ORIGINAL ARTICLE

Arterial stiffness in moderate-severe obstructive sleep apnea

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Abstract: Objectives – Obstructive sleep apnea (OSA) has been linked to arterial stiffness and increased cardiovascular risk. The aim of this study was to analyse the relationship between OSA severity, arterial stiffness and clinico-biological parameters in moderate-severe OSA subjects. **Methods –** We assessed arterial stiffness using the Arteriograph (Tensiomed, Hungary) in 41 patients with newly diagnosed moderate-severe OSA prior to the initiation of positive pressure therapy. **Results –** Our study included 18 and 23 patients with moderate and severe OSA, respectively. Mean apnea hypopnea index (AHI) 40.69 events/h. Desaturation index, minimum nocturnal O2 saturation, erythrocyte sedimentation rate (ESR), ejection duration and return time were significantly different between the two subgroups. AHI was correlated with the other OSA severity parameters but also with pulse wave velocity (PWV), C reactive protein and ESR. PWV was negatively correlated with magnesium. Mean nocturnal oxygen saturation, age, body mass index and abdominal circumference did not significantly differ between the moderate and severe OSA subgroups. **Conclusions –** PWV and inflammation markers are correlated with OSA severity. We also found a negative correlation between serum magnesium and PWV in moderate-severe OSA patients.
Keywords: arterial stiffness, obstructive sleep apnea, subclinical inflammation.

Rezumat: Obiective – Apneea obstructivă în somn (AOS) se asociază rigidității arteriale și unui risc cardiovascular crescut. Scopul studiului a fost analiza relației dintre severitatea apneei, rigiditatea arterială și parametri clinico-biochimici la un lot de pacienți cu AOS moderat-severă. **Metode –** Am analizat rigiditatea arterială (cu ajutorul dispozitivului Arteriograph, Tensiomed, Ungaria) la 41 de pacienți cu AOS moderat-severă înainte de inițierea ventilației non-invazive. **Rezultate –** Am inclus 18 pacienți cu AOS moderată și 23 de pacienți cu AOS severă. Indicele apnee-hipopnee mediu (AHI) a fost 40,69. Am înregistrat diferențe semnificative între cele 2 subgrupe de severitate în ceea ce privește indicele de desaturări, saturația minimă nocturnă în oxigen, viteza de sedimentare a hematiilor (VSH), durata ejecției și reflexia undei de puls. AHI s-a corelat cu ceilalți parametri de severitate ai apneei, dar și cu viteza de propagare a undei de puls (PWV), proteina C reactivă și VSH. Am descoperit o corelație negativă între PWV și nivelul seric de magneziu. Nu am înregistrat diferențe semnificative între subloturi în ceea ce privește saturația medie nocturnă în oxigen, vârsta, indicele de masă corporală și circumferința abdominală. **Concluzii –** PWV, markerii inflamației și magneziul seric s-au corelat cu severitatea AOS.
Cuvinte cheie: rigiditate arterială, sindromul de apnee obstructivă în somn, inflamație subclinică.

INTRODUCTION

Intermittent upper airway collapse leads to obstructive sleep apnea (OSA) and thus to recurrent oxygen desaturations, micro awakenings, oxidative stress and overactivation of the RAAS (renin angiotensin aldosterone) and sympathetic systems[1,2]. Through its frequent association with hypertension and obesity, vascular remodelling (endothelial dysfunction, increased arterial stiffness with elevated aortic pulse wave velocity and augmentation index) is common among OSA patients[2]. The pulse wave is formed by the summation of both the forward traveling and the reflected waves. While the forward pulse wave is produced by the left ventricular systole, the returning wave is its reflection

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by the aortic bifurcation and the peripheral arteries[3]. Aging promotes the replacement of the elastin fibres from the medial layer of arteries with fibrous tissue, leading to arterial stiffness. This leads to the premature fusion of the two pulse waves, and thus to an increased amplitude of the systolic pulse wave, in the detriment of the diastolic wave amplitude[4]. The modified pulse wave pattern is thus associated with isolated systolic hypertension (HBP) (the most common form of HBP among the elderly) and a reduced BP value during diastole. Reduced diastolic perfusion of the coronary arteries along with the growing oxygen necessities of the hypertrophied heart muscle favours myocardial ischemia[4]. Diabetes, obesity, smoking, hypertension, inflammation (high C reactive protein levels), moderate chronic kidney disease, menopausal status and a sedentary lifestyle are also associated with increased arterial stiffness[5], which is also associated with a higher stroke risk, due to elevated central PP (pulse pressure) and subsequent arterial remodelling[4,5].

