Editorial

Do the blood pressure changes in association with continuous positive airway pressure compliance play an important role to improve cardiovascular outcomes?

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Ning Ding (Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Kawada T. Effect of CPAP Therapy on the Cardiovascular Outcomes in Patients with Nonsleepy Obstructive Sleep Apnea. Am J Respir Crit Care Med 2017. [Epub ahead of print].

Submitted Jun 22, 2017. Accepted for publication Jun 27, 2017.
doi: 10.21037/jtd.2017.07.20
View this article at: http://dx.doi.org/10.21037/jtd.2017.07.20

Obstructive sleep apnea (OSA) is a common chronic condition, observed in 5–10% of the general population, though it is more prevalent in patients with cardiovascular disease (CVD) (up to 50%) (1). The high prevalence of OSA in patients with CVD raises several questions, such as, can OSA [which is known to have adverse cardiovascular (CV) effects (2)] contribute to the incidence and/or development of CVD? In other words, are there any causal relationships between OSA and poor CV outcomes?

Results from epidemiological studies and longitudinally followed observational studies may help to answer these questions. At least one population-based study has shown that subjects with moderate to severe OSA [defined as an apnea-hypopnea index (AHI) ≥15 events/h] have a 2.89 greater likelihood of developing hypertension, than those with an AHI of 0 (3). In addition, other population-based studies have found a significant association between AHI and the occurrence of incident heart failure (HF) in men (4) and between AHI and incident stroke in both men (5) and women (6). Furthermore, two population-based studies revealed that the risk for both all-cause and CV mortality in subjects with severe OSA, was significantly higher compared to those without OSA (7,8). Several studies have also reported that the presence of OSA can have a prognostic impact on patients with CVD. For instance, the co-existence of OSA with: stable coronary artery disease (CAD), acute coronary syndrome (ACS), acute myocardial infarction (MI) and HF, is associated with an increased risk of CV mortality and morbidity (9-14).

For further confirmation on the causal relationships between OSA and CVD, we must elucidate whether the alleviation of OSA can improve CV outcomes. As such, several RCTs investigating the effects of OSA treatment [by continuous positive airway pressure (CPAP), the most effective and established treatment for OSA], on CV morbidity and mortality had been performed. So far, none of these RCTs have shown a beneficial effect of CPAP treatment on CV outcomes, based on primary endpoints. Barbe *et al.* conducted a multicenter RCT to investigate whether treatment of OSA with CPAP can reduce the later occurrence of CV events in patients with no history of CVD. They showed that in non-sleepy patients with OSA (defined as an Epworth Sleepiness Scale score ≤10 and an AHI ≥20 events/h) but without any CV events at baseline, CPAP treatment compared with usual care did not result in a statistically significant reduction in the incidence of hypertension and/or CV events (nonfatal MI, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, HF, or CV death) (15). The Sleep Apnea Cardiovascular Endpoints study (SAVE),

an international multicenter RCT, showed that CPAP treatment (compared with usual care) for less-sleepy OSA patients (defined as an Epworth Sleepiness Scale score ≤15 and an 4% oxygen desaturation index ≥12 events/h) with a previous diagnosis of CAD or cerebrovascular disease, was not associated with a statistically significant reduction in the incidence of composite primary endpoints, including: MI, stroke, hospitalization for HF, ACS, transient ischemic attack, or CV death (16). A single center, RCT [The Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA (RICCADSA)], investigated the secondary prevention of CVD by assessing patients with CAD following percutaneous and surgical revascularization. They found that CPAP treatment, compared with usual care, did not produce a statistically significant reduction in the incidence of composite primary endpoints, including: repeat revascularization, MI, stroke and CV death among non-sleepy OSA patients (defined as an Epworth Sleepiness Scale score ≤10 and an AHI ≥15 events/h) who underwent percutaneous coronary intervention or coronary artery bypass surgery (17).

