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Original Article

The effect of continuous positive airway pressure therapy on arterial stiffness and endothelial function in obstructive sleep apnea: a randomized controlled trial in patients without cardiovascular disease

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality which may be mediated by increased arterial stiffness and endothelial dysfunction. Continuous positive airway pressure (CPAP) therapy improves excessive daytime somnolence (EDS), but its effect on vascular function in patients without preexisting cardiovascular disease (CVD) is unclear.
Methods: Fifty-three patients with OSA defined as an apnea–hypopnea index (AHI) of $\geqslant$15 and without CVD were recruited into a double-blind, randomized, placebo-controlled, crossover trial of 12 weeks of CPAP therapy, of whom 43 participants completed the study protocol. Arterial stiffness was assessed by measuring the augmentation index (AIx) and pulse wave velocity (PWV) by applanation tonometry and cardiovascular magnetic resonance imaging to determine aortic distensibility. Endothelial function was assessed by measuring vascular reactivity after administration of salbutamol and glyceryl trinitrate.
Results: CPAP therapy lowered systolic blood pressure (SBP) (126 mmHg [standard deviation {SD}, 12] vs 129 mmHg [SD, 14]; $P = .03$), with a trend towards reduced AIx (15.5 [SD, 11.9] vs 16.6 [SD, 11.7]%; $P = .08$) but did not modify endothelial function. When subjects with ($n = 24$) and without ($n = 19$) EDS were separately examined, no effect of CPAP therapy on vascular function was seen.
Conclusions: In patients without overt CVD, CPAP therapy had a nonsignificant effect on AIx and did not modify endothelial function.

1. Introduction

Obstructive sleep apnea (OSA) is common and is caused by repetitive obstruction of the upper airway during sleep. When OSA leads to excessive daytime somnolence (EDS) it is termed *obstructive sleep apnea–hypopnea syndrome (OSAHS)*, affecting 2–4% of the middle-aged population with an even greater proportion having evidence of OSA without EDS [1].

OSA is associated with increased cardiovascular morbidity and mortality [2,3] and is an independent risk factor for hypertension [4]. Many mechanisms linking OSA and cardiovascular disease (CVD) have been proposed, with individual obstructive events associated with transient increases in blood pressure (BP) [5], arterial stiffness [6], and sympathetic activity [7]; all of which, along with systemic inflammation [8] and intrathoracic pressure swings, may contribute to endothelial dysfunction. We previously showed [9] that subjects with OSAHS in the absence of known CVD had evidence of increased arterial stiffness and impaired endothelial function when compared to well-matched control subjects.

Observational studies suggest that cardiovascular morbidity and mortality is lower in patients treated with continuous positive airway pressure (CPAP) therapy [2,10,11]. Randomized controlled trials (RCTs) have shown that CPAP therapy lowers BP [12,13], and it also has been shown to improve endothelial function in small studies [14,15]; however, many of these studies did not exclude patients with CVD [12,13,15]. To our knowledge, the effects of CPAP therapy on arterial stiffness had not yet been investigated prior to beginning our trial.

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The aim of our double-blind, randomized, placebo-controlled, crossover trial was to examine the effects of CPAP therapy on arterial stiffness and endothelial function in subjects with OSA in the absence of overt CVD or diabetes mellitus (DM).

2. Methods

2.1. Subjects

Fifty-three subjects with OSA (apnea–hypopnea index [AHI] of $\geqslant$15 on polysomnography), with no history of CVD or DM, were recruited through the Department of Sleep Medicine, Royal Infirmary of Edinburgh (Fig. 1). Exclusion criteria were previous CPAP therapy, respiratory failure, medications affecting BP, sleepiness when driving, professional driving, contraindications to magnetic resonance imaging, and intercurrent illness. EDS was defined as a score of $\geqslant$11 on the Epworth Sleepiness Scale (ESS). A detailed medical history was taken and medical records were examined to exclude a history of CVD or hypertension. A fasting venous glucose sample was taken to exclude DM.

Sixteen channel, inpatient, overnight polysomnography (Compumedics Ltd., Abbotsford, Australia) was performed in all subjects with sleep scored using standard Rechtschaffen and Kales criteria [16], and apnea and hypopneas were defined per the 2007 American Academy of Sleep Medicine standard criteria [17].

Subjects were recruited between March 2007 and August 2008. Sample size was determined using pilot data to provide a 90% chance of detecting a 10% difference in mean aortic distensibility (AoD) at a significance level of 5% ($n = 40$). Therefore, we aimed to recruit 60 subjects to allow for the occurrence of dropouts. The study was approved by Lothian Local Research Ethics Committee (ref. 06/S1102/54) and written informed consent was obtained from all subjects.

