented problems with the use of frequentist statistics in contemporary science (3). Bayesian analysis is sometimes proposed as an improved way to draw statistical conclusions from clinical data because it allows for the incorporation of information external to the trial (prior information) and makes it easy to answer the question, what is the probability that the intervention has a benefit of at least X%? Incorporating prior information in critical care trials is helpful because critical illness is rare, and so it may be wise to use all available information when analyzing a trial. Calculating the probability of benefit is also useful in critical care medicine, where morbidity and mortality are common, and so it may be helpful to identify interventions where frequentist analysis has failed to reject the null hypothesis but the probability of benefit is still high, as in the case of ANDROMEDA-SHOCK.

One common clinical reasoning approach that is similar to Bayesian analysis is the use of diagnostic tests. Consider a patient with shortness of breath and a swollen leg. A clinician may suspect a pulmonary embolism based on the clinical data (analogous to prior information) and order a diagnostic test such as a D-dimer. The D-dimer test result (analogous to a clinical trial or experiment) will have a different likelihood depending on whether or not a patient actually has a...