Pulse wave velocity (PWV) reflects the speed at which the pressure waves travel along the arteries, reflecting their elasticity, distensibility and compliance6. Carotid-femoral PWV is considered the gold standard method for non-invasive arterial stiffness assessment[3,5]. The Arteriograph (Tensiomed, Budapest, Hungary) is an oscillometric method which records the early and the late systolic peaks (the wave reflected from the aortic bifurcation) using a blood pressure cuff placed in the upper arm region. The algorithm has been validated for the assessment of AoPWV (aortic pulse wave velocity), aortic and brachial Aix (augmentation indexes), return time (RT) and central SBP (which correlates well with the central SBP measured through invasive methods)[3,7].

Ao PWV is correlated with serum cholesterol and with mean carotid IMT (intima-media thickness) ($p<0.001$). PWV is a marker of arterial rigidity in the analysed segment, while Aix is a composite vascular function parameter, providing information regarding the wave reflection site and velocity, endothelial function but also a measure of the peripheral resistance against which the heart has to pump. Early atherosclerosis can be recognized by Aix values greater than 33%. PWV becomes elevated in more advanced stages of atherosclerosis, after the vessels have become narrower and thus stiffer[3]. Although the previous cut-off point for arterial stiffness was set to 12 ms-1, current guidelines consider a threshold of 10 ms-1 in the risk stratification of hypertensive patients, stating that aortic stiffness is independent risk factor for cardiovascular events in these patients[8,9]. RT measures the period of time in which the pulse wave travels from the aortic root to the aortic bifurcation and then returns to the initial emergence point. Smaller RT values (<124ms) are associated with aortic stiffness[5,10].

The Arteriograph report includes a series of other parameters, such as mean arterial pressure (MAP), pulse pressure (PP), ejection duration (ED), diastolic reflection area (DRA), systolic and diastolic area index (SAI and DAI). A PP value greater than 60 mmHg (representing the difference between the systolic and diastolic BP values) is associated with increased cardiovascular risk. SAI and DAI represent the areas from beneath the pulse wave curve that correspond to the systole and diastole, respectively. Thus, higher DRA (>40) and DAI (>50%) values are associated with superior coronary perfusion. SAI should not exceed 50% in healthy individuals[10]. Heart failure is associated with a reduced ejection duration (ED), measuring the time between the opening of closure of the aortic sigmoid valves[5,10]. While aortic PWV reflects only arterial stiffness, the other 3 markers are influenced by the reflectance point, the amplitude of the reflected pulse wave, ventricular systolic function and heart rate. It seems that aging has a greater influence on Aix in subjects younger than 50, and a more important impact on aortic PWV in patients older than 50 years old[5].

Several drugs (beta-blockers, renin-angiotensin-aldosterone system inhibitors, aldosterone antagonists), as well as non-pharmacological measures (exercise training, weight loss, moderate alcohol consumption) are able to reduce arterial stiffness[5]. Renin-angiotensin-aldosterone system (RAAS) inhibitors have proven effective in reducing PWV, independent from their BP reduction effect. However, further studies are required in order to assess their superiority in reducing arterial stiffness, compared to other antihypertensive agents[8].

METHODS

Our research included 41 patients with newly diagnosed moderate-severe OSA, referred to our Cardiovascular Rehabilitation Clinic prior to the initiation of CPAP (continuous positive airway pressure) therapy. The obstructive sleep apnea syndrome diagnosis was made by ambulatory or in-hospital six-channel cardiorespiratory polygraphy, using either a Porti 7 device (from DeVilbiss) or an Alice Night One (from Philips Respironics). The cardiorespiratory polygraphy

was manually scored by a trained doctor, according to the American Academy of Sleep Medicine (AASM) standards. The CPAP effective pressure was autotitrated in the sleep lab using either a DreamStation Auto CPAP (from Philips Respironics) or an Airsense 10 Autoset (from Resmed).

