

## Ventricular-arterial coupling in obstructive sleep apnea

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# Accepted Manuscript

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**Ventricular-arterial coupling in obstructive sleep apnoea**

Shantsila. Ventricular-arterial coupling

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**Abstract**

*Objectives:* Arterial and systolic elastance are important parameters determining effective functional interaction of heart and vessels. The aims of this study were to (i) compare arterial [arterial elastance index (EaI)] and ventricular [End-systolic elastance (Ees) and End-diastolic elastance (Eed)] elastance in subjects with obstructive sleep apnoea (OSA) and patients with treated 'high-risk' hypertension (HHT), and (ii) test whether these parameters in OSA patients can be improved by continuous positive airway pressure (CPAP) therapy.

*Methods:* Echocardiographic parameters of cardiac and vascular stiffness (EaI, Ees and Eed) were quantified in 28 patients with OSA (mean [SD] age 51 [11] years, 79% male) and 28 treated subjects with HHT (mean [SD] age 48 [12] years, 61% male). Twenty three OSA patients were treated with CPAP for median of 26 weeks. Ea was calculated from stroke volume and systolic BP and adjusted by body area (EaI). Both study groups had preserved and comparable left ventricle (LV) contractility.

*Results:* There was no significant differences in arterial elastance index (EaI,  $p=0.94$ ), end-systolic elastance (Ees,  $p=0.5$ ), end-diastolic elastance (Eed,  $p=0.63$ ) and arterial-ventricular interaction (Ees/Ea,  $p=0.62$ ) between OSA and HHT groups. After CPAP therapy, there was a significant reduction in arterial elastance index (EaI; paired t-test,  $p=0.013$ ), and arterial-ventricular interaction (Ees/Ea; paired t-test,  $p=0.004$ ). End-systolic elastance (Ees,  $p=0.17$ ), end-diastolic elastance (Eed,  $p=0.66$ ) parameters did not change significantly.

*Conclusions:* OSA patients and HHT patients have similar parameters of elastance and ventricular-arterial coupling. CPAP treatment in OSA patients significantly improved ventricular-arterial coupling.

**Condensed abstract**

There was no significant differences in arterial elastance index (EaI,  $p=0.94$ ), end-systolic elastance (Ees,  $p=0.5$ ), end-diastolic elastance (Eed,  $p=0.63$ ) and arterial-ventricular interaction (Ees/Ea,  $p=0.62$ ) between obstructive sleep apnoea and high risk hypertension groups. After continuous positive airway pressure therapy, there was a significant reduction in arterial elastance index (EaI), and arterial-ventricular interaction (Ees/Ea). End-systolic elastance (Ees), end-diastolic elastance (Eed) parameters did not change significantly. As a result patients with obstructive sleep apnoea and high risk hypertension have similar parameters of elastance and ventricular-arterial coupling. Continuous positive airway pressure treatment in patients with obstructive sleep apnoea significantly improves ventricular-arterial coupling.

**Key words:** obstructive sleep apnoea; arterial elastance; ventricular elastance; ventricular-arterial couplings

## Introduction

Obstructive sleep apnoea (OSA) is a pathological condition associated with recurrent hypoxia, disturbed sleep, and ultimately excessive negative intrathoracic pressure that leads to detrimental effects on cardiovascular system and an increased cardiovascular morbidity.[1, 2] Mechanisms of OSA-related cardiac and arterial damage are diverse and still insufficiently understood. Hypertension is common in OSA and predisposes to cardiac diastolic dysfunction, arterial stiffening as well as endothelial dysfunction.[3-6] The pathogenic mechanisms of OSA also involve increase sympathetic activity, inflammation and oxidative stress, and might thus disturb cardiovascular performance even in patients without overt hypertension.

Impairment of cardiac and vascular elastic properties is recognised as a critical element of cardiovascular pathophysiology.[7, 8] Large arteries do not just server as passive conduits of blood, but are active component of a variety of cardiovascular functions.[9] Increased arterial and cardiac stiffness are also important contributors to cardiac systolic and diastolic dysfunction and is determined by the composition of the extracellular matrix, arterial smooth muscle tone and relaxation capacity of cardiomyocytes.[10] Ability of normal large arteries to stretch during systole and to maintain some of the blood volume (and to consequently return it to the circulation during diastole) is crucial for smoothening cyclic fluctuations in blood pressure (BP). This process also reduces cardiac afterload and improves coronary perfusion in diastole.