2.2. Study design

Our double-blind, randomized, placebo-controlled, crossover trial examined the effects of CPAP therapy on arterial stiffness and endothelial function in subjects with OSA. The study is registered with the International Standard Randomized Controlled Trial Number Register (ISRCTN48783995).

Subjects underwent vascular assessments at baseline and were randomized to receive either CPAP therapy (S8 Autoset™, ResMed, Abingdon, UK) or sham CPAP for 12 weeks before crossing into the second arm of the study for a further 12 weeks. Sham CPAP was achieved by setting the CPAP flow to the lowest possible setting and adding a flow-restricting connector and extra holes to the circuit, allowing air to escape [13,15]. Randomization was performed by a single researcher (MV) who was not involved in the measurement of vascular outcomes, using a computer generated balanced block. Both the subjects and the researchers who assessed vascular outcomes (AJ and MC) were blinded to treatment allocation. Optimum CPAP pressures were determined at overnight inpatient CPAP titration (Spirit™, ResMed, Abingdon, UK). CPAP usage was determined using time-clock data, which measured time spent at the prescribed pressure throughout the entire study period.

Vascular assessments were repeated after each arm of the study and were conducted at the same time of day, with subjects having fasted overnight and abstained from cigarettes, alcohol, and caffeine use for at least 10 h prior to beginning the study. Resting BP and heart rate were recorded in duplicate using an automated sphygmomanometer (Omron 705IT, Milton Keynes, UK) with the mean used for analysis.

2.3. Assessment of arterial stiffness and endothelial function by applanation tonometry

All studies were performed in the supine position in a temperature-controlled room after at least 30 min of rest and in accordance with the Expert Consensus Document on Arterial Stiffness [18] by a single operator (AJ).

2.3.1. Pulse wave analysis

Radial artery pressure waveforms were continuously measured by tonometer (CBM 7000, Colin Corp., Komaki City, Japan) and the SphygmoCor® system (version7, AtCor Medical, Sydney, Australia), which applied a validated transfer function to the mean of approximately 10 waveforms, giving an aortic pressure waveform. From this mean, the augmentation index (AIx) corrected to a heart rate of 75 beats per minute as previously described [9], was determined. AIx is a measure of stiffness throughout the arterial tree and represents the difference between the first and second systolic peaks, expressed as a percentage of the pulse pressure. Repeated measurements of AIx were taken at baseline and the mean value was used for analysis. Readings with >10% variability in pulse height or in the diastolic portion of the waveform were excluded.

Noninvasive assessment of endothelial function was performed by measuring endothelium-dependent change in AIx following the administration of salbutamol and endothelium-independent change in AIx following glyceryl trinitrate [19]. As previously described [9], after baseline recordings 500 μg of glyceryl trinitrate tablet was given sublingually for 3 min and then was removed. AIx was then recorded every minute for 10 min and then every 5 min for a further 15 min. A dose of 400 μg of inhaled salbutamol via a spacer device was subsequently administered, with recordings of AIx every minute for 10 min and then every 5 min for a further 10 min. The greatest change in AIx following the administration of each drug was used for analysis [19].

2.3.2. Pulse wave velocity

Pulse wave velocity (PWV) increases with arterial stiffness and measures the speed at which the systolic pressure wave reaches the peripheries. Carotid-femoral (aortic) PWV was measured as previously described [9] using a micromanometer (Millar Instruments, Houston, TX) and the SphygmoCor® system by sequential acquisition of carotid and femoral pressure waveforms gated to the *R*-wave of a simultaneously recorded electrocardiogram. Only those readings that met quality-control standards [20] were accepted for analysis. We aimed to repeat each recording three times, with the mean PWV used for analysis.

2.4. Assessment of aortic distensibility (AoD)

Cardiovascular magnetic resonance imaging (1.5 Tesla, Philips Medical Systems, Best, Netherlands) was used to determine AoD. Sagittal oblique images of the aorta in the supine position were used to define planes orthogonal to the aortic axis for electrocardiogram-gated steady-state free precession cine imaging with full *R–R* coverage in the ascending and descending aorta at the level of the right pulmonary artery and at the level of the diaphragm. BP measurements (S/5™ monitor, Datex-Ohmeda, Helsinki, Finland) were taken in the scanner immediately before and after each image was acquired, and the mean was used to determine the pulse pressure. Image analysis was performed using an automated algorithm (EasyVision, Philips Medical Systems) by a single operator (MC) who was blinded to treatment allocation, with AoD calculated as $(A_{max} - A_{min})/(A_{min} \times \text{pulse pressure})$ in which A_{max} and A_{min} were the maximum and minimum aortic areas during the cardiac cycle.