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JOURNAL CLUB

PAP and Cardiovascular Events in Adults With Sleep Apnea: Is PAP Useful?

Commentary on Yu et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. *JAMA*. 2017;318(2):156–166.

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SUMMARY OF YU ET AL.

Question

In individuals with obstructive sleep apnea (OSA) or central sleep apnea (CSA), does the treatment of sleep apnea with positive airway pressure therapy (PAP) reduce the incidence of the primary composite end point (acute coronary syndrome [ACS] events, stroke, or vascular death [major adverse cardiovascular events]; cause-specific vascular events; and death)?

Methods

Design

A meta-analysis of randomized controlled trials (RCTs) of sleep apnea and the effect of PAP therapy on cardiovascular events.

Data Sources and Study Selection

A systematic review of the literature was done according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement for the conduction of meta-analyses of intervention studies. RCTs were selected from searches using MEDLINE via Ovid (from January 1, 1946, to March 2017), EMBASE (from January 1, 1974, to March 2017), and the Cochrane Library database (Cochrane Central Register of Controlled Trials, no date restriction) using medical subject headings related to randomized trials, and sleep apnea. Two investigators judged the quality of each included RCT according to the Cochrane Collaboration's tool for assessing risk of bias.

Trial Inclusion Criteria

RCTs evaluating the association of PAP compared with standard care (or sham PAP) among adults age 18 years or older with OSA or CSA.

Trial Exclusion Criteria

Studies were excluded if they were duplicates, lasted 12 weeks or less, enrolled less than 100 patient-years of follow-up per randomized group, did not report on outcomes of interest, or only reported pooled trial data where the individual trials could not be identified.

Analysis

Summary relative risks (RRs) and risk differences (RDs) with 95% confidence intervals (CI) were estimated for primary and secondary outcomes using the DerSimonian and Laird random-effects model. Heterogeneity across the pooled results was estimated using the I^2 statistic and by the *P* value for heterogeneity. Random-effects meta-regression analyses were used to investigate the associations of length of follow-up, adherence to PAP, and sleep apnea severity with the observed RR for each trial. Subgroup analyses were done by dividing trials into groups according to adherence to PAP (< 4 versus ≥ 4 h/d), type of sleep apnea (OSA versus CSA), type of intervention (continuous positive airway pressure [CPAP] versus adaptive servoventilation [ASV]), and whether vascular outcomes or death were prespecified outcomes. Presence of publication bias was determined by visual inspection of the funnel plots and calculating the Egger regression test for funnel asymmetry.

Outcome Measures

The primary endpoint was defined as a composite endpoint of major adverse cardiovascular events (cardiovascular death, nonfatal ACS, and nonfatal stroke) and major adverse cardiovascular events with hospitalization for unstable angina.

Also reported were cause-specific outcomes: fatal or nonfatal ACS, fatal or nonfatal stroke, hospitalization for unstable angina, and fatal or hospitalized heart failure. All-cause death, cardiovascular death, and non-cardiovascular death were studied as well.

RCT Characteristics and Patient Follow-Up

Ten RCTs were included in the analysis, representing a total of 7,266 patients. CPAP was used in all but 1 study that included ASV as its active intervention arm. Individual study sample size ranged from 83 to 2,717 participants. Median study follow-up range was 6 to 68 months. Mean or median adherence to the

study intervention ranged between 1.4 and 6.6 h/d. For the most part, funnel plots did not show any significant publication bias.

Main Results

Among the included trials, 356 major adverse cardiovascular events, 635 major adverse cardiovascular events with hospitalization for unstable angina, and 613 deaths were reported. More than 80% of participants were male with a mean age of 60.9 years, and a mean body mass index of 30 kg/m^2.

There was no significant association of PAP with major adverse cardiovascular events, RR, 0.77 (95% CI, 0.53 to 1.130); P = .19, cardiovascular death, RR, 1.15 (95% CI, 0.88 to 1.50; P = .30 or all-cause death, RR, 1.13 (95% CI, 0.99 to 1.29); P = .08.

No significant associations were found for the other outcomes studied, including ACS, stroke, and heart failure. Meta-regressions identified no differences in outcomes based on different levels of apnea severity, follow-up duration, or adherence to PAP. Although analyses did not show any significant differences in cardiovascular outcomes among the various subgroups, the summary point estimate for the 4 trials with subjects with PAP adherence ≥ 4 hours did show a trend in favor of PAP for reduction in major adverse cardiovascular events, with a 95% CI that just excluded 1 trial (RR, 0.58 [95% CI, 0.34 to 0.99]).

Conclusions

In predominantly male subjects with sleep apnea, randomized to PAP therapy versus no therapy/sham, there was no statistically significant difference in a composite primary outcome of ACS events, stroke, or vascular death (major adverse cardiovascular events); cause-specific vascular events; and death.

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COMMENTARY ON YU ET AL.

The systematic review and meta-analysis of 10 RCTs by Yu and colleagues recently published in *JAMA* concluded that the use of PAP compared with no treatment or sham was not associated with a reduction in risk of adverse cardiovascular (CV) events or mortality and that the findings did not support PAP treatment for prevention of these outcomes.[1] Although it is indeed conceivable that PAP therapy of sleep apnea may not convey significant benefit in terms of CV events, there is much that needs to be clarified before we can be comfortable with that conclusion. The estimated RR for the association between PAP and the composite endpoint of adverse CV events and death was 0.77 (95% CI 0.53–1.13; P = .19) which was not statistically significant, but suggestive of a tendency toward benefit. There are several considerations that could potentially explain the lack of clear benefit of PAP therapy.

