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REVIEW

Increased arterial stiffness in obstructive sleep apnea: a systematic review

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Obstructive sleep apnea is a prevalent disease that is associated with significant morbidity and mortality, particularly due to cardiovascular disease. An emerging cardiovascular risk factor, arterial stiffness, may also be involved in the cardiovascular complications of obstructive sleep apnea. The purpose of this review was to summarize the current literature regarding the effect of obstructive sleep apnea on arterial stiffness. We conducted a systematic literature review using PubMed, Embase and the Cochrane Library. We identified 24 studies that met search criteria investigating the effect of obstructive sleep apnea on arterial stiffness. Arterial stiffness was found to be increased in obstructive sleep apnea patients compared with controls or increased in severe compared with mild sleep apnea. In some studies, a positive correlation was identified between the degree of arterial stiffness and sleep apnea severity. In the two randomized, controlled trials and the two nonrandomized trials identified, treatment of obstructive sleep apnea with continuous positive airway pressure led to significant decreases in arterial stiffness. Obstructive sleep apnea appears to have an independent effect on arterial stiffness, which may be one of the mechanisms accounting for sleep apnea-associated cardiovascular risk.
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Keywords: arterial stiffness; obstructive sleep apnea; pulse wave velocity; sleep disordered breathing

BACKGROUND

Obstructive sleep apnea (OSA) is a prevalent disease with roughly 1 of every 5 adults having at least mild OSA (defined by apnea–hypopnea index (AHI) $\geqslant 5$) and 1 of every 15 having at least moderate OSA (AHI $\geqslant 15$).[1] The high prevalence rates are disturbing considering that OSA patients have an increased risk of morbidity and mortality, particularly due to cardiovascular disease.[2–7] OSA patients are often excessively sleepy during the daytime causing traffic crashes and work injuries, and they commonly have an increased number and severity of cardiovascular risk factors, such as hypertension, obesity, atherosclerosis, insulin resistance, the presence of increased inflammatory markers and endothelial dysfunction.[8] Although OSA patients commonly demonstrate one or more established cardiovascular risk factors, there is now a considerable body of evidence indicating that OSA itself is an independent cardiovascular risk factor.[3,9–16]

Arterial stiffness determines how quickly the pulse wave generated by the contracting heart travels to the periphery and is reflected back. The larger arteries of the cardiovascular system are critical in the conduction of blood flow to the periphery. The elastic properties of these vessels, which are dependent on the stiffness of the arterial walls, allow for the smoothing of oscillations in blood pressure, reduction of the pulse pressure and perfusion of the myocardium.[17,18] Central pressure and arterial stiffness offer an accurate estimation of the load imposed on the coronary arteries, cerebral arteries and aorta, and, in turn, of overall vascular damage and prognosis.[19–24]

Arterial stiffness can be measured noninvasively by applanation tonometry, echotracking and Doppler ultrasound. These techniques have very good reproducibility and have been widely applied.[25] The most simple and reproducible noninvasive technique to date is the measurement of arterial waveforms (obtained by applanation tonometry), and more specifically pulse wave velocity (PWV), as recommended by the European Network for Non-invasive Investigation of Large Arteries[25] and the European Society of Hypertension European Society of Cardiology Guidelines for the Management of Arterial Hypertension.[26] PWV is inversely related to arterial distensibility[27] and expresses the speed of the pressure wave traveling through the arteries. The pulse travels at a higher velocity in a stiff artery, and *vice versa*. Carotid-femoral PWV (cfPWV) is considered the 'gold-standard' measurement of the stiffness of the aorta.[25,26] It has been used extensively and has the largest amount of epidemiological evidence to support its predictive value for cardiovascular events in the general and diseased populations.[25,28–32]

Measurements of arterial stiffness are believed to reflect global arterial endothelial function.[33] A strong correlation between arterial stiffness and the development of atherosclerosis at various sites in the arterial tree has been noted.[34–36] In fact, a recent study showed that

