Treatment of Sleep Apnea With CPAP Lowers Central and Peripheral Blood Pressure Independent of the Time-of-Day: A Randomized Controlled Study

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BACKGROUND
Obstructive sleep apnea (OSA) is a risk factor for hypertension and randomized controlled trials have shown that OSA treatment with continuous positive airway pressure (CPAP) reduces peripheral blood pressure and arterial stiffness. Arterial stiffness is known to augment central aortic blood pressure independent of peripheral brachial blood pressure. Currently, it is unclear whether the reduction in blood pressure with CPAP is similar between central and peripheral sites. It is also unknown whether there are any time-of-day influences on central blood pressure changes after CPAP.

METHODS
Thirty-eight patients received therapeutic and sham CPAP in random order for 8 weeks each with an intervening 1-month washout. Peripheral and central blood pressure and arterial stiffness (augmentation index and time to reflection) were measured by pulse wave analysis at end-of-treatment visits. Measurements were taken in the afternoon (~2 pm) and the next morning (~9 am).

RESULTS
Compared to sham, CPAP significantly reduced central systolic (mean difference: −4.1 mm Hg; P = 0.003), central diastolic (−3.9 mm Hg; P = 0.0009), peripheral systolic (−4.1 mm Hg; P = 0.004), and peripheral diastolic (−3.8 mm Hg; P = 0.001) blood pressure. These effects were not influenced by time-of-day. Time to reflection was improved with CPAP compared to sham (3.7 ms; P = 0.01). There was no overall difference in augmentation index however when examined by time-of-day, a modest reduction with CPAP was observed in the morning (−2.5%; P = 0.03) but not in the evening (0.12%; P = 0.91).

CONCLUSION
CPAP reduces both central and peripheral blood pressure independent of the time-of-day. In contrast, modest improvements in conduit arterial stiffness after CPAP may only occur in the morning.

Keywords: arterial stiffness; blood pressure; central aortic pressure; continuous positive airway pressure; hypertension; obstructive sleep apnea; pulse wave analysis.

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Obstructive sleep apnea (OSA) is a common condition characterized by periods of obstructed breathing during the night which result in sleep fragmentation and intermittent hypoxia. OSA is associated with an increased all-cause and cardiovascular mortality risk as well as incident coronary heart disease, stroke, and heart failure. 1-4 OSA is the most common cause of secondary hypertension, 5,6 and this pathway may explain some of the increased cardiovascular risk in OSA. Additionally, arterial stiffness, a relatively novel marker of cardiovascular risk, 7 is increased in OSA compared to matched controls, positively correlated with increasing OSA severity and is reduced with continuous positive airway pressure (CPAP) and therefore has also been posited as a potential mechanism. 8

Arterial stiffness can cause an increase in central aortic pressure without necessarily resulting in increased peripheral blood pressure. In this regard, noninvasively assessed central aortic pressure using the pulse wave analysis (PWA) technique has been shown to be a superior predictor of cardiovascular risk, target organ damage, and left ventricular hypertrophy compared to peripheral blood pressure. 9-11 Furthermore, the Conduit Artery Function Evaluation study, using PWA, found differential reductions in central aortic pressure with 2 antihypertensive agents despite equivalent responses in peripheral blood pressure. 12 This variation in peripheral vs. central antihypertensive effects may also be applicable to other forms of treatment such as CPAP for OSA. We have previously shown similar results after CPAP treatment in an observational study where central blood pressure and arterial stiffness improved.

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significantly after 2 months of CPAP treatment but there was no equivalent reduction in peripheral blood pressure.\textsuperscript{13} To date, the effect of CPAP on central blood pressure has only been studied in a single short-term (3 weeks) randomized controlled study in hypertensive patients who prior to the CPAP treatment period received a 3-week specific antihypertensive medication regimen.\textsuperscript{14} It is therefore important to determine whether CPAP can improve central blood pressure in a more generalizable OSA population.

Additionally, we have previously shown that arterial stiffness is systematically modified across the sleep period in untreated OSA patients.\textsuperscript{15} A morning increase in arterial stiffness also resulted in an increase in central aortic pressure but not peripheral blood pressure. The overnight change in arterial stiffness and central aortic pressure suggests that treatment effects may also be influenced by the time of day the assessment is taken. That is, the improvement in arterial stiffness and central aortic pressure may only occur during the night and into the early morning. Despite previous randomized studies reporting reductions in different measures of arterial stiffness\textsuperscript{16,17} with CPAP, no study has investigated whether there is a time-of-day influence on these improvements. Furthermore, no randomized controlled study has examined whether central blood pressure improves independent of peripheral blood pressure.

