COMMENTARY

Does Untreated Obstructive Sleep Apnea Lead to Death?

A commentary on Young et al. Sleep 2008;31:1071-8 and Marshall et al. Sleep 2008;31:1079-85.

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IN THIS ISSUE OF SLEEP, THERE ARE TWO PROSPECTIVE STUDIES SHOWING THAT UNTREATED MODERATE-TO-SEVERE SLEEP APNEA IS ASSOCIATED WITH increased mortality even after controlling for relevant covariates. These studies are based on general population cohorts rather than clinical samples. The first report by Marshall and colleagues is from the Busselton study in Australia[1] that was first established by Dr. Helen Bearpark, who was tragically killed in a road accident. The second report by Young and colleagues is from the highly productive Wisconsin Sleep Cohort.[2] Both studies show increased all-cause mortality. The Australian study shows a hazard ratio of the order of 4.4-6.2 for moderate-to-severe sleep apnea (RDI ≥ 15 episodes/hour) after controlling for different covariates.[1] The Wisconsin study shows no significant increase in all-cause mortality in individuals with an AHI between 15 and 30 episodes/hour but a hazard ratio of the order of 2.7 to 3.8 for severe OSA (AHI ≥ 30 episodes/hour), depending on which subjects and confounding variables were included in their analyses.[2]

While not addressed in the Busselton study, the Wisconsin study specifically looked at cardiovascular mortality. Elevated mortality from cardiovascular deaths was observed. This association was significant in the subgroup of subjects with severe sleep apnea who were untreated (i.e., excluding the small number of subjects on CPAP). This association is not surprising, since previous cohort studies[3] have shown an increased incidence of coronary artery disease in untreated patients with severe OSA.

Both groups argue that population studies have the advantage over studies in clinical samples since they avoid referral bias. Population studies do, however, have the disadvantage of having small numbers of individuals with moderate-to-severe disease. In the Busselton study,[1] 18 of the 380 subjects assessed had an RDI ≥ 15 episodes/hour while only 3 had an RDI ≥ 30 events/hour. In the larger study from Wisconsin,[2] 145 of the 1522 subjects had an AHI ≥ 15 episodes/hour and 63 with severe OSA (AHI ≥ 30 episodes/hour). (Since the two studies used different strategies to assess sleep disordered breathing, the metrics of sleep disordered breathing cannot be directly compared.) These relatively low numbers of individuals with disease potentially limit the power of the data analyses to detect true associations.

Epidemiological studies demonstrating association always have the challenge of proving that the association is not produced by confounding. While both studies in this issue of SLEEP have addressed confounding, a particular concern is obesity which is highly associated with the presence and severity of OSA. Some have suggested that OSA modifies the effect of obesity as a cardiovascular risk factor.[4] It is not simply obesity that needs to be considered but rather the degree of visceral obesity, which is more clearly associated with the metabolic syndrome.[5] Visceral fat volume contributes to variation in metabolic risk factors for cardiovascular disease even after controlling for BMI and waist circumference.[5] Thus, despite efforts to control for obesity as a covariate, there is the lingering concern that there could be differences in the degree of visceral obesity between those with OSA who died and those who did not.

The results of these community studies are congruent with earlier studies[6-8] and recent studies in large clinical cohorts.[9-11] By design, studies in clinical samples have much larger numbers of untreated patients with severe disease. Studies in clinical samples also show that untreated OSA is associated with an increased rate of cardiac events and cardiovascular mortality. Indeed, the estimate of the increased risk of death of 2-4 is of similar magnitude to that reported in these new community-based studies.

Thus, the new information presented in these two manuscripts in this issue of SLEEP, when combined with studies in clinical samples, leads to the highly likely conclusion that untreated severe OSA is an important risk factor for cardiovascular mortality. There are caveats that make the conclusions less than foolproof. There is the issue of residual confounding as discussed above. In the clinical cohorts, when death rates in individuals on CPAP treatment are compared to those not using CPAP,[10] there is the issue of whether this is specific to OSA or whether non-use of CPAP is a marker for generally non-adherent behavior. The studies also lead to the conclusion that mild OSA (AHI from 5 to 15 episodes/hour) is <u>not</u> associated with increased mortality.[1,2] The conclusion about the lack of mortality risk from untreated moderate OSA is less clear.[1,2]

An important issue is whether treatment of severe OSA with CPAP reduces mortality rates. Studies in clinical cohorts indicate it does[8,10] and suggest that cardiovascular event rates and

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death rates in patients with severe OSA on CPAP treatment are not different than controls or snorers without OSA and with similar degrees of obesity.[10] The Wisconsin study adds support to the effect of treatment by demonstrating that exclusion from the analysis of the surprisingly few individuals with OSA who were treated with CPAP (n = 126) increased the hazard ratio for all-cause and cardiovascular mortality.[2]

It is important to address both the implications of these findings for clinical practice and for a future research agenda. From the clinical perspective, given that we have a safe and effective therapy for OSA (i.e., nasal CPAP[12]), all patients with severe OSA should be treated regardless of whether they are symptomatic with excessive sleepiness. One accepts that the data are not perfect but the risk-benefit clearly favors treatment. The data indicate, however, that this is not so for mild disease in the absence of sleepiness (AHI $\geq 5 < 15$ episodes/hour). For moderate disease, patients with excessive sleepiness should be treated. There is a need for further studies to determine whether patients with moderate OSA have an elevated risk for cardiovascular events and death.

Ultimately, from a research perspective, we would need a large randomized trial to show that active treatment of OSA with CPAP reduces cardiovascular event rates and deaths. Our cardiology colleagues are accustomed to evaluating this type of evidence and may not be fully convinced without it. Such a trial will not require use of sham CPAP, since the endpoints are definitive and not affected by blinding. Such a trial is, however, ethically challenging since OSA patients are frequently excessively sleepy and at risk for crashes.[13] Sleepy patients cannot be randomized to no treatment for many years. There are, however, patients even with severe OSA who are not excessively sleepy. While some have argued that patients without sleepiness may also be "protected" from the cardiovascular risk,[14] the data from the Wisconsin study do not support this assertion. Rather, Young and colleagues[2] found that the relationship of OSA to mortality is independent of self-reported sleepiness and present even in individuals without excessive sleepiness. Thus, it is conceivable that a randomized trial focusing on patients with severe OSA with minimal or absent sleepiness is feasible.

In conclusion, these new prospective studies are important and add to the growing evidence base as to OSA being a risk factor for death. Given the epidemic of obesity with its cardiovascular consequences, we need to pursue identification and treatment of individuals with severe OSA and, as a field, move to more definitive randomized trials.

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