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arterial stiffness is an early marker of atherosclerosis, as it is affected to a greater extent when compared with intima-media thickness in patients with vascular disease.[37] This result is in line with another study, which showed that arterial stiffness is an independent predictor of vascular health and coronary artery disease above and beyond intima-media thickness.[38] Arterial stiffness increases chronically with age, with the development of chronic conditions (for example, hypertension), and with the presence of vascular risk factors (for example, smoking).[39–41]

These observations have prompted researchers investigating OSA–cardiovascular interactions to study the role of OSA in increasing arterial stiffness. The purpose of this systematic review was to collect evidence from the available literature regarding the effect of OSA on arterial stiffness to determine if arterial stiffness is increased in OSA patients.

METHODS

Data sources and study selection

Studies were identified through PubMed, Embase and the Cochrane Library using the keywords shown in Figure 1. Relevant articles were extracted using the search terms, reference lists and the 'related articles' links of articles selected for review. Included studies satisfied the following criteria: (1) controlled clinical observational studies and/or randomized controlled trials, and (2) the participants were OSA patients in which arterial stiffness was measured using a validated technique.

The search for articles was limited to those published between 1985 and November 2009, and written in English without any other limitations. Three independent researchers (RJD, PS and ML) conducted the search. All the authors participated in the final selection of the included studies.

RESULTS

Arterial stiffness in OSA *vs.* control groups: observational studies and baseline measurements from interventional studies

A total of 24 relevant studies were identified, confirmed by all authors and included in this review. Figure 1 illustrates the search and study selection procedure. Tables 1–3 summarize the basic study and patient characteristics and the main findings of the included studies.

Several studies evaluated central arterial stiffness by measuring cfPWV. Tsioufis *et al.*[42] found a higher cfPWV in OSA patients compared with controls. Drager *et al.*[43] noted that although cfPWV was higher in OSA patients than in controls, it was even higher in OSA patients with hypertension. Another study by the same group compared the cfPWV of non-OSA controls with a mild to moderate OSA group, and a severe OSA group. Although they did not find the mild to moderate group to significantly differ from either the controls or the severe OSA group, they did note a significant difference between severe and non-OSA participants. A further study by Drager *et al.*[44] examined the effect of the presence of OSA in patients with metabolic syndrome on arterial stiffness. They found cfPWV to be significantly higher in the presence as compared to the absence of OSA in these patients. Moreover, there was a significant positive correlation between cfPWV and AHI.[45] A subsequent study by the same group examined arterial stiffness in OSA patients with and without masked hypertension.[46] It was found that, whereas both types of OSA patients showed significantly higher arterial stiffness as compared to healthy controls, OSA patients with masked hypertension had the highest arterial stiffness. Chung *et al.*[47] compared cfPWV in patients with mild to moderate OSA, severe OSA and control subjects. They found cfPWV to be significantly higher in patients with severe OSA as compared to both mild to moderate OSA and normal controls. Protogerou *et al.*[48] determined cfPWV, augmentation index (AIx) and central blood pressure in mild, moderate and severe OSA patients. They found that these arterial stiffness parameters did not increase with the severity of OSA after adjustment for age, gender, body mass index, heart rate, mean blood pressure, smoking and diabetes mellitus. However, respiratory disturbance index (RDI) was found to be an independent predictor of cfPWV.

Shiina *et al.*[49] measured brachial-ankle PWV (baPWV) in OSA patients and found that they had a higher baPWV compared with