This randomized, sham-controlled cross-over study investigated the effect of 8 weeks of CPAP treatment on arterial stiffness and blood pressure, both centrally and peripherally, compared to sham treatment in obese men with severe OSA. Furthermore, whether potential improvements with CPAP are influenced by time-of-day was also investigated.

**METHODS**

**Participants**

The details of the protocol and complete participant details have been previously reported in analyses of the effects of CPAP on the primary outcome of postprandial lipidemia.\textsuperscript{18} Briefly, participants were recruited from tertiary referral sleep clinics at the Royal Prince Alfred Hospital, St Vincent's Hospital, and the Woolcock Institute of Medical Research. Eligible participants were men and women (aged ≥ 21 years), with moderate to severe OSA (defined as an Apnea Hypopnea Index ≥ 25 and Oxygen Desaturation Index ≥ 20) by overnight polysomnography and CPAP naïve. Participants were excluded if they had uncontrolled type II diabetes or if they had a body mass index ≥ 35 kg/m\textsuperscript{2}. A full list of eligibility criteria is available on the ANZCTR 12605000066684.

**Design, randomization, and concealment**

This was an 8-week randomized, double-blind, sham-controlled, cross-over study. Eligible participants were randomized to receive 8 weeks of CPAP and sham CPAP in random order with an intervening 1-month washout in between the 2 treatment periods. Prior to the first treatment period, all participants underwent a single baseline visit for assessment of arterial stiffness, identical to the posttreatment visits. The sham devices were identical in appearance to the real CPAP devices (Remstar Auto, Philips Respironics) but delivered airflow with an ineffective therapeutic pressure of 0.5 cm H\textsubscript{2}O. At randomization, subjects received a number in ascending order that correspond to a preallocated treatment order. The randomized list was computer generated, using random block sizes of 2, 4, and 6. The individual responsible for the allocation of the treatment did not participate in data collection or analysis. Researchers who collected and analyzed the data were blinded to the treatment allocation for the duration of the study. The study complied with the Declaration of Helsinki, the Good Clinical Practice guidelines, and applicable regulatory requirements. All participants provided written informed consent to participate in the study, which was approved by the Central Ethics Committee (RPAH Zone). The study is registered with the Australia New Zealand Clinical Trials Registry (ANZCTR 12605000066684 available at [http://www.anzctr.org.au](http://www.anzctr.org.au)).

**Blood pressure and arterial stiffness**

Central blood pressure and arterial stiffness were measured during the 24-hour laboratory protocol at baseline and the end of each treatment period in the supine position after 15 minutes rest by PWA of the radial artery waveform, a method that our group has previously implemented\textsuperscript{13} (SphygmoCor; AtCor Medical, Sydney, New South Wales, Australia). The timing of the 2 measurements included a mid-afternoon time point (approximately at 2 pm) on the first day prior to the polysomnography, and a morning time point the next day after awakening (approximately at 9 am). The rationale for choosing these times was based on a previous study in healthy subjects which showed arterial stiffness is highest in the morning and lowest in the mid-afternoon.\textsuperscript{19} The timing of the measurements were the same in each patient at all visits and were conducted after at least 4 hours of fasting and caffeine consumption. Tests were always performed in the supine position after 15 minutes of rest. Peripheral (brachial) blood pressure was measured (from the mean of 3 readings) during the PWA protocol using an oscillometric device (Omron T5 Oscillometric BP monitor; Omron Healthcare Inc., Kyoto, Japan) with appropriately sized arm cuffs. Approximately, 9 PWA measurements were taken and the average of each parameter was calculated. A validated transfer algorithm was used to calculate the augmentation pressure, augmentation index, time to reflection, and central aortic blood pressure. The augmentation pressure and augmentation index were both corrected for a heart rate of 75 beats per minute (AP\textsubscript{75} and AIx\textsubscript{75}, respectively) using an automatic calculation determined by the PWA software. The augmentation index is the ratio of the augmentation pressure (due to the reflected component of the pulse pressure wave) to pulse pressure, expressed as a percentage. A decrease in AIx\textsubscript{75} and an increase in time to reflection indicate improvements in arterial stiffness.

