Editorial

Lessons from randomised controlled trials of continuous positive airways pressure therapy in the prevention of cardiovascular morbidity and mortality

Nadia Gildeh[1,2], Ivana Rosenzweig[1,2], Brian D. Kent[1,2]

[1]Sleep and Brain Plasticity Centre, CNS, IoPPN, King's College London, London, UK; [2]Sleep Disorders Centre, Guy's and St Thomas' Hospitals, London, UK

Correspondence to: Brian D. Kent. Sleep Disorders Centre, Guy's Hospital, London SE1 9RT, UK. Email: Brian.kent@gstt.nhs.uk.

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Obstructive sleep apnoea (OSA) has an established independent relationship with cardiovascular disease, with a multitude of clinical cohort and longitudinal population studies showing a significantly increased risk of cardiovascular morbidity and mortality in subjects with severe OSA (1-3). This association is used by many sleep clinicians to justify continuous positive airways pressure (CPAP) usage even in patients without excessive sleepiness, in particular in those with established cardiovascular disease. Lending further support to this practice are a number of retrospective or observational studies which suggest that CPAP usage may lead to a reduction of cardiovascular events (4-6). Until very recently, however, there were few prospective, randomised trials examining the impact of CPAP therapy on long-term cardiovascular outcomes. Helpfully, 2016 saw the publication of two well-conducted high quality RCTs in this area (7,8).

First to appear was the Swedish RICCADSA study, which examined 5-year outcomes in 244 non-sleepy patients with OSA and newly revascularized coronary artery disease (7). This was followed within months by the much larger, multinational, multicentre SAVE trial, wherein 2,687 patients were followed up to the study end point (8). SAVE enrolled patients with moderate-severe OSA and established cardiovascular or cerebrovascular disease, randomised them to therapeutic CPAP or usual care, and followed them for an average of 3.7 years. The majority of patients participating in SAVE were non-sleepy. To the surprise of many, and the dismay of some, both of these trials produced negative results—CPAP therapy did not lead to a reduction in cardiovascular morbidity or mortality. Taken at face value, this would suggest that sleep physicians should focus entirely on symptom control, and abandon semi-abstract concepts such as reducing possible risk of heart attack or stroke. As ever in clinical research, however, it may not be quite that straightforward.

These studies illustrate what can be achieved in sleep research, but also show why it can be so challenging. First, average CPAP compliance during the SAVE study was 3.3 hrs per night and only 42% of participants met the criteria for good compliance (average 4 hrs per night). Widely accepted compliance is a minimum of 4 hrs a night to achieve an improvement in ESS, based on multiple previous studies, with increased hours of usage shown to improve symptoms further (9). Therefore one could argue that participants in SAVE may have been undertreated. Barbé *et al*. (10) performed a RCT in which they found that non-sleepy patients with OSA and hypertension did have a reduction in systolic and diastolic blood pressure, with the greatest reductions seen in participants with 5.6 hrs or more usage. Furthermore, the low number of hours of CPAP usage may suggest that CPAP was used earlier in the night, as patients typically start the night with CPAP *in situ* but cease to use it when they can no longer tolerate it.

Given an average sleep time of 6–7 hours in most adults (11), participants in this study were using CPAP for little over, and often less than, half of the night. Moreover, rapid eye movement (REM) sleep tends to be longer and more frequent later in the night and early morning. Hypoxaemic episodes are typically more pronounced in REM, and REM OSA has been strongly associated with incident hypertension (12,13). Underscoring this point, a statistically significant improvement in cardiovascular outcomes was seen in RICCADSA participants with an average nightly CPAP usage of ≥4 hours. The pivotal question of whether improved adherence to CPAP would have led to improved outcomes in the SAVE study remains unanswered.

Second, patients in both SAVE and RICCADSA were not subjectively sleepy; it has been argued that non-sleepy patients may be at lower risk of cardiovascular disease than their sleepy counterparts (14). Supporting this theory, the MOSAIC study, which examined the impact of CPAP on minimally symptomatic OSA patients, did not show any improvement in daytime blood pressure following treatment (15), while other investigators have found OSA to be associated with metabolic disease only in sleepy cohorts (16). These findings are far from universal—no difference was seen in mortality in sleepy and non-sleepy patients in the Wisconsin sleep cohort (17)—and ethical concerns make it challenging to conduct long term controlled studies in sleepy OSA patients. Nonetheless, it should be borne in mind that neither the SAVE nor RICCADSA patient cohorts were necessarily representative of typical sleep clinic populations.