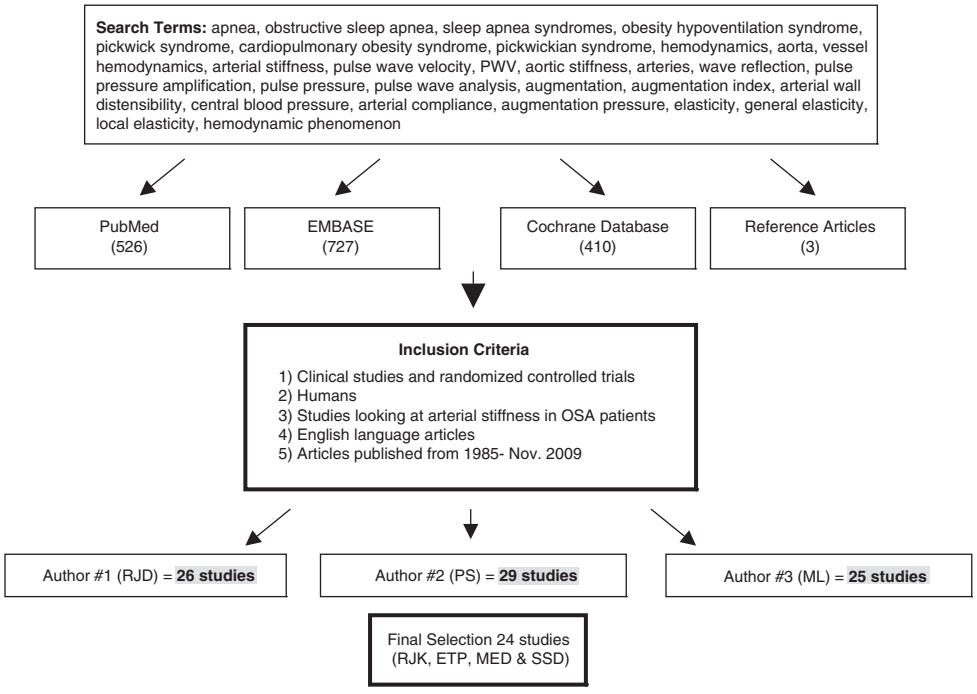

Figure 1 Search procedure.

