Cardiovascular Morbidity and Obstructive Sleep Apnea

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Obstructive sleep apnea, a relatively common disorder in adults, is characterized by sleep-related periodic breathing, upper-airway obstruction and asphyxia, sleep disruption, and acute autonomic, arterial, and hemodynamic perturbations. Epidemiologic data show a strong association between untreated obstructive sleep apnea and incident cardiovascular morbidity and mortality.\(^1\)\(^2\) It is implicit that obstructive sleep apnea causes or propagates adverse cardiovascular outcomes and that its treatment may have a mitigating effect, and there are numerous instances in which explicit data have documented the efficacy of the treatment of obstructive sleep apnea in preventing or attenuating such outcomes. However, obstructive sleep apnea is typically identified along with cardiovascular, metabolic, and inflammatory disorders, and this “complicit” association confounds interpretation of the implicit and explicit associations between the treatment of obstructive sleep apnea and cardiovascular risk and outcomes.

In this issue of the Journal, two randomized clinical trials\(^3\)\(^4\) offer incrementally novel, related data regarding the treatment of obstructive sleep apnea and the effects of treatment on cardiovascular morbidity and on markers of metabolism and inflammation that are associated with increased cardiovascular risk. The primary markers studied were systemic arterial blood pressure and the level of C-reactive protein (CRP).

In the study by Gottlieb et al.,\(^3\) which used blood pressure as the primary outcome, the design was derived from the implicit concern that repetitive hypoxemia and reoxygenation in obstructive sleep apnea propagates chronic systemic hypertension. This effect has not been documented in obstructive sleep apnea, nor does the hypoxemia of obstructive events alone appear to explain the acute elevations in blood pressure with which it is associated.\(^5\) The rationale for the study was also derived from the explicit high-grade evidence documenting the efficacy of continuous positive airway pressure (CPAP) in lowering blood pressure in patients with obstructive sleep apnea,\(^6\) including those with resistant hypertension.\(^7\) Participants were obese, had moderate-to-severe obstructive sleep apnea (as determined by the apnea–hypopnea index and the nocturnal hypoxemia burden) and were already receiving treatment for cardiovascular or metabolic risk factors and disorders (the “complicit” context). Most participants also had systemic hypertension, coronary artery disease (but not heart failure), or both. Participants underwent randomization to one of three study groups in which they received 12 weeks of healthy sleep and lifestyle education alone or in addition to either CPAP or nocturnal supplemental oxygen. Both CPAP and nocturnal supplemental oxygen successfully treated nocturnal hypoxemia, but a greater, arguably clinically significant decrease in adjusted 24-hour mean arterial blood pressure was found only in the CPAP group as compared with the group receiving nocturnal supplemental oxygen and the group receiving education alone. The use of nocturnal supplemental oxygen was not significantly more effective in this regard than education alone. Of particular interest is the effect that CPAP had on nocturnal blood pressure, given that blood pressure during sleep may be a particularly strong marker of cardiovascular outcomes.\(^8\) In the study by Chirinos et al.,\(^4\) in which a decrease in CRP level was the primary outcome, the design proceeds from implicit and complicit research questions.

In summary, these studies add important new data regarding the effects of treating obstructive sleep apnea on cardiovascular outcomes and metabolic and inflammatory markers. Further randomized trials exploring the relative efficacies and adverse events associated with CPAP and nocturnal supplemental oxygen treatment of obstructive sleep apnea are needed to determine which treatment is best for the clinical conditions described in each study.

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matters regarding the effects of obesity on cardiovascular risk in patients with obstructive sleep apnea. The authors then use explicit data from numerous case–control studies to focus on the use of CPAP to reduce levels of systemic markers of inflammation, including CRP. 9 Obese participants with moderate-to-severe obstructive sleep apnea underwent randomization to 6 months of therapy for obstructive sleep apnea with CPAP, a weight-loss intervention, or both. Primary analyses excluded patients who did not adhere to the regimen for CPAP therapy; efficacy was also assessed with the use of an intention-to-treat analysis. The major findings were that CPAP alone did not lower CRP levels significantly but that the weight-loss intervention (and combination therapy) did. (Participants in both groups that included a weight-loss intervention, unlike those in the group receiving CPAP alone, had a mean weight loss of approximately 7 kg.) CPAP was associated with decreased adjusted CRP levels and with reductions in waking systolic and mean blood pressure (although neither was a primary outcome); the reductions in blood pressure were greater with the weight-loss intervention plus CPAP for 4 or more hours per night on at least 70% of nights, as compared with either CPAP or weight loss alone. 4

Matters of design, and disparities in the means of measurement and assay between these two studies and among preexisting relevant data, greatly limit definitive interpretation of the explicit findings. For example, consider that ultimately there was relatively low nightly use of CPAP, although the nocturnal effect of CPAP on blood pressure was described as being “dose-dependent.” The assays and statistical handling of CRP values, which were skewed and had large ranges at baseline, were unlike those of previous investigators, whose results informed the current study design and data interpretation. 3,4,7,10 The variability of the CRP level within the same participant and the variability of the CRP level as an independent measure of cardiovascular risk, particularly in patients receiving statin therapy, also raise concerns. 12 In both studies, the absence of a comprehensive analysis of the severity of disordered breathing during sleep after the treatment period hampers the interpretation of complicit interactions among breathing, blood pressure, the control of metabolic and inflammatory markers (e.g., CRP level, leptin level, and extent of insulin resistance), and sleepiness. In addition, it is not clear that the Epworth Sleepiness Scale correlates with objective measures of sleepiness in patients with sleep apnea.

Pathogenic implications and systemic–clinical (complicit) interactions also remain to be defined. For example, the failure to reverse hypertension with the use of oxygen supplementation may not negate the proposition that hypoxemia resulting from obstructive sleep apnea initiates or propagates chronic hypertension if the vascular lesion is no longer readily reversible.

Within these limitations, two important explicit and complicit treatment considerations for obstructive sleep apnea emerge from these two studies. First, in obese patients with moderate-to-severe obstructive sleep apnea, the use of CPAP alone, but not oxygen supplementation alone, during sleep may ameliorate systemic hypertension and cardiovascular risk, even in patients treated for hypertension and cardiovascular risk who do not have “subjective” sleepiness. 2 Second, weight loss may decrease cardiovascular morbidity and risk when CPAP is prescribed for these patients.

Furthermore, these two studies task us to design larger, and longer, trials that appropriately augment the extensive epidemiologic and experimental data already available. 2,6,9 Such trials, which must always maintain patient safety, would be characterized by designs, assays, and analyses that are calibrated and coordinated among investigators to comprehensively address the explicit, implicit, and complicit treatment imperatives of obstructive sleep apnea and cardiovascular health.

The author reports being a member of the data and safety monitoring board for the study conducted by Chirinos et al. 4 Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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5. Ringler J, Basner RC, Shannon R, et al. Hypoxemia alone...


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