Arterial and left ventricular (LV) actions (i.e., ventricular-arterial coupling) are normally well coordinated and can be measured using echocardiography, as parameters of arterial and

cardiac elastance.[11] Ventricular-arterial interactions can be disturbed in conditions associated with increased arterial and cardiac stiffness, such as hypertension. Given that there is well documented enhanced arterial stiffness in OSA, it is plausible that ventricular-arterial coupling can also be impaired in OSA, but this has not been previously investigated.[12]

Continuous positive airway pressure (CPAP) treatment of mild to moderate OSA has been shown to improve symptoms, quality of life and outcomes, and has been accepted as the 'gold standard' treatment in OSA[13]. The effects of CPAP on cardiovascular function in hypertension free OSA patients without pre-existing cardiovascular disease has not been established.[14, 15] The data on effect of CPAP on cardiac function are controversial, although scarce data are available on the effect of CPAP treatment on the parameters of arterial and cardiac elastance.[16-18]

In this study, we tested the hypothesis that abnormal arterial [arterial elastance ( $E_a$ ); arterial elastance index ( $E_{aI}$ )] and ventricular [End-systolic elastance ( $E_{es}$ ) and End-diastolic elastance ( $E_{ed}$ )] elastances are present in untreated OSA patients, compared to treated 'high-risk' hypertension (HHT) patients, and second, that these parameters in OSA can be improved after CPAP therapy.

## Methods

In this prospective study twenty eight consecutive subjects with a confirmed diagnosis of moderate-severe OSA have been compared with 28 treated 'high risk hypertensives' (HHT). OSA group included subjects with apnea-hypopnoea index (AHI)>15, established by multi-channel polysomnography (FSI Grey Flash recorder, Stowood Scientific Instruments Ltd, Oxford UK) and recruited from the Sleep laboratory in City Hospital, Birmingham, UK. HHT was defined by the presence of established hypertension associated with one or more of the following cardiovascular risk factors: LV hypertrophy (Sokolow-Lyon or Cornell voltage criteria), age >55 years, peripheral vascular disease, or known family history of CAD, a definition used in contemporary clinical trials[19]. Exclusion criteria were: secondary hypertension related to renal, renovascular or endocrine causes, CAD, valvular heart disease, LV ejection fraction <50%, diabetes mellitus, liver disease, serum creatinine >200  $\mu\text{mol/L}$ , malignancy, recent (<3 months) arterial or venous thromboembolic disease, active infections and/or a history of inflammatory or connective tissue disorders.

Participants were asked to abstain from alcohol, tea, coffee and smoking for 24 hours prior to the study. Participants were asked not to take their medications on the study day. All scans were done in a darkened, quiet, temperature controlled room after rest for 15-20 minutes. After baseline scan, patients with OSA were provided with an automated CPAP device (REMstar Pro M Series with C-Flex, Phillips Respironics, Pennsylvania, USA). CPAP compliance was monitored/recorded throughout the study at regular intervals. It was considered satisfactory when used minimum 4 hours per night for at least 6 nights per week. Twenty three OSA patients completed this part of the study with a mean duration of CPAP therapy of 26 weeks prior to the second examination.



### *Echocardiography*

M-mode, 2D echocardiography (2DE), tissue Doppler imaging (TDI) and 3D echocardiography (3DE) were performed using Phillips iE33 ultrasound machine (Bothell, WA, USA) and analysed by off-line QLAB software (Xcelera, Phillips Ultrasound Quantification Module, USA). All parameters were measured in triplicate and averaged. Measurements of arterial-vascular interaction were made as reported and validated previously.[20-22] Effective arterial elastance index (EaI) was calculated as an effective arterial elastance (Ea, based on 3DE stroke volume and systolic BP) adjusted by body area. End-systolic elastance (Ees) was calculated using systolic and diastolic BP, stroke volume, pre-ejection and total systolic times. End-dystolic elastance (Eed) was established from the ratio of mitral inflow early diastolic filling velocity and the mitral annular early diastolic TDI velocity (E') divided by volume filling during diastole. In the absence of significant aortic regurgitation, stroke volume can be used as an indicator of ventricular filling volume. The Ea/Ees ratio was used as a measure of arterial-ventricular interaction. The inter- and intra-observer variability for echocardiography parameters was 11% and 6.8%, respectively.

