Continuous positive airway pressure therapy and cardiovascular outcomes in obstructive sleep apnoea syndrome: where are we now?

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Obstructive sleep apnoea syndrome (OSA) is highly prevalent with recent epidemiological reports indicating prevalence for moderate or severe sleep disordered breathing (SDB) of up to 50% in the general male population, although the prevalence of a clinically significant syndrome is considerably less (1,2). Cardiovascular co-morbidity is also common among patients with OSA, and many reports have indicated an independent relationship between OSA and various cardiovascular diseases, especially systemic hypertension (3). The mechanisms of this relationship are complex, but likely include sympathetic excitation, systemic inflammation, and endothelial dysfunction (4). Several long-term observational studies have reported beneficial effects of continuous positive airway pressure therapy (CPAP) on cardiovascular morbidity and mortality (5-8), but these reports have typically suffered from the major methodological limitation that successful CPAP therapy was compared to CPAP non-compliance, which clearly indicates the likelihood of patient selection bias. Short-term randomized placebo-controlled studies of CPAP therapy have indicated significant reductions in blood pressure levels both in hypertensive and non-hypertensive patients (9-11), but until recently there has been a dearth of longterm randomized placebo controlled trials of CPAP effects on cardiovascular morbidity and mortality.

In this context, two recent studies have evaluated the long-term cardiovascular outcomes of CPAP therapy

in patients with moderate or severe OSA, defined as an apnea-hypopnea frequency per hour (AHI) greater than 15 (12,13). Both trials recruited patients with established cardiovascular disease who were relatively non-sleepy and thus represent a highly selected population. The sleep apnea cardiovascular endpoints (SAVE) trial (13) is a large multi-centre, multi-national study of 2,717 patients with pre-existing cardiovascular or cerebrovascular disease who were randomised to best usual care with or without CPAP therapy, and followed for a mean period of 3.7 years. Patients were predominantly Asian (64%) and middle-aged (average 61 years) with a mean AHI of 29, Epworth score of 7.5, and average body mass index of 28.5. They were evenly split between those suffering from coronary artery or cerebrovascular disease, and the majority of patients (78%) were hypertensive. At follow-up, there was no difference between the two groups in the the primary composite end point of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. These data indicate no significant benefit from CPAP therapy added to best usual care in the secondary prevention of cardiovascular morbidity and/or mortality in non-sleepy patients with moderate or severe OSA. However, CPAP therapy was associated with significantly reduced daytime sleepiness [Epworth Sleepiness Score (ESS) fell by an average 3.1 points in the CPAP group vs. -0.7 points in the usual care

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group] and there was also a significant improvement in health-related quality of life and mood in the CPAP group. The mean compliance with CPAP was relatively low at 3.3 hours per night, which could be a factor in the lack of cardiovascular benefit from this therapy. Although not commented in the discussion by the authors, there was a small (0.7 mmHg) but significant (P=0.05) reduction in diastolic blood pressure in the CPAP-treated group.

The RICCADSA (Randomized Intervention with Continuous positive airway pressure in Coronary Artery Disease and OSA) trial (12) is a single centre study investigating the effects of CPAP on the risk of cardiovascular events in patients with established coronary artery disease (CAD) and concomitant moderate or severe OSA without daytime sleepiness. A total of 244 patients with angiographically-verified CAD, AHI ≥15, and ESS <10 were randomized to CPAP or no CPAP and followed for a median of 57 months. Patients had a similar age profile and OSA severity as in the SAVE trial. At follow-up, the incidence of the primary endpoint (the first event of repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality) did not differ significantly in patients who did versus did not receive CPAP. However, there was a significant cardiovascular risk reduction in those who used CPAP for more than 4 hours per night compared to those using less than 4 hours or those who did not receive treatment (hazard ratio, 0.29; 95% confidence interval, 0.10-0.86; P=0.026).

These two trials add important new data to the evidence regarding the potential benefit or otherwise of CPAP therapy in improving cardiovascular outcomes in patients with OSA. Overall, these reports do not indicate a significant benefit from CPAP therapy in the secondary prevention of cardiovascular morbidity or mortality in this patient population. However, a number of important factors must be considered in this context. First, the data do not provide any information on the potential role of CPAP in the primary prevention of cardiovascular disease. Second, the overall compliance with CPAP was relatively low in both studies, and the RICCADSA trial demonstrated a significant benefit in cardiovascular outcomes among patients who used CPAP for more than 4 hours per night. Finally, both studies were performed in relatively non-sleepy subjects, who represent a selected population of patients with moderate-severe OSA, and thus the conclusions may be limited to this group. Thus, caution should be exercised in interpreting these findings, and particularly to avoid the conclusion that these reports indicate no benefit to cardiovascular outcomes in all patients with moderate-severe OSA treated with CPAP.

These reports provide useful evidence in the planning of further randomized trials of CPAP therapy in OSA patients. Prior to this latest evidence there had been a growing consensus that CPAP therapy benefited cardiovascular outcomes in OSA, particularly in patients with severe OSA, which was based on the previous evidence from long-term observational studies. The present evidence counteracts this consensus, and thus brings the broad topic of the impact of CPAP therapy on cardiovascular outcomes back to a degree of clinical equipoise. Thus, the present evidence clearly justifies further long-term randomized controlled studies on this topic, and particularly to evaluate outcomes in patients adequately compliant with CPAP therapy and in patients without pre-existing cardiovascular disease. Furthermore, since the mechanisms of cardiovascular disease may differ between specific disorders such as systemic hypertension and CAD (3), the potential benefit of CPAP therapy may also vary between these disorders.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

- Arnardottir ES, Bjornsdottir E, Olafsdottir KA, et al. Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. Eur Respir J 2016;47:194-202.
- Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310-8.
- McNicholas WT, Bonsigore MR; Management Committee of EU COST ACTION B26. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007;29:156-78.
- Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J 2009;33:1195-205.
- 5. Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nuñez N, et al. Role of sleep apnea and continuous positive

McNicholas. CPAP and cardiovascular outcomes in OSA

airway pressure therapy in the incidence of stroke or coronary heart disease in women. Am J Respir Crit Care Med 2014;189:1544-50.

- Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046-53.
- Doherty LS, Kiely JL, Swan V, et al. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest 2005;127:2076-84.
- Martínez-García MA, Campos-Rodríguez F, Catalán-Serra P, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. Am J Respir Crit Care Med 2012;186:909-16.
- Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea.

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Circulation 2003;107:68-73.

- Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002;359:204-10.
- Martínez-García MA, Capote F, Campos-Rodríguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013;310:2407-15.
- 12. Peker Y, Glantz H, Eulenburg C, et al. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. Am J Respir Crit Care Med 2016;194:613-20.
- McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med 2016;375:919-31.

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