We performed clinical examination – resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), along with anthropometric evaluation - weight, height, body mass index (BMI) and abdominal circumference (AC). Our subjects underwent arterial stiffness examination using the Tensiomed Arteriograph (Tensiomed, Budapest, Hungary)[3]. Statistical analysis was performed in Microsoft Excel and Statistical Package for the Social Sciences (SPSS) 20.0. Chi square and student's *t* test were used for comparisons between groups. A potential relationship between variables was evaluated using Pearson correlation coefficient. A *p* value <0.05 was considered statistically significant.

RESULTS

Our study group included 18 and 23 patients with moderate and severe OSA, respectively (Table 1). The only significant differences between the moderate and severe OSA groups were regarding desaturation index, minimum nocturnal O_2 saturation, CPAP pressure requirements, ejection duration and erythrocyte sedimentation rate (ESR) (Tables 1-3).

Both ED and RT were significantly lower in the severe OSA group, with an average value for RT below the known 124ms cut-off point for arterial stiffness (Table 2). Although PWV, Aortic SBP and PP were higher in the severe OSA group, the differences did not reach statistical significance.

AHI was significantly correlated with other OSA severity parameters, including CPAP pressure requirements (Table 4). AHI was positively correlated with aortic PWV and inflammation markers (ESR, CRP) but negatively correlated with ED and RT (the latter with borderline statistical significance p=0.05) (Table 4). We found a negative correlation between apnea severity and Aortic Aix (r=-0.31, p=0.04). PWV was significantly correlated with both AHI and desaturation index, but not with average or minimum nocturnal O_2 saturation. No significant correlation was found between BMI, age, ESR, CRP, lipid profile, renal function, glycemic control and PWV. PWV was negatively correlated with serum magnesium in moderate-severe OSA patients (Table 4). Aortic Aix was correlated with resting HR, BP values but also with uric acid, CRP and age.

Table 1. Characterization of our study group, with stratification according to OSA severity

	Moderate OSA	Severe OSA	P value
Number of patients	18	23	
AHI	23.15	54.42	
HBP	88.88%	100%	
Diabetes	38.88%	34.78%	
Impaired fasting glucose	22.22%	21.73%	
Hipercholesterolemia	55.55%	73.91%	
Mixt dyslipidemia	16.66%	8.69%	
Hypertriglyceridemia	5.55%	8.69%	
Active smokers	0%	21.71%	
Past smokers	77.77%	52.17	
Average pack years (among smokers)	20.76	27.07	0.7 (ns)
Desaturation index (nr/h)	23.57	49.93	0.000
Mean nocturnal O_2 saturation (%)	92.,49	90.63	0.12 (ns)
Minimum nocturnal O_2 saturation (%)	79.88	69.86	0.001
CPAP pressure setting (cmH_20)	10.31	12.67	0.002
Age (years)	55.83	57.34	0.5 (ns)
BMI (kg/m^2)	34.65	35.71	0.5 (ns)
AC (cm)	116.15	117.56	0.7 (ns)
Resting HR (bpm)	69.05	73.86	0.1 (ns)
SBP (mmHg)	135.72	136.21	0.9 (ns)
DBP (mmHg)	85.61	84.34	0.6 (ns)
Arm circumference (cm)	33.27	33.6	0.7 (ns)

OSA – obstructive sleep apnea; AHI – apnea hypopnea index; O_2 – oxygen; CPAP – continuous positive airway pressure; BMI – body mass index; AC – abdominal circumference; HBP – high blood pressure; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure. ns – nonsignificant.