Two possible explanations to explain why these RCTs failed to show any beneficial effects of CPAP on CV outcomes are: (I) the exclusion of sleepy patients and (II) a variation in compliance with CPAP. Secondary analyses of these trials have shown that CPAP treatment may have been effective if it was used for ≥4 hours per night. In a post hoc analysis of the RCT run by Barbe and colleagues, CV outcomes were better in patients who had used CPAP for ≥4 hours per night, compared with controls (15). Propensity-score matched analysis of the SAVE trial suggested that there might be beneficial effects of CPAP on cerebral events (16). On-treatment analysis of the RICCADSA trial, revealed that the usage of CPAP for ≥4 hours per night, was significantly associated with better CV outcomes, compared to CPAP usage for <4 hours per night or no CPAP treatment (17). Compliance issues in these RCTS have already been discussed in a previous editorial in this journal (18).

Recently, Kawada suggested that changes in blood glucose homeostasis and insulin resistance do not explain the differences observed in the CV outcomes seen in patients with increased CPAP compliance (19). This reasoning was due to the results of a previous study by Steiropoulos and colleagues, which showed that there were no significant changes in blood glucose homeostasis and insulin resistance, in both CPAP-compliant and less-compliant groups, despite the effective alleviation of OSA in both groups (20). We suspect that the differences in CV outcomes according to the CPAP compliance status can be explained by changes in the control of blood pressure.

In general, CPAP reduces blood pressure in patients with OSA, in particular those with baseline hypertension (1). Indeed, in the SAVE trial (where approximately 80% of participants had hypertension), CPAP tended to reduce diastolic blood pressure (16). Interestingly, in the aforementioned multicenter RCT by Barbe and colleagues, although changes in blood pressure during the study period were not specifically mentioned, more baseline hypertensive patients were compliant to CPAP therapy and these patients had better CV outcomes when compared with less-compliant patients (15). In a RCT which investigated the effects of CPAP on blood pressure in non-sleepy, hypertensive patients with OSA (defined as an Epworth Sleepiness Scale score <11 and an AHI >19 events/h), a significant reduction in diastolic blood pressure was observed in the CPAP group. When the analysis was subdivided according to CPAP compliance, this reduction in blood pressure was only observed in the CPAP-compliant group (>5.6 hours per night) (21). Taken together, these findings suggest that in patients with OSA, CPAP-compliance can be associated with changes in blood pressure and that better CV outcomes may be derived from the reduction of blood pressure associated with CPAP compliance. If this is the case, even non-sleepy OSA patients should be motivated to maintain CPAP compliance. Further RCTs investigating the effects of OSA treatment on CV outcomes are currently being undertaken. These include: the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome (ISAACC) trial, where the effects of CPAP treatment on CV outcomes in patients with OSA and ACS are investigated (22); a Multi-Centre, Randomized Study to Access the Effects of Adaptive Servo Ventilation on Survival and Frequency of Hospital Admissions in Patients with Heart Failure and Sleep Apnea (ADVENT-HF) trial, where the effects of treating OSA (or central sleep apnea) by adaptive servo-ventilation (ASV) on CV outcomes in HF patients with reduced ejection fraction are investigated (23); and the Effects on Short-and Long-term Outcome and CPAP Treatment Efficacy (SAS-CARE) trial, where the effects of CPAP on cerebrovascular outcomes in patients who have experienced an acute cerebrovascular event are being investigated (24). Sub-analysis of these trials will provide further insights into the relationship between blood pressure changes associated with CPAP compliance and CV outcomes.

In summary, the aforementioned epidemiological studies and RCTs regarding the effects of CPAP treatment on CV outcomes, help to answer the questions that we proposed earlier in the text. OSA does contribute to the incidence and/or development of CVD and there are causal relationships between OSA and poor CV outcomes. However, more data from the ongoing RCTs and an investigation of the detailed mechanisms linking CPAP compliance with CV outcomes are still required.

Acknowledgements

None.

Footnote

Conflicts of Interest: T Kasai is affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare and Fukuda Denshi. A Murata has no conflicts of interest to declare.

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Cite this article as: Murata A, Kasai T. Do the blood pressure changes in association with continuous positive airway pressure compliance play an important role to improve cardiovascular outcomes? J Thorac Dis 2017;9(8):2255-2258. doi: 10.21037/jtd.2017.07.20