Published in final edited form as:

Chest. 2008 October ; 134(4): 675–676. doi:10.1378/chest.08-1491.

Metabolic Syndrome, Obstructive Sleep Apnea, and Continuous Positive Airway Pressure:

A Weighty Issue

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The current obstructive sleep apnea (OSA) literature regarding cardiovascular (CV) risk has been missing the “holy grail” of studies: the definitive multicenter randomized trial assessing hard CV outcomes and mortality. Until this trial can be achieved, we will always be asking if OSA, independent of obesity, contributes to increased CV morbidity and mortality despite compelling evidence from *in vitro*, animal, epidemiologic, cross-sectional, and observational studies.^{1,2} Focusing on certain populations with known increased risk of CV disease and assessing treatment of concomitant OSA may be an acceptable strategy for now. In this issue of *CHEST* (see page 686), Dorkova et al³ study the effect of continuous positive airway pressure (CPAP) on CV risk in a well-defined cohort of patients with metabolic syndrome. Although the predictive value of the various components of the metabolic syndrome has been called into question,⁴ many features of syndrome X have been associated with OSA (so-called *syndrome Z*).⁵

The results of the study by Dorkova et al,³ that treatment of OSA in patients with metabolic syndrome improves insulin sensitivity, reduces systemic inflammation, and decreases CV risk, are promising. The authors acknowledge, however, that this study has the same limitations that have plagued other OSA/CV studies: relying on surrogate measures of CV outcomes, and comparing adherent CPAP users to nonadherent CPAP users.

One of the surrogate measures used in this study was a calculation of CV risk using a sex-specific multivariable risk factor algorithm derived from the Framingham Heart study.⁶ Reduction of the calculated risk score was observed in the OSA group adherent to CPAP but not in the nonadherent group. What does this mean? Can we assume that a reduction of risk in a treated group translates to a “real” risk reduction? For instance, previous research has shown that for a given BP, patients undergoing antihypertensive treatment have a higher CV risk than nontreated patients.^{7,8} The recent Framingham risk algorithm takes into account treated BPs vs non-treated BPs. However, the algorithm is not necessarily able to predict CV risk for those undergoing changes in risk factors from other types of medical treatment, *eg*, CPAP. The decreases in BP and cholesterol in the CPAP group reduced the calculated CV risk, but does this necessarily translate to reduced CV events?

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Dr. Yim Yeh has no conflict of interest to disclose. Dr. Rahangdale has no conflict of interest to disclose. Dr. Malhotra has received consulting and/or research funds from Respiromics, Pfizer, Itamar Medical, Restore Medical, Inspiration Medical, Apnex, NMT Medical, and Cephalon.

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Despite this concern, the lowering of BP in the CPAP group was impressive in this study. Previous studies⁹ have shown only modest differences in BP in CPAP vs control. Many of these studies, however, were looking at differences in BP among normotensive participants. Dorkova et al³ observed almost 10 mm Hg reductions in both systolic and diastolic BPs in subjects with baseline hypertension. Similarly, the CPAP-induced improvement in insulin sensitivity (measured with the Homeostasis Model Assessment–Insulin Resistance) and cholesterol is also notable. To see differences before and after treatment with OSA, there may have to be an underlying abnormality. Even in the nonadherent CPAP group, the total cholesterol was within normal limits, and so one may not have expected a change in total cholesterol even if CPAP treatment were successful. However, the exclusion of known cardiovascular comorbidities in order to assess the independent effect of OSA on CV outcomes has become more common place. A “clean” cohort, however, may not in the end be able to detect the beneficial effects of CPAP seen in sicker patients.

Although the results of this study are encouraging, the study design comparing CPAP adherent to CPAP nonadherent groups may be problematic. Prior studies^{10,11} have revealed that adherent patients have better outcomes than nonadherent ones (regardless of the intervention), presumably because adherence is a marker of a more educated, more motivated patient who may be more likely to follow diet, exercise, medication instructions. For example, minor dietary changes may underlie some of the improvements in lipids observed in the present study. Further, we can see that the CPAP-nonadherent group has a higher body mass index, which may play a role in the differences noted between the two groups. One also wonders if there is a difference the pathogenesis of OSA. Whether these underlying differences affected the outcomes is unclear. It is also discouraging to see that despite intensive counseling and monitoring by Dorkova et al³ that 50% of the participants were nonadherent to CPAP, despite their being motivated to participate in a clinical trial. We are reminded that despite having an effective treatment for OSA, CPAP is difficult to use for many patients and new therapeutic targets are needed.

Some researchers are moving away from comparing CPAP-adherent vs CPAP-nonadherent groups and using placebos in the form of pills or sham CPAP. The ethical dilemma of not treating OSA, however, is not trivial especially in sleepy patients. Untreated OSA patients have increased risk of car accidents and work-place accidents.^{12,13} It does not seem right to withhold treatment in symptomatic OSA patients in order to study whether they may or may get heart disease, a process that takes years. Other researchers are working around this problem by randomizing nonsleepy OSA patients to CPAP (who may have poor adherence to therapy), or by doing research in countries that would otherwise not have any access to CPAP therapy. Whether these approaches are ethical or not is still debated, but there are not many other options. Even the use of sham CPAP controls have been criticized since “sham” can still provide partial treatment of OSA or cause sleep disruptions.¹⁴

Although these results are promising, the link between OSA and CV outcomes requires further study. What is a researcher to do? As long as we recognize potential limitations and understand the context of the outcomes reported, there is still valuable information to be gleaned. Targeting patients with OSA and metabolic syndrome and observing the benefits of CPAP therapy may alert physicians in other fields, such as endocrine, renal, or cardiology, to send their patients for sleep evaluations. At the end of the day, we all just want OSA to be recognized and treated whenever appropriate.

Acknowledgments

Support was provided by the National Sleep Foundation Pickwick Fellowship and National Heart, Lung, and Blood Institute R01HL73146 and American Heart Association Established Investigator Award.

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