Table 2. Arterial stiffness parameters, according to OSA severity

	Moderate OSA	Severe OSA	P value
Ao SBP (mmHg)	117.7	121.91	0.3 (ns)
Ao PP (mmHg)	42.2	44.87	0.4 (ns)
Brachial Aix (%)	-26.14	-30.33	0.5 (ns)
Aortic Aix (%)	24.41	22.29	0.5 (ns)
ED (ms)	317.22	298.04	0.04
DRA	56.11	48.95	0.2 (ns)
SAI (%)	45.92	45.63	0.8 (ns)
DAI (%)	54.07	54.36	0.8 (ns)
PWV (m/s)	8.55	9.23	0.1 (ns)
RT (ms)	127.77	117.47	0,06
PWV ≥10 m/s	4 (22.22%)	8 (34.78%)	

OSA – obstructive sleep apnea; Ao SBP – aortic systolic blood pressure; Ao PP – aortic pulse pressure; Aix – augmentation index; ED – ejection duration; DRA – diastolic reflection area; SAI – systolic area index; DAI – diastolic area index; PWV – pulse wave velocity; RT – return time; ns – nonsignificant.

Table 3. Biological profile of OSA patients

	Moderate OSA	Severe OSA	P value
Hb (g/dl)	14.08	13.81	0.5 (ns)
ESR (mm/h)	10.61	22.06	0.012
Fasting glucose (mg/dL)	113.39	115.71	0.8 (ns)
Uric acid (mg/dL)	4.92	5.09	0.6 (ns)
TC (mg/dL)	170.56	185.80	0.1 (ns)
HDL (mg/dL)	49.22	52.28	0.4 (ns)
LDL (mg/dL)	89.95	99.23	0.3 (ns)
TG (mg/dL)	158.42	161.37	0.9 (ns)
Magnesium (mg/dL)	2.09	1.9	0.1 (ns)
Creatinine (mg/dL)	0.98	1.08	0.3 (ns)
EGFR (ml/min/1,73 m^2)	80.82	74.97	0.8 (ns)
CRP (mg/dL)	0.72	1.17	0.1 (ns)
HbA1c (%)	6.72	6.5	0.7 (ns)

OSA – obstructive sleep apnea; Hb – hemoglobin; ESR – erythrocyte sedimentation rate; TC – total cholesterol; HDL – high density lipoproteins; LDL – low density lipoproteins; TG – triglycerides; EGFR – estimated glomerular filtration rate; CRP – C reactive protein; HbA1c – glycated haemoglobin; ns – nonsignificant.

DISCUSSION

RT was significantly lower in the severe OSA group, reaching an average value below the 124ms cut-off point for arterial stiffness (Table 2). We also found a significant difference regarding ED between the moderate and severe OSA groups, but not regarding PWV, Aortic SBP and PP (although average PWV was higher in the severe OSA group). A recent report did not find a correlation between PWV and OSA severity parameters (AHI, desaturation index, minimal nocturnal O2 saturation) in 101 elderly patients with OSA and a mean age of 75.3 years[11]. However, we should note that the subjects presented a milder form of OSA (mean AHI 17.8 events/h) and that obesity was less prevalent among the study group (mean BMI 25.7 kg/m^2). The authors did report that patients with AHI greater than 30 (severe OSA) presented higher PWV despite having a similar BMI[11]. Although we did not find a statistically significant correlation between average or minimum nocturnal O_2 saturation and AHI, previous reports showed that intermittent nocturnal desaturations induce sympathetic nervous system hyperactivation, promote inflammation and endothelial dysfunction, thus playing a pivotal role in OSA-related cardiovascular consequences[12]. The magnitude of nocturnal hypoxemia in Sforza's study was low, thus explaining the lack of association between PWV and OSA severity[11].

Another study found a mild but statistically significant correlation between AHI and PWV (r=0.350, p=0.000) in OSA patients who developed an ischemic stroke[13]. A stronger correlation between the 2 parameters was reported by Cortuk et al (r=0.521, p<0.001) in 90 patients with OSA[14]. We also found a mild but statistically significant correlation between PWV and AHI (r=0.315, p=0.004) and a similar correlation between PWV and desaturation index (r=0.351 and p=0.047). A recently published meta-analysis