Other factors should also be considered in the interpretation of these data. For example, in patients with established cardiovascular disease, there may be a limited degree of reversibility, similar to some of the data from parallel studies on the effect of OSA on the central nervous system (18,19). It may therefore be expected that mortality and morbidity would be equally high in both groups, and CPAP may provide limited benefit. Similarly, the study populations of SAVE and RICCADSA were comprised of patients with moderate or severe OSA. Recent meta-analyses suggest that more severe OSA is associated with the highest risk for development of cardiovascular complications (20). Again, it remains unknown if a study including only patients with severe disease would have produced different results

A number of the centres participating in the SAVE trial had limited resources, therefore the diagnosis of OSA was made via home sleep studies, while control of sleep disordered breathing was assessed via data from CPAP machines. These data are not always accurate due to movement at night, sleep-wake transitions and other factors. Therefore it has not been confirmed, via gold standard polysomnography (PSG), whether OSA was fully controlled on treatment. This is of particular importance when patients are relatively asymptomatic and therefore cannot reliably confirm if they are experiencing benefit. Furthermore, a high proportion of other studies looking at cardiovascular disease risk in OSA used PSG to determine diagnosis (20).

Finally, although these patients had a relatively low OSA-related symptom burden, the secondary outcomes in the SAVE study did show significant improvements in the CPAP group, including sleepiness, mood, and quality of life. This implies that even partial treatment can be of symptomatic benefit in non-sleepy patients, mirroring the results of the MOSAIC study (15).

In summary, the results of these studies call into question the growing practice of using CPAP therapy as a panacea, including its use as a preventative measure in asymptomatic cardiovascular patients. Moreover, they also raise key questions regarding patient adherence to treatment and the polymorphic trajectory of illness. Finally, we would argue that, rather than closing the book on the subject, these studies underscore the need for further prospective, outcome-based research into sleep disordered breathing and its impact on cardiovascular disease and death.

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Footnote

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

References

1. Lévy P, Ryan S, Oldenburg O, et al. Sleep apnoea and the heart. Eur Respir Rev 2013;22:333-52.
2. Kent BD, Garvey JF, Ryan S, et al. Severity of obstructive sleep apnoea predicts coronary artery plaque burden: a coronary computed tomographic angiography study. Eur

Respir J 2013;42:1263-70.
3. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009;6:e1000132.
4. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012;307:2161-8.
5. 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.
6. 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.
7. 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.
8. 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.
9. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep 2007;30:711-9.
10. Barbé F, Durán-Cantolla J, Capote F, et al. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. Am J Respir Crit Care Med 2010;181:718-26.
11. Bin YS, Marshall NS, Glozier N. Secular trends in adult sleep duration: a systematic review. Sleep Med Rev 2012;16:223-30.
12. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. Am J Respir Crit Care Med 2014;190:1158-67.
13. Appleton SL, Vakulin A, Martin SA, et al. Hypertension Is Associated With Undiagnosed OSA During Rapid Eye Movement Sleep. Chest 2016;150:495-505.
14. Robinson GV, Smith DM, Langford BA, et al. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. Eur Respir J 2006;27:1229-35.
15. Craig SE, Kohler M, Nicoll D, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. Thorax 2012;67:1090-6.
16. Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. Thorax 2009;64:834-9.
17. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071-8.
18. Rosenzweig I, Glasser M, Crum WR, et al. Changes in Neurocognitive Architecture in Patients with Obstructive Sleep Apnea Treated with Continuous Positive Airway Pressure. EBioMedicine 2016;7:221-9.
19. Rosenzweig I, Glasser M, Polsek D, et al. Sleep apnoea and the brain: a complex relationship. Lancet Respir Med 2015;3:404-14.
20. Wang X, Ouyang Y, Wang Z, et al. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. Int J Cardiol 2013;169:207-14.

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