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Original Article

Arterial stiffness and endothelial function in obstructive sleep apnoea/hypopnoea syndrome

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ABSTRACT

Background: Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) is associated with increased cardiovascular morbidity and mortality. Our study examined arterial stiffness and endothelial function in subjects with OSAHS with no known cardiovascular disease compared to well-matched controls.
Methods: Twenty subjects with OSAHS (defined as apnoea–hypopnoea index [AHI] $\geqslant$15 and Epworth Sleepiness Scale score $\geqslant$11) without cardiovascular disease and 20 well-matched controls underwent a comprehensive evaluation of arterial stiffness and endothelial function. Arterial stiffness was measured by applanation tonometry and cardiovascular magnetic resonance imaging (MRI) and endothelial function assessed by measuring vascular reactivity after administration of glyceryl trinitrate and salbutamol.
Results: Subjects with OSAHS had increased arterial stiffness (augmentation index 19.3 [10.9] vs. 12.6 (10.2)%; $p = 0.017$) and impaired endothelial function (change in augmentation index following salbutamol −4.3 (3.2) vs. −8.0 (4.9)%; $p = 0.02$) compared to controls. Aortic distensibility, a measure of arterial stiffness, was negatively correlated with the AHI.
Conclusions: Our findings suggest that even in the absence of known cardiovascular disease, subjects with OSAHS have increased arterial stiffness and impaired endothelial function and are at increased risk for cardiovascular disease.

1. Introduction

Obstructive sleep apnoea is caused by repetitive obstruction of the upper airway during sleep and when it leads to excessive daytime somnolence is called obstructive sleep apnoea–hypopnoea syndrome (OSAHS). OSAHS affects 2% to 4% of the middle-aged population [1] with a further 20% having frequent apnoeas and hypopnoeas in the absence of excessive daytime somnolence [2].

Obstructive sleep apnoea is an independent risk factor for hypertension [3] and also has been associated with increased cardiovascular morbidity and mortality [4–8].

The mechanisms for these associations are not completely understood, but each obstructive event is associated with transient increases in blood pressure [9], arterial stiffness [10], and sympathetic activity [11] that may contribute to endothelial dysfunction. Prior to beginning our study, previous studies in small numbers of patients suggested that subjects with obstructive sleep apnoea had increased arterial stiffness [12] and evidence of endothelial dysfunction [13,14].

The aim of our study was to comprehensively examine both arterial stiffness and endothelial function in subjects with OSAHS, without overt cardiovascular disease (CVD) or diabetes mellitus (DM) compared to well-matched controls. It was our hypothesis that OSAHS leads to increased arterial stiffness and endothelial dysfunction independent of pre-existing CVD.

2. Methods

2.1. Subjects

Twenty subjects with OSAHS (defined as apnoea-hypopnoea index [AHI] $\geqslant$15 on overnight polysomnography (PSG) and an Epworth Sleepiness Scale score $\geqslant$11) with no history of CVD or DM were recruited through the Department of Sleep Medicine. Exclusion criteria were: previous continuous positive airway pressure, respiratory failure, medications affecting blood pressure,

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sleepiness when driving, professional driving, contraindications to magnetic resonance imaging (MRI), and intercurrent illness. Twenty control subjects with no history of OSAHS, CVD, or DM were recruited via advertisement (within the hospital and on the hospital and university intranet) and a local general practitioner practice. Control subjects were required to have an AHI $\leqslant$10 on PSG and an Excessive Sleepiness Scale score <11 and also were subject to the exclusion criteria. We were able to match 20 subjects with OSAHS for age (within 5 years), sex, and body mass index (within 10%) on a one-to-one basis with the control subjects (Table 1).

To exclude a history of CVD, a detailed medical history was taken from all subjects and their medical records examined. Subjects with a raised clinic blood pressure also were excluded and all subjects underwent a fasting blood glucose measurement to exclude DM.

A 16-channel in-patient PSG (Compumedics Ltd., Abbotsford, Victoria, Australia) was performed in all subjects. Sleep was scored using standard Rechtschaffen and Kales criteria [15]. Apnoea was defined as a reduction in airflow of $\geqslant$90% from baseline for at least 10 s and hypopnoea as a reduction in airflow of $\geqslant$30% for at least 10 s with an oxygen desaturation of $\geqslant$4% from baseline or a $\geqslant$50% reduction in airflow for at least 10 s with a $\geqslant$3% oxygen desaturation or associated arousal [16].