The inclusion of trials of subjects with CSA and heart failure adds complexity to the analysis. CSA and OSA represent distinct pathophysiologic entities and it is difficult to make meaningful clinical conclusions, particularly about mortality, if the results of trials of subjects with CSA and OSA are pooled together. This caveat applies to 2 of the 10 studies in this meta-analysis. The early CANPAP study examined the effects of CPAP on CSA in patients with systolic heart failure, and did not show any benefit of PAP.[2] The recent SERVE-HF trial, the second largest study included in the meta-analysis, demonstrated an increased mortality risk with use of ASV in patients with symptomatic heart failure with reduced ejection fraction and CSA; there has been much discussion about possible explanations for the adverse outcomes in the treated group that is beyond the scope of this journal club commentary.[3,4]

Yu et al. postulate that the absence of a significant association between PAP and intermediate markers of CV risk such as blood pressure, glucose, and cholesterol levels, could explain the lack of association of PAP with CV outcomes. The meta-analysis, however, showed a borderline statistically significant effect on systolic blood pressure reduction (P = .05) with PAP treatment and conclusions regarding other intermediate markers were based only on 2 trials with very low PAP adherence (median usage of 1.4 and 2.4 h/night), wherein patients in whom OSA was diagnosed based on cardiorespiratory polygraphy recordings with oxyhemoglobin desaturation indices that were lower than the apnea-hypopnea cutoffs in the other included studies.[5,6] The authors noted that the absence of benefit of PAP on surrogate markers of CV risk was contrary to what has previously been reported in the literature regarding the effects of PAP, and suggested that this may have contributed to the absence of benefit on hard CV outcomes. Nevertheless, they acknowledge that other important factors might explain the main results of the meta-analysis.

The first factor is PAP adherence. The results of this meta-analysis are largely driven by the recent negative SAVE study (in addition to the aforementioned SERVE-HF study), that examined the effects of PAP on secondary prevention of CV events.[7] The results of SAVE are in contrast to the findings of previous observational studies and meta-analyses on the beneficial effects of PAP on CV outcomes in patients with OSA.[8–10] As pointed out by the authors of the current meta-analysis and the accompanying editorial in *JAMA*, as well as in previous commentaries on the SAVE study,[11–13] the mean number of hours of PAP use per night was low, at only 3.3 hours in the SAVE study. Many sleep clinicians would not consider a patient "adherent" or adequately treated with a mean nightly PAP usage of 3.3 hours; indeed, the Centers for Medicare and Medicaid Services and many insurance companies in the United States would not continue to cover the cost of a PAP device in this instance. Rapid eye movement sleep occurs predominantly in the second half of the sleep period and OSA tends to be worse in this stage of sleep. It is conceivable that PAP treatment during this time is necessary to mitigate the effects of OSA on CV risk.[14] Thus, although there may be a dose-response effect in terms of improvement in daytime sleepiness with increasing hours of nightly PAP usage, to demonstrate a reduction in CV risk, consistent PAP use of more than 4 or 5 hours a night may be required. It is relevant that there was a trend toward reduction in CV events in subjects who utilized PAP for ≥ 4 hours

in a subanalysis conducted in the SAVE trial using propensity scores to predict likelihood of PAP adherence. Furthermore, all 4 RCTs included in the current meta-analysis, of patients with ≥ 4.5 hours of nightly PAP usage, followed for a median of 36 to 68 months, also showed a significant reduction in adverse CV outcomes in those who utilized PAP for ≥ 4 h/night compared to those who did not utilize CPAP or used it for < 4 h/night.

Second, patients with severe OSA with significant hypoxemia were excluded from most of the trials, including SAVE, partly for ethical reasons. It is possible that the positive effects of PAP are more marked in this group of patients and account for the lack of association with CV sequelae seen in this meta-analysis. Third, subjects in the RCTs included in the meta-analysis were generally not sleepy. Several studies show a differential effect of PAP on CV outcomes in sleepy versus nonsleepy individuals with OSA.[15,16] It may be that the effect of PAP on CV risk is observable in patients with OSA who are more symptomatic.

Nevertheless, the importance of the meta-analysis, as well as of the individual trials included, needs to be acknowledged. The respective investigators should be commended for their pioneering approach in conducting challenging and highly overdue randomized trials to better understand the relationship between sleep apnea and cardiovascular disease. At the very least, their efforts will help develop the road map for future studies. Specifically, further RCTs with subjects who are more adherent to PAP treatment are needed to clarify this issue, as well as in various subgroups of patients with OSA, because these patients may have different risk profiles and outcomes with treatment. A RCT of PAP in subjects with acute coronary syndromes is underway (NCT01335087), as is the ADVENT study of patients with sleep apnea and heart failure (NCT01128816). The risk of a cerebrovascular event in SAVE was significantly lower in patients using PAP for ≥ 4 hours versus controls. Further studies of PAP for secondary prevention of stroke would be helpful to shed more light on this matter. Strategies to improve PAP adherence are needed at this juncture, as well as effective and more tolerable alternative treatment options for sleep-disordered breathing. In the meantime, in clinical settings, one would likely need to treat even the relatively asymptomatic patient with severe OSA and hypoxemia. These patients were excluded from most of the trials incorporated in this meta-analysis. The question of whether adequate PAP treatment mitigates long-term CV risk, particularly in the sleepy patient with severe nocturnal hypoxemia, remains unresolved.

CITATION

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