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Arousability in Obstructive Sleep Apnea: Friend or Foe?

Obstructive sleep apnea (OSA) afflicts 3–9% of women and 10–17% of men in the United States (1) and is associated with a host of comorbid cardiovascular and metabolic conditions, including hypertension, diabetes, coronary artery disease, and stroke. Despite decades of research, it remains unclear which, if any, patients with OSA are at greatest risk for developing these possible complications and which might be safely left untreated. A number of previous epidemiologic and case–control studies identified the greatest risk to be in the group with "severe OSA," which is to say the group with an apnea–hypopnea index (AHI) $>$ 30 events/h (2, 3). However, recent randomized controlled trials that enrolled patients based on their AHI have not confirmed these findings, leaving investigators and clinicians wondering whether there might not be better ways to stratify risk in patients with OSA (4, 5).

OSA is characterized by repeated episodes of upper-airway occlusion during sleep, which can be complete (apnea) or incomplete (hypopnea) and of varying duration. Obstructive episodes trigger a number of ensuing pathophysiologic disturbances, including hypoxemia, hypercapnia, sympathoexcitation, and intrathoracic pressure swings. Although there has been some debate on this point, the traditional model of OSA posits that airway occlusion is terminated when the subject experiences an arousal from sleep, thereby restoring pharyngeal dilator muscle tone and opening the airway. Viewed from this perspective, longer apneas or hypopneas must therefore be characterized by some relative failure of the arousal's normal protective function, either due to inadequate chemostimulation leading to arousal or due to some defect of the arousal response itself. When obstructive episodes last longer, downstream effects such as hypoxemia and sympathoexcitation will be worse, not only because the subject is exposed to them for a longer period of time but also because of their increasing magnitude. Stated plainly, it seems that longer apneas must be physiologically worse than shorter apneas.

In this issue of the *Journal*, Butler and colleagues (pp. 903–912) analyze data from the Sleep Heart Health Study and show us that things are not so simple (6). Among 5,712 subjects, almost a quarter of whom died during the 11 years of follow-up, individuals with the shortest-duration obstructive events had a significantly increased risk of death (1.31; 95% confidence interval, 1.11–1.54) after adjusting for the AHI, demographic factors, and prevalent cardiovascular and metabolic disease. The relationship was observed in both men and women, and was strongest in those with moderate OSA.

How can we reconcile this observation with our established knowledge of OSA pathophysiology? First, we should recognize that perhaps we have paid too much attention to the presence and morphology of OSA during polysomnography as it relates to downstream effects, and not enough to *upstream* effects. That is to say, OSA manifests uniquely in a given subject based on a large number of underlying factors, which are only incompletely understood. Obesity and anatomical crowding of the upper airway are obvious predispositions. Chemical control instability and loop gain are less obvious, but are supremely important in the pathogenesis of Cheyne-Stokes respiration and central sleep apnea, and increasingly recognized as contributing to OSA as well (7, 8). Cheyne-Stokes respiration may be a particularly instructive example: although its presence surely predicts a worse prognosis, its treatment does not seem to improve that prognosis (9), possibly because the upstream disturbances that *cause* the sleep apnea are the relevant ones, not the downstream disturbances that are *caused by* the sleep apnea.

Similarly, although it is difficult to imagine why a shorter apnea should be more harmful than a longer one when viewed in the light of its lesser downstream effects, it is easy to envision some upstream predisposing host factor that prematurely causes apnea termination (the authors call it "arousability"). It is possible that the mortality risk demonstrated in this study stems not from the shorter apneas *per se*, but rather from this predisposing factor. If this is the case, then treatment of OSA in these individuals would not be expected to confer a mortality benefit, as treatment would decrease the frequency of apneas and apnea-related arousals, but would not be expected to improve arousability itself. On the other hand, it is possible that increased arousability exerts its effects through sleep fragmentation. However, that explanation is not borne out by the data, as sleep efficiency was not different between the groups. Why

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might one patient be more arousable than another? Genetic factors surely play a role, and the authors have previously described a genetic locus associated with apnea duration (10). Other predisposing factors, such as frailty, unrecognized physical or mental illness, and sympathetic overactivity, might also contribute.

The study has some limitations. Because the subjects were drawn from a community-based sample, there was a paucity of severe cases. Only 12% of the subjects had severe OSA, and the mean apnea length in the longest quartile was only 27.8 seconds, which is not long enough to result in the profound hypoxemia that is often seen in clinic populations. It is telling that measures of oxygen saturation (minimum Sa_{O_2} and total sleep time $Sa_{O_2} < 90\%$) were either not significantly different or only minimally different across the apnea length quartiles. Therefore, these findings should not be generalized to patients with very severe OSA and lengthy apneas resulting in severe hypoxemia.

It is always the unexpected result that drives new research and moves the field forward. Increased arousability causing shorter apneas has been believed for decades to be a protective mechanism against the harmful effects of OSA. If shorter apneas actually confer greater risk, then clearly our understanding of OSA is still in its infancy. We do not even know who is friend and who is foe. ■

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