### *Power calculation*

On the basis on our previous work on parameters of elastance, we calculated that a sample size of at least 15 patients in each group would have an 80% power to detect a significant difference  $\geq 0.5$  standard deviation in effective arterial elastance.[22]

### *Statistical methods*

Data are presented as mean [standard deviations, SD] for normally distributed data; or median [inter-quartile range, IQR] for non-normally distributed data. Comparisons between

OSA and HHT groups were performed by unpaired T-test (for normally distributed variables) or Mann-Whitney test (for non-normally distributed variables). Paired T-test (for normally distributed variables) or Mann-Whitney test (for non-normally distributed variables) was used to assess effect of CPAP therapy on OSA patients. Correlation analysis was performed using Pearson method for normally-distributed data and Spearman method for non-normally distributed variables. A two-tailed p-value of  $<0.05$  was considered statistically significant. SPSS 17 (SPSS, Inc, Chicago, Illinois, USA) software was used to perform the analysis.

## Results

Groups of patients with OSA and HHT were well matched for age, sex, body mass index, cardiovascular risk factors and LV ejection fraction (Table 1). Patients in the OSA group were free of pharmaceutical therapy at the time of the study. In the hypertension group 15 (54%) patients received an angiotensin enzyme inhibitors or angiotensin receptor antagonist, 8 (29%) a calcium channel blocker, 9 (32%) a diuretic, 5 (18%) a  $\alpha$ 1-blocker, 3 (11%) a beta-blocker, 1 (4%) hydralazine, 4 (14%) a statin and 1 (4%) aspirin. Twenty three OSA patients completed follow up of at least 23 weeks of CPAP therapy (mean follow-up of 26 weeks).

### *Vascular-ventricular interactions*

There were no significant differences in arterial elastance index (EaI,  $p=0.94$ ), end-systolic elastance (Ees,  $p=0.50$ ), end-diastolic elastance (Eed,  $p=0.63$ ) and arterial-ventricular interaction (Ea/Ees,  $p=0.62$ ) between OSA and HHT groups (Table 1). In the OSA group, Eed was positively correlated with age ( $r=0.40$ ,  $p=0.037$ ) and Ees was positively correlated with heart rate ( $r=0.42$ ;  $p=0.026$ ).

### *Effect of CPAP therapy in obstructive sleep apnoea patients*

Systolic blood pressure was significantly reduced after CPAP therapy ( $p<0.001$ ), and there was a significant improvement in LVEF on 2DE ( $p=0.02$ ) (Table 2).

CPAP therapy resulted in significant reduction in arterial elastance index (EaI,  $p=0.013$ ), and arterial-ventricular interaction (Ees/Ea,  $p=0.004$ ) (Figure 1). End-systolic elastance (Ees,  $p=0.17$ ), end-diastolic elastance (Eed,  $p=0.66$ ) parameters did not change significantly.

## Discussion

In this study, we show *for the first time* that arterial elastance and arterial-ventricular interactions in patients with OSA are significantly improved by CPAP therapy. We found that OSA patients and HHT patients had similar parameters of elastance and ventricular-arterial coupling. The non-invasive nature of our approach makes it applicable for clinical use and particularly for monitoring of treatment effects, for example, with CPAP therapy. Indeed, parameters of elastance used in the study provide an advance in the assessment of the cardiovascular elastic properties and the echocardiographic method has been validated by direct comparisons with invasive analysis of pressure-volume curves.[20, 21]

Of interest, the study has not found any difference in parameters of elastance and vascular-cardiac interactions between normotensive subjects with OSA and patients with HHT. This indicates presence of abnormal ventricular-arterial coupling in OSA irrespectively of hypertensive status that is common in this condition.

Arterial elastance characterises the artery's capacity to expand and contract in synchrony with cardiac cycle. Cardiac elastance reflects increased myocardial mass, a shift in the myocardial content characterised by reduced myocyte number and enhanced collagen deposition and cross-linking.[23] Impaired cardiac elastance is likely to contribute to cardiac overload and diastolic dysfunction common in OSA, whilst high Ees may result in increased myocardial oxygen consumption, and disturb myocardial perfusion reserve.[24] Appropriate coupling of heart to artery (e.g., estimated by the  $E_a/E_{es}$  ratio) is essential for effective transfer of blood from heart to the peripheral circulation without excessive changes in blood pressure and it is a significant factor of overall cardiovascular performance..[25, 26] Accordingly, our study

observations of equally abnormal ventricular-arterial interactions in OSA and HHT can represent another factor mediating the high risk of cardiovascular events in OSA.