Table 4. Statistically significant correlations in our OSA group

		r	P value
AHI and	Desaturation index	0.906	0.000
	Mean nocturnal O_2 saturation	-0.515	0.001
	Minimum nocturnal O_2 saturation	-0.628	0.000
	CPAP pressure requirement	0.398	0.016
	Brachial Aix	-0.311	0.04
	Aortic Aix	-0.31	0.04
	ED	-0.471	0.002
	PWV	0.315	0.04
	RT	-0.306	0.05
	ESR	0.371	0.017
	CRP	0.353	0.02
Aortic Aix and	Resting HR	-0.426	0.006
	SBP	0.324	0.039
	DBP	0.359	0.021
	Uric acid	-0.373	0.016
	CRP	-0.32	0.04
	Age	0.385	0.013
PWV and	AHI	0.315	0.004
	Desaturation index	0.351	0.025
	Magnesium	-0.315	0.047

OSA – obstructive sleep apnea; Ao SBP – aortic systolic blood pressure; Ao PP – aortic pulse pressure; Aix – augmentation index; ED – ejection duration; DRA – diastolic reflection area; SAI – systolic area index; DAI – diastolic area index; PWV – pulse wave velocity; RT – return time.

found that PWV in OSA patients is not significantly correlated with OSA severity parameters and is instead influenced by age, BMI and SBP[15]. However, our results show quite the opposite – we found that PWV is significantly correlated with both AHI and desaturation index, but not with age, BMI or BP values.

Although other authors have cited a correlation between hypomagnesemia and arterial stiffness[16,17], to our knowledge, this is the first study to report a negative correlation between PWV and serum magnesium in moderate-severe OSA patients. Further studies are required in order to assess a potential influence of magnesium supplementation on overall cardiovascular risk in OSA.

We found that aortic Aix is significantly correlated with SBP, DBP and age (r=0.324, p=0.039; r=0.359, p=0.021 and r=0.385, p=0.013, respectively). A previous report showed that augmentation index is significantly higher in morbidly obese OSA patients than in controls with similar BMI (24.5% versus 10.5%, p<0.001)[2]. Although we obtained a similar aortic Aix value (24.41%), we found a paradoxical negative association between AHI and aortic Aix (r=-0.31, p=0.04) and between Aortic Aix and resting HR (r=-0.426, p=0.006). Given fact that AHI was positively correlated with PWV could suggest that PWV is a more reliable arterial stiffness parameter in moderate-severe OSA patients, that probably have a more advanced stage of subclinical atherosclerosis. This paradoxical association could also be explained by a more important influence of the applied treatment regimen applied to those with more severe OSA, due to associated comorbidities. The fact that CPAP therapy seems to improve aortic stiffness parameters in OSA patients is an indirect argument that sleep apnea induces arterial stiffness[1,2].

ESR was significantly higher in the severe OSA group and we found a positive correlation between OSA severity and ESR, CRP (r=0.371, p=0.0017 and r=0.353 p=0.02, respectively). This is in line with current evidence that supports an association between OSA and subclinical inflammation[18]. However, our analysed inflammation markers were not significantly correlated with PWV, although current literature reports have linked subclinical inflammation with both OSA and arterial stiffness[18].

Our study's limitations include the small number of patients but also the use of brachial artery stiffness parameters, known to be inferior to carotid-femoral PWV according to the Framingham study[9]. Our results are also influenced by the fact that although all patients were under antihypertensive drugs, not all of them were using RAAS blockers, which could be the most effective agent in reducing arterial stiffness and PWV[8]. Further studies on CPAP naïve OSA patients who do not follow any therapeutic regimen should be

performed in order to accurately assess the impact on arterial stiffness of OSA alone.

CONCLUSIONS

Mean nocturnal O_2 saturation, age, BMI and AC did not significantly differ between the moderate and severe OSA subgroups. Multiple arterial stiffness parameters (PWV, ED, RT), but also inflammation markers (ESR and CRP) are correlated with OSA severity. PWV could be a more appropriate arterial stiffness evaluation parameter in OSA patients. Further studies are required in order to determine whether arterial stiffness is correlated with a poorer prognosis in OSA patients and the role of pharmacological and non-pharmacological interventions in reducing arterial stiffness in OSA. We found a negative correlation between serum magnesium and PWV in moderate-severe OSA patients which should be confirmed by larger studies.

Conflict of interest: none declared.

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