CHEST

Effect of Continuous Positive Airway Pressure on Cardiovascular Biomarkers

The Sleep Apnea Stress Randomized Controlled Trial

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BACKGROUND: Although existing research highlights the relationship of OSA and cardiovascular disease, the effect of OSA treatment on cardiovascular biomarkers remains unclear. We evaluated the effect of OSA treatment on oxidative stress/inflammation measures.

METHODS: We conducted a parallel, randomized controlled trial in moderate to severe OSA (apnea-hypopnea index ≥ 15) patients to examine effects of 2-month CPAP vs sham-CPAP on the primary outcome of oxidative stress/inflammation (F2-isoprostanes: ng/mg) and myeloperoxidase: pmol/L) and secondary oxidative stress measures. Exploratory secondary analyses included vascular and systemic inflammation markers. Linear models adjusted for baseline values examined effect of CPAP on biomarker change (least squares means, 95% CI) including secondary stratified analyses examining CPAP adherence and degree of hypoxia.

RESULTS: Of 153 participants, 76 were randomized to CPAP and 77 to sham-CPAP. In an intent-to-treat analyses, no significant change was observed in the sham and CPAP groups respectively: F2-isoprostanes (−0.02 [−0.12 to 0.10] vs −0.08 [−0.18 to 0.03]) or myeloperoxidase (−3.33 [−17.02 to 10.37] vs −5.15 [−18.65 to 8.35]), nor other oxidative markers; findings that persisted in analyses stratified by adherence and hypoxia. Exploratory analyses revealed percentage reduction of soluble IL-6 receptor (ng/mL) levels (−0.04 [−0.08 to −0.01] vs 0.02 [−0.02 to 0.06], $P = .019$) and augmentation index (%) (−6.49 [−9.32 to −3.65] vs 0.44 [−2.22 to 3.10], $P < .001$) with CPAP compared with sham, respectively.

CONCLUSIONS: In moderate to severe OSA, 2-month CPAP vs sham did not reduce oxidative stress despite consideration of a broad range of measures, positive airway pressure adherence, and hypoxia burden. These findings suggest that nonoxidative stress pathways primarily modulate OSA-related cardiovascular consequences.

TRIAL REGISTRATION: ClinicalTrials.gov NCT00607893. CHEST 2016; 150(1):80-90

KEY WORDS: CPAP; inflammation; obstructive sleep apnea

ABBREVIATIONS: AHI = apnea-hypopnea index; AIx = augmentation index; CVD = cardiovascular disease; DBP = diastolic blood pressure; IRB = institutional review board; SBP = systolic BP; sIL-6R = soluble interleukin-6

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OSA, characterized by repetitive episodes of complete or partial upper airway obstruction, is common and increasingly prevalent.[1] Data generated from several longitudinal cohort studies provide strong evidence for an increased risk of hypertension and cardiovascular disease (CVD) in individuals with OSA.[2-4] OSA represents an independent risk factor for cardiovascular morbidity and cardiovascular-specific mortality.[5] Physiologic perturbations including surges in sympathetic activation, intermittent hypoxia/reoxygenation, intrathoracic pressure alterations, and sleep fragmentation have been implicated.[6-8] Recently, efforts have focused on inter-related domains of oxidative stress, systemic inflammation, and endothelial dysfunction as potential mechanistic facilitators of cardiovascular risk in OSA.

Oxidative stress, in particular, has engendered interest given the rationale that OSA morbidity results from intermittent hypoxia—oftentimes quite profound—and reoxygenation, resulting in flux of reactive oxygen species and end-organ injury (eg, endothelial damage and alterations in chemoreception).[7,9] Although experimental intermittent hypoxia models clearly demonstrate increased vascular production of reactive oxygen species,[10-12] activation of nicotinamide adenine dinucleotide phosphate oxidase, and enhanced lipid peroxidation,[13-15] clinical results in OSA are less conclusive.[16-20] However, some signal has been observed with F-2 isoprostanes, an established stable marker of lipid peroxidation recognized to play a role in atherogenesis.[16,21]

The effect of OSA treatment with CPAP on cardiovascular biomarkers, particularly oxidative stress, remains largely unknown. Prior attempts have been hampered by heterogeneity of methodologies used, limited consideration of confounding influences, use of a nonrandomized study design, relatively small sample sizes, and inconsistency in findings.[22-27] In the present study, we sought to examine the effect of CPAP use in moderate to severe OSA on markers of oxidative stress/inflammation (primary outcomes: F2-isoprostanes and myeloperoxidase). Secondarily, vascular measures and markers of inflammation were examined. We postulate that reversal of OSA pathophysiology with CPAP results in improvement in levels of oxidative stress and, secondarily, improvement in systemic inflammation and measures of arterial stiffness. Some of the results of this study have been previously reported in the form of abstracts.[28,29]

Materials and Methods

Study Design

The Sleep Apnea Stress Study (National Institutes of Health clinical trials registry NCT00607893) is a single-center, parallel-group, randomized, double-blind, sham-controlled trial involving recruitment from the sleep programs of two hospital systems of Case Western Reserve University (ie, University Hospitals Case Medical Center and MetroHealth Medical Center; additional details can be found in the e-Appendix).

The study was designed to investigate the effect of CPAP treatment compared with control (sham CPAP) for improvement in cardiovascular measures in patients with moderate to severe OSA (apnea hypopnea index ≥ 15) naïve to OSA therapy. Cardiovascular measures were obtained at the baseline assessment and after 8 weeks of treatment. A 2-week run-in period on CPAP with a 1-month washout period was implemented to ascertain acceptable CPAP adherence as an entry criterion into the trial. The study was funded by the National Heart, Lung, and Blood Institute (K23 HL079114) and the CPAP machines were donated by the Philips Respironics Corporation. A Data Safety Monitoring Board was assembled to provide oversight of study progress, including recruitment and safety monitoring according to a prespecified Data Safety Monitoring Plan. A blinded physician observer (safety monitor) was responsible for assessing participant safety. Participants were contacted at regular intervals to assess for adverse events. The research protocol was approved by the institutional review board (IRB; University Hospitals IRB 07-06-25, MetroHealth Medical Center IRB 10-00370, and Cleveland Clinic IRB 13-716) and all participants provided written informed consent. The authors had sole access to the data with direct supervision of data collection, performed the statistical analyses, and manuscript writing without input or review by the study sponsor or the Philips Respironics Corporation. All authors vouch for the completeness and accuracy of the data.

Participants

Inclusion criteria were those 20 to 75 years of age with apnea-hypopnea index (AHI) ≥ 15 based upon in-laboratory clinical polysomnography. The optimal pressure to address OSA with the goal of AHI < 5 was identified in the clinical sleep laboratory. Those with CPAP adherence of ≥ 4 h for ≥ 70% of the time monitored during a 2-week run-in period were eligible to proceed to randomization. Exclusion criteria were current or planned use of OSA treatment outside of the clinical trial, use of supplemental

Some of the results of this study have been previously reported in the form of abstracts at the 28th Annual Meeting of Associated Professional Sleep Societies, June 2014, Minneapolis, MN.

FUNDING/SUPPORT: This study was supported by the National Heart, Lung and Blood Institute [Grant K23HL079114] and National Institutes of Health (NIH) National Center for Research Resources [Grant UL1 RR024989]. Dr Hazen was supported by NIH [Grant P01 HL076491]. Mass spectrometry studies were performed on instruments housed within a core partially supported by an AB SCIEX Center of Innovation grant.

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DOI: http://dx.doi.org/10.1016/j.chest.2016.03.002