The exact mechanisms by which CPAP improves cardiac and vascular elastance are not entirely clear at present. These are likely to be mediated by a reduction in blood pressure and intrathoracic pressure, and vascular tone, and amelioration of hypoxia and related beneficial effects on LV remodelling.[27] During episodes of obstructive apnoeas the patients experience negative intrathoracic pressure against an occluded upper airway, which leads to elevation of LV transmural pressure and LV afterload.[28] Cyclic increases in the BP at the end of apnea further contribute to raise in LV afterload.[28] These disturbances in cardiac haemodynamics could be diminished by regular CPAP usage. Also, improvement in sub-endocardial perfusion and enhanced oxyhaemoglobin concentrations could play a role.[29] Our study results are also consistent with previous reports on improvement in vascular function in patients with OSA by treatment with CPAP and the effects might have also been mediated by improvements in endothelial function, as previously demonstrated.[30, 31]

### *Limitations*

The study groups are relatively small and larger studies are essential to established outcome-related impact on the observed changes in elastance after CPAP therapy. Also, the study does not provide a complete mechanistic explanation of the findings, which would also need to be done in appropriately designed studies.

### *Conclusions*

OSA patients and HHT patients have similar parameters of elastance and ventricular-arterial coupling. CPAP treatment in OSA patients significantly improved arterial elastance and

ventricular-arterial coupling, which may contribute to the clinical effectiveness of this treatment.

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**Conflict of interest:**

Professor Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

Other authors – none declared, as relevant to this manuscript.

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**Figure 1.** Effect of continuous positive airway pressure (CPAP) therapy on parameters of elastance.

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**Table 1. Demographic and clinical characteristic of the study groups**

	OSA (n=28)	HHT (n=28)	p value
Age, years	51 [11]	48 [12]	0.39
Male, n [%]	22 [79]	17 [61]	0.15
Systolic BP, mm Hg	138 [16]	148 [22.8]	0.06
Diastolic BP, mm Hg	82 [12]	84 [10]	0.43
Heart rate, bpm	72 [12]	68 [14]	0.26
Body mass index, kg/m <sup>2</sup>	31 [4]	30 [6]	0.83
Total cholesterol, mmol/l	5.0 [1.1]	5.2 [1.0]	0.40
Smoking, n [%]	11 [39]	12 [43]	0.79
Ejection fraction (2D), %	66 [10]	68 [9]	0.45
Arterial elastance index (EaI), mm Hg/ml/m <sup>2</sup>	1.3 [0.5]	1.3 [0.5]	0.94
End-systolic elastance (Ees), mm Hg/ml	3.5 [1.4]	3.2 [1.2]	0.50
End-diastolic elastance (Eed), mm Hg/ml	0.10 [0.06-0.14]	0.11 [0.08-0.13]	0.63
Ea/Ees	0.81 [0.19]	0.83 [0.19]	0.62

Values expressed as mean [SD] or median [IQR]. HHT, High risk hypertension; OSA, obstructive sleep apnoea

**Table 2. Effect of continuous positive airway pressure therapy in obstructive sleep apnoea**

	Baseline	After	p value
Systolic BP, mm Hg	140 [16]	130 [10]	<0.001
Diastolic BP, mm Hg	82 [13]	79 [7]	0.18
Ejection fraction (2D), %	65 [10]	69 [7]	0.02
Arterial elastance index (EaI), mm Hg/ml/m <sup>2</sup>	1.3 [0.5]	1.07 [0.4]	0.013
End-systolic elastance (Ees), mm Hg/ml	3.4 [1.5]	3.1 [1.3]	0.17
End-diastolic elastance (Eed), mm Hg/ml	0.10 [0.06-0.15]	0.10 [0.07-0.14]	0.66
Ea/Ees	0.82 [0.19]	0.73 [0.13]	0.004

Values expressed as mean [SD] or median [IQR]