**CPAP compliance**

Objective CPAP compliance was downloaded from each machine at the end of each treatment arm and is reported as mean hours per night for each treatment period.
Statistical analysis

All patients with complete PWA data were included in the analysis. Differences at baseline between afternoon and morning readings were determined by paired t-tests. Mixed model analysis was used to determine the posttreatment effect of CPAP vs. sham. Order effects were also analyzed using mixed models by including the order variable as well as an interaction term of order * treatment. The significance of these variables was examined. As there were no order effects detected on any outcome, these 2 variables (order and order * treatment) were removed from the final model. Additionally, an interaction term of treatment * time was used to determine whether there was a time-of-day influence (PM vs. AM) on the treatment effect. Possible time-of-day influence was defined when the interaction term was P < 0.1 (as defined a priori) and the between treatment group differences were examined at each time point. Where the interaction term was P > 0.1, the interaction term was removed from the mixed model, and the overall between-group effects (CPAP vs. sham), regardless of time, were examined. Unpaired t-tests were used to assess the influence of sleepiness and hypertension status on outcomes.

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Data were considered significantly different at P < 0.05 (2 sided). The data are presented as mean (SD), mean difference (95% CI), or median (interquartile range) as indicated.

RESULTS

The flow of participants is shown in Figure 1. Details of reasons for withdrawn participants has been previously reported. Thirty-eight participants (34 men) were randomized into the study and 29 (27 men) completed the 2 treatment periods. There were no changes to antihypertensive medications throughout the study. Complete PWA data was available for 26 (24 men) participants. There was no order effect detected for any outcome variable. Four participants (2 men) with PWA data on only one of the treatment periods were also included in the mixed model analysis. A per-protocol analysis excluding these 4 participants did not change the results (data not shown). Baseline characteristics of participants included in the final analysis (n = 30) are presented in Table 1. Compliance rates were similar between treatment arms with 4.3 (2.3) hours/night on CPAP and 3.3 (2.3) hours/night on sham (P = 0.15). At baseline and during sham treatment, AIx75 increased overnight by 4.9% (95% CI: 4.97–6.9, P < 0.0001) and 3.4% (1.11–5.60, P = 0.004), respectively, but not during the CPAP period (0.69%, −1.56 to 2.93, P = 0.54). There were no significant overnight changes in any blood pressure measurements (Table 2).

As previously reported, OSA was successfully treated with CPAP compared to sham. In this group of participants, there was a significant reduction in both Apnea Hypopnea Index (mean difference [95% CI]: −34.6 events/hour [−45.4 to −23.8], P < 0.0001) and the Oxygen Desaturation Index (−33.7 events/hour [−42.9 to −24.6], P < 0.0001). Compared to sham, CPAP significantly reduced central systolic and diastolic blood pressures by approximately 4.0 mm Hg after 8 weeks of treatment (Table 3). Similar reductions were also shown in peripheral systolic and diastolic blood pressures (Table 3). These reductions were not influenced by the time of day the measurement was recorded as indicated by nonsignificant time * treatment interaction terms (all P > 0.1). There were no between-group differences observed in peripheral or central pulse pressures (Table 3).

Overall, across both time points, CPAP did not decrease either the AP75 or the AIx75 compared to sham but did

Table 1. Baseline characteristics of participants

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.1 ± 13.6</td>
</tr>
<tr>
<td>Male/female</td>
<td>26/4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>96.9 ± 15.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 ± 4.2</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>40.0 ± 23.4</td>
</tr>
<tr>
<td>ODI (events/hour)</td>
<td>30.6 ± 22.6</td>
</tr>
<tr>
<td>Minimum saturation (%)</td>
<td>78.8 ± 11.0</td>
</tr>
<tr>
<td>T &lt; SaO₂ 90%</td>
<td>6.7 ± 11.1</td>
</tr>
<tr>
<td>Sleepiness</td>
<td></td>
</tr>
<tr>
<td>Epworth sleepiness scale (0–24)</td>
<td>10.5 ± 5.0</td>
</tr>
</tbody>
</table>

Medical history and medication

| Hypertension, n (%)   | 7 (23)        |
| Antihypertensive agents, n (%) | 7 (23)     |
| ACE inhibitors, n (%)  | 2 (6.7)       |
| ARB, n (%)            | 3 (10)        |
| ARB and CCB, n (%)    | 1 (3.3)       |
| ARB and ACE inhibitor, n (%) | 1 (3.3) |

Data are presented as mean ± SD unless stated otherwise. Data shown for the 30 patients with pulse wave analysis data. Abbreviations: ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; AHI, Apnea Hypopnea Index; BMI, body mass index; CCB, Calcium channel blocker; ODI, Oxygen Desaturation Index; T < SaO₂ 90%, time spent below 90% of blood oxygen saturation.
The effect of CPAP on the outcome does not differ between time points. This is indicated by a nonsignificant interaction term (IntX) in Table 3. However, when the between-group difference was examined at each time point, CPAP was shown to decrease the Alx75 across the night. This was indicated by a reduction in CPAP in the morning (−2.5% [−4.8 to −0.26], P = 0.03) but not in the previous afternoon (0.13% [−2.2 to 2.4], P = 0.91). The overall improvement in time to reflection was also observed to be mainly due to an increase in the morning (6.0 ms [2.0–10.0], P = 0.01) but not the previous afternoon (1.4 ms [−2.6 to 5.3] P = 0.50) (Figure 2).