Table 1 Subject characteristics of included studies

Study	*Subjects*	n	*Gender (female/male)*	*AHI/RDI*	*Age*	*BMI*	*Time measured*
Chung *et al.*[47]	Controls	29	0/29	3.2 ± 1.6	43.9 ± 6.2	27.2 ± 2.9	Morning
	Moderate OSA	39	0/39	17.1 ± 6.9	44.5 ± 9.1	26.7 ± 2.7	
	Severe OSA	44	0/44	56.8 ± 20.0	43.6 ± 6.4	27.9 ± 3.4	
Drager *et al.*[45]	Controls	12	1/11	3.1 ± 0.3	42 ± 2	28.9 ± 0.7	Early afternoon
	Mild–moderate OSA	15	1/14	16.2 ± 1.7	43 ± 1	28.4 ± 0.6	
	Severe OSA	15	2/14	55.7 ± 5.9	44 ± 1	29.3 ± 0.8	
Drager *et al.*[43]	Controls	15	3/12	3 ± 0.4	44 ± 1	28.6 ± 0.8	NR
	OSA	15	2/12	53 ± 4	44 ± 1	29.2 ± 0.8	
	HT	15	3/12	3 ± 0.4	44 ± 1	29.8 ± 0.8	
	OSA + HT	15	3/13	54 ± 4	47 ± 1	29.4 ± 0.8	
Drager *et al.*[43]	OSA − CPAP	12	0/12	62 ± 22	47 ± 6	29.7 ± 2.9	1400–1600 hours
	OSA + CPAP	12	0/12	56 ± 22	44 ± 7	29.9 ± 3.0	
Drager *et al.*[47]	MS − OSA	30	13/17	4.4 ± 3.3	45 ± 7	31.6 ± 2.7	Early afternoon
	MS + OSA	51	12/39	51 ± 27	47 ± 7	31.9 ± 3.3	
Drager *et al.*[47]	Controls	18	18	2.6 ± 1.6	43 ± 6	28.2 ± 2.9	NR
	OSA − mHT	30	30	53 ± 19	43 ± 7	29.1 ± 3.2	
	OSA + mHT	13	13	52 ± 25	47 ± 7	28.9 ± 2.5	
Kasikcioglu *et al.*[56]	Controls	14	0/14	1.7 ± 1.1	51.8 ± 12.9	27.9 ± 2.5	Morning
	OSA	14	0/14	32.9 ± 7.1	49.7 ± 11.6	28.7 ± 2.9	
Kohler *et al.*[53]	Controls	14	2/13	2.9 ± 1.1	58.1 ± 6.9	31.7 ± 2.6	NR
	OSA	64	7/57	23.1 ± 15.6	57.9 ± 6.8	32.9 ± 6.25	
Kohler *et al.*[58]	Subtherapeutic CPAP	51	0/51	NR	48.7 ± 10.6	34.5 ± 5.0	NR
	Therapeutic CPAP	51	0/51	NR	48.1 ± 9.5	35.8 ± 7.3	
Keles *et al.*[60]	Controls	17	6/11	2.6 ± 0.8	41.1 ± 11.3	27.8 ± 2.7	NR
	OSA	24	4/20	60.7 ± 22.7	44.8 ± 10.8	29.9 ± 5.7	
Kitahara *et al.*[62]	OSA	17	1/16	38.5 ± 4.2	58.6 ± 2.0	25.4 ± 0.8	1000–1100 hours
Kumagai *et al.*[52]	Mild OSA	74	14/60	10.5 ± 3.0	52.9 ± 11.9	25.8 ± 4.3	NR
	Moderate–severe OSA	469	43/426	41.3 ± 18.7	53.7 ± 13.0	26.6 ± 4.0	
Nagahama *et al.*[50]	Controls	104	12/92	NR	53.3 ± 7.7	26.2 ± 2.3	NR
	OSA	104	12/92	41.7 ± 27.1	53.3 ± 9.5	26.1 ± 2.4	
	Controls (HT−)	90	NR	NR	52.8 ± 7.7	NR	
	OSA (HT−)	48	NR	NR	51.0 ± 9.4	NR	
Noda *et al.*[54]	Controls	71	0/71	NR	56.2 ± 7.6	23.3 ± 2.2	NR
	OSA	45	0/45	NR	56.0 ± 9.6	25.7 ± 4.6	
	Severe OSA	31	11/20	40.3 ± 5.8	55.2 ± 1.8	36.2 ± 1.7	
	Very severe OSA	23	12/11	69.7 ± 19.7	52.9 ± 2.1	41.9 ± 2.1	
Phillips *et al.*[61]	CPAP intervention	20	19/0	58.5 ± 30	20–65	33.5 ± 6	0900–1700 hours
	CPAP withdrawal	20	NR	46.0 ± 26	18–75	36.0 ± 6	Morning and evening
Protogerou *et al.*[48]	Moderate OSA	20	7/13	20.8 ± 5.1	58.5 ± 2.1	35.4 ± 2.1	Morning
Saito *et al.*[64]	OSA − HT	98	0/98	60.3 ± 26.0	42.9 ± 8.9	28.9 ± 4.4	NR
	OSA + HT	114	0/114	72.7 ± 24.0	46.8 ± 9.3	30.3 ± 5.5	
Shiina *et al.*[63]	OSA (AHI >20)	50	5/45	53.6 ± 22.1	54 ± 10	27.4 ± 3.4	Morning
Shiina *et al.*[49]	OSA−/MS−	75	31/44	4.2 ± 0.4	47 ± 2	24.9 ± 0.5	NR
	OSA−/MS+	15	4/11		49 ± 4	29.8 ± 0.8	
	OSA+/MS−	53	4/49	47.2 ± 2.0	52 ± 2	26.1 ± 0.5	
	OSA+/MS+	41	2/39		51 ± 2	30.8 ± 0.7	
Tanriverdi *et al.*[55]	Controls	24	5/19	3 ± 1.5	51.9 ± 5.2	29.4 ± 3.9	Morning
	OSA	40	8/32	25.3 ± 11.4	51.3 ± 9	29.8 ± 5.3	
Tanriverdi *et al.*[55]	Controls	24	5/19	3 ± 1.5	51.9 ± 5.2	29.4 ± 3.9	Morning
	OSA	40	8/32	25.3 ± 11.4	51.3 ± 9	29.8 ± 5.3	
Tavil *et al.*[57]	Controls	29	8/21	2.5 ± 0.8	49 ± 11	29 ± 5	NR
	OSA	29	10/19	25 ± 16	48 ± 10	29 ± 6	
	HT	28	11/17	2.2 ± 1.1	56 ± 8	26 ± 2	
	OSA + HT	19	7/12	37 ± 26	54 ± 9	31 ± 7	
Tomiyama *et al.*[51]	Controls	14	2/12	2.1 ± 1.2	44 ± 10	23.6 ± 2.8	NR
	Mild OSA	65	6/59	19.7 ± 6.1	46 ± 11	25.0 ± 3.1	
	Moderate–severe OSA	85	7/78	51.2 ± 18.1	49 ± 11	27.0 ± 3.7	
Tsioufis *et al.*[42]	Controls	53	13/40	2.4 (1–5)	49 ± 5	29.3 ± 4	NR
	OSA	46	11/35	40.24 (5–96)	49 ± 8	31.4 ± 4	