Subjects were recruited between March 2007 and February 2009. Our study was approved by Lothian Local Research Ethics Committee (ref. 06/S1102/54) and written informed consent obtained from all subjects.

2.2. Study design

All vascular studies were conducted at the same time of day and subjects and controls had fasted overnight and abstained from smoking, alcohol, and caffeine for at least 10 h prior to the vascular studies.

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

All studies were carried out by a single operator (AJ) in accordance with the Expert Consensus Document on Arterial Stiffness [17]. Measurements were recorded supine in a temperature-controlled room after at least 30 min of rest. Resting blood pressure and heart rate were recorded in duplicate using an automated sphygmomanometer (Omron 705IT, Milton Keynes, UK) and the mean used for analysis.

2.3.1. Pulse wave analysis

Radial artery pressure waveforms were continuously measured by tonometer (Colin Corp., Komaki City, Japan) and the SphygmoCor® system (version 7, AtCor Medical, Sydney, Australia). A validated mathematical transfer function was applied to the mean of approximately 10 waveforms to derive an aortic pressure waveform [18]. From this, the augmentation index (AIx), a measure of central-pressure augmentation, was determined. AIx is a measure of stiffness throughout the arterial tree and is calculated as the difference between the first and second systolic peaks, expressed as a percentage of the pulse pressure. AIx is affected by heart rate and was corrected to a heart rate of 75 beats per minute, as previously described [19]. Readings with >10% variability in pulse height or in the diastolic portion of the waveform were excluded. Repeated measurements of AIx were taken at baseline, with the mean value used for analysis.

Endothelial function was assessed by measuring endothelium-dependent change in AIx following inhaled salbutamol and endothelium-independent change in AIx following sublingual glyceryl trinitrate (GTN) [20,21].

After baseline recordings, 500 μg of GTN tablet was given sublingually for 3 min and then removed. AIx was then recorded every minute for 10 min and then every 5 min for a further 15 min. Previous studies demonstrated that the haemodynamic effects of GTN can persist for up to 25 min [22] and therefore, 400 μg of inhaled salbutamol via a spacer device was given 30 min after the GTN. AIx was then recorded 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 [20].

2.3.2. Pulse wave velocity

Pulse wave velocity (PWV) increases with arterial stiffness and records the time taken by the systolic pressure wave to reach the peripheries. Carotid–femoral (aortic) PWV was measured by a micromanometer (Millar Instruments, Houston, TX, USA) and the SphygmoCor® system by sequential acquisition of carotid and femoral pressure waveforms gated to the R wave of a simultaneously recorded electrocardiogram. The SphygmoCor® system applied the intersecting tangent algorithm to determine the onset of the forward wave and the difference in transit time between the carotid and the femoral locations was used to calculate the PWV. Readings that met quality control standards were accepted for analysis [23]. We aimed to repeat each recording three times and the mean PWV was used for analysis.

Table 1
Baseline characteristics.

	Subjects with OSAHS (n = 20)	Control subjects (n = 20)	p Value
Age (y)	44 (7)	44 (7)	0.94
Sex	13 men	13 men	
BMI (kg/m^2)*	29.7 (27.4–32.7)	29.4 (27.4–33.5)	0.20
Neck circumference (cm)*	40.5 (38.1–41.9)	39.0 (36.6–41.5)	0.02
Waist to hip ratio	0.94 (0.07)	0.93 (0.08)	0.54
Systolic blood pressure (mmHg)	127 (14)	124 (11)	0.33
Diastolic blood pressure (mmHg)	76 (10)	75 (9)	0.75
MAP (mmHg)	93 (11)	91 (9)	0.42
Fasting glucose (mmol/L)	4.9 (0.5)	4.9 (0.3)	0.68
Total cholesterol (mmol/L)	5.5 (1.0)	5.6 (0.9)	0.79
Current smokers	30%	5%	0.13
Ex-smokers	35%	40%	1.00
Apnoea/hypopnoea index *	32 (22–41)	4 (3–6)	Part of selection criteria
Epworth Sleepiness Scale score*	16 (14–18)	4 (2–8)	Part of selection criteria

Mean (standard deviation) unless indicated.
BMI, body mass index; MAP, mean arterial blood pressure; OSAHS, obstructive sleep apnoea–hypopnoea syndrome.
* Median (interquartile range).