A subanalysis did not demonstrate any difference in treatment response for any blood pressure or arterial stiffness measure between patients with sleepiness at baseline (Epworth Sleepiness Scale ≥ 10) compared to those without sleepiness. There was also no difference in treatment response between hypertensive and nonhypertensive patients (results not shown).

### DISCUSSION

This study has shown significant improvements in central and peripheral blood pressure following treatment with CPAP.
of OSA with CPAP. These improvements were shown in measurements taken both in the afternoon and the following morning. In contrast, there were no overall changes in augmentation pressure or the augmentation index. However, there was a significant improvement in the time to reflection suggesting an overall reduction in aortic but not conduit arterial stiffness. There was however a modest improvement in augmentation index when only the morning measurements were examined.

The reduction in central aortic pressure with CPAP treatment observed in this study is consistent with our own observational data and is the first study to demonstrate a positive CPAP effect using a randomized sham-controlled design. In the only other randomized study to examine arterial stiffness and central blood pressure after CPAP and Sham CPAP, atherothrombotic CPAP but not Sham CPAP reduced both indexes when compared to antihypertensive therapy alone. However, the differences between CPAP and Sham CPAP did not appear reported. In contrast, we were able to document clear reductions in both indexes that were directly attributable to CPAP. It is becoming increasingly recognized that central aortic pressure is an accurate early marker of cardiovascular risk and target organ damage. This improvement in central aortic pressure, despite being relatively modest, is of clinical relevance in terms of future cardiovascular risk. Studies have shown decreases of less than 4 mm Hg to be associated with a reduction of cardiovascular mortality and stroke by approximately 25%.

Despite a relative reduction in central aortic pressure with CPAP compared to Sham CPAP, we did not observe a parallel improvement in arterial stiffness (determined by augmentation index), as may have been expected. Indeed when the current data was analyzed by time point, a reduction, albeit a modest one, was found in the morning but not in the afternoon. A previous study which showed a parallel improvement in arterial stiffness with CPAP treatment including a reduction in endothelial dysfunction and sympathetic tone. While we did measure urinary catecholamines in the primary study, data were pooled into sleep vs. wake periods and it would be difficult to attribute this pooled data to single measures of arterial stiffness.

Several limitations should be acknowledged with our study. Firstly, we did not use gold-standard assessments to measure arterial stiffness from pulse wave velocity, instead relying on a surrogate measure (time to reflection) derived from the PW A device. Secondly, although PW A has been shown to be highly reproducible, it is reliant on accurate measurements taken both in the afternoon and the following morning. In contrast, there were no overall changes in augmentation pressure or the augmentation index. However, there was a significant improvement in the time to reflection suggesting an overall reduction in aortic but not conduit arterial stiffness. There was however a modest improvement in augmentation index when only the morning measurements were examined.

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assessments of peripheral blood pressure from the brachial cuff sphygmomanometer to calibrate derived central pressures. In this regard, oscillometric devices have been criticized. However, in order to minimize this error, in this current study, we performed several calibration readings per test to obtain a more reliable estimate of peripheral blood pressure. Thirdly, the participants in this study were either normotensive or being concurrently treated with antihypertensives and had severe OSA, so this data may not be generalizable to both untreated hypertensive OSA and less severe populations. Fourthly, we were unable to repeat the baseline visit after the washout period. However, we believe that the long washout period of 4 weeks was sufficient time for any changes which occurred with treatment to return to baseline levels. Moreover, no order effect was found. In addition, this was only an 8-week study and it is therefore possible that larger improvements may have occurred with longer treatment. Furthermore, the study was conducted in a single centre. Finally, as these were not the primary outcomes which the study was powered on, it is possible that the study was not adequately powered to detect an overall difference in arterial stiffness determined from the augmentation index.

In conclusion, 8 weeks of CPAP significantly reduced both peripheral and central aortic blood pressure compared to sham treatment and these improvements were not influenced by time-of-day. Several surrogate markers of arterial stiffness, including augmentation index and time to reflection, were reduced with CPAP, however the majority of this improvement was observed in the morning only. In order to fully appreciate how time-of-day changes in arterial stiffness impact on central blood pressure relative to peripheral blood pressure, 24-hour ambulatory arterial stiffness and central aortic pressures ideally needs to be measured.

ACKNOWLEDGMENTS

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DISCLOSURE

The authors report no relationships that could be construed as a conflict of interest.

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