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure treatment; HT, hypertension; mHT, masked hypertension; MS, metabolic syndrome; NR, not reported; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

Table 2 Arterial stiffness in OSA compared with control groups (cross-sectional studies)

Study	*Inclusion criteria*	*Comparison*	*Outcome*	P-*value*
Chung *et al*.[47]	Male patients with untreated, newly diagnosed OSA, free from medication and inflammatory, pulmonary and CVD	Mild–moderate OSA (AHI > 5, AHI < 30), severe OSA (AHI > 30), and normal controls	*cfPWV (m/s)* Controls: 8.8 ± 1.2 Moderate: 9.0 ± 1.4 Severe OSA: 9.8 ± 1.6	< 0.01
Drager *et al*.[45]	Patients with mild–moderate OSA and severe OSA, with no history of diabetes or HT	Mild–moderate OSA, severe OSA and matched controls with no OSA	*cfPWV (m/s)* Controls: 8.7 ± 0.2 Mild–moderate OSA: 9.2 ± 0.2 Severe OSA: 10.3 ± 0.2 cfPWV significantly associated with AHI: r=0.61	Severe *vs.* mild–moderate < 0.01 Severe *vs.* controls < 0.001 < 0.0001
Drager *et al*.[43]	Patients with severe OSA (AHI > 30 events/h), no other medical conditions except HT	Comparison of controls with no OSA, HT and OSA + HT	*cfPWV (m/s)*Controls: 8.7 ± 0.3 OSA: 10.2 ± 0.2 HT: 10.7 ± 0.3 OSA + HT: 12.1 ± 0.4 cfPWV was independently associated with AHI: r=0.40	OSA and HT groups *vs.* controls < 0.05 OSA + HT *vs.* controls < 0.01 0.002
Drager *et al*.[44]	Patients recently diagnosed with metabolic syndrome	Metabolic syndrome patients with and without OSA	*cfPWV (m/s)* MS − OSA: 9.6 ± 1.0 MS + OSA: 10.6 ± 1.6	< 0.001
Drager *et al*.[44]	Male normotensive patients with or without masked hypertension and with moderate–severe OSA	Age- and BMI-matched healthy controls	*cfPWV (m/s)* Controls: 8.7 ± 0.7 *O*SA − mHT: 9.4 ± 1.0 OSA + mHT: 10.6 ± 1.1	Controls *vs.* OSA-mHT: 0.004 Controls *vs.* OSA+mHT: 0.002 OSA-mHT *vs.* OSA+mHT: < 0.001
Kasikcioglu *et al*.[56]	Patients with newly diagnosed moderate–severe OSA, normotensive, no medications	OSA patients, matched controls with no OSA	*Stiffness index (%)* Controls: 2.1 ± 0.1 OSA: 4.5 ± 0.3 Correlation between aortic stiffness and AHI: coefficient=0.49 *Aortic distensibility ($10^{-6}cm^2$/dyn)* Controls: 3.9 ± 1.5 OSA: 2.4 ± 1.2	0.001 0.002 0.009
Kohler *et al*.[53]	Patients with OSA, no history of excessive daytime sleepiness that would justify CPAP therapy	Patients with and without OSA	*AIx (%)* Controls: 21.0 (8.0–27.0) OSA: 26.0 (19.0–29.5)	0.04
Kumagai *et al*.[52]	Patients with OSA, without CVD, cerebrovascular or renal disease	Mild OSA (AHI > 5, AHI < 15), moderate–severe OSA (AHI > 15)	*Cardio-ankle vascular index (m/s)* Mild OSA: 7.3 ± 1.2 Moderate–severe OSA: 7.7 ± 1.4	0.034
Nagahama *et al*.[50]	OSA patients with or without HT	OSA patients with and without HT, matched controls with no OSA with and without HT	*baPWV (m/s)* Controls (with and without HT): 14.36 ± 2.78 OSA (with and without HT): 16.45 ± 3.49 Controls (no HT): 13.74 ± 2.13 OSA (no HT): 14.53 ± 2.16 Controls (no risk factors): 11.98 ± 0.79 OSA (no risk factors): 14.00 ± 2.00	< 0.0001 < 0.05 < 0.05
Noda *et al*.[54]	Male OSA patients referred to sleep clinic for screening and treatment, free from medication, no history of CVD	OSA patients and matched controls with no OSA	*AIx (%)* Controls: 18.6 ± 9.0 OSA: 23.5 ± 8.7 *Aortic augmentation pressure (mm Hg)* Controls: 6.4 ± 3.4 OSA: 9.0 ± 4.1	0.02 < 0.001
Protogerou *et al*.[48]	Patients with OSA with RDI ⩾ 10	Moderate OSA (RDI = 10–30), severe OSA (RDI = 31–50) and very severe OSA (RDI > 50)	AIx (%) Moderate OSA: 102.1 ± 5.9 Severe OSA: 110.0 ± 4.6 Very severe OSA: 109.4 ± 6.8 *cfPWV (m/s)* Moderate OSA: 8.5 ± 0.6	0.57 (NS) 0.227 (NS)

Table 2 Continued

Study	*Inclusion criteria*	*Comparison*	*Outcome*	P-*value*
			Severe OSA: 8.7 ± 0.4	
			Very Severe OSA: 10.2 ± 0.7	
			RDI was an independent predictor of cfPWV: β=0.359, r^2=12%	0.016
Shiina *et al.*[49]	Patients referred for treatment of OSA, no medical history of heart disease or stroke	OSA patients, matched controls with no OSA	*baPWV (m/s)*	<0.05
			baPWV was higher in patients with OSA than without OSA	
			Significant correlation between OSA and baPWV: r^2=0.41	<0.01
Tanriverdi *et al.*[55]	Patients with no cardiovascular conditions referred for evaluation of snoring and possible sleep apnea	OSA patients, matched controls with no OSA	*Stiffness index (%)*	0.0001
			Controls: 6.42 ± 1.56	
			OSA: 7.1 ± 1.88	
			Distensibility (10^{-6}cm^2/dyn)	0.0001
			Controls: 11.8 ± 3.36	
			OSA: 9.47 ± 1.33	
Tanriverdi *et al.*[55]	Patients with OSA, no primary heart disease or HT	OSA patients, matched controls with no OSA	*Stiffness index (%)*	0.0001
			Controls: 6.42 ± 1.56	
			OSA: 7.1 ± 1.88	
			Distensibility (10^{-6}cm^2/dyn)	0.0001
			Controls: 11.8 ± 3.36	
			OSA: 9.47 ± 1.33	
Tavil *et al.*[57]	Patients with HT, OSA or OSA and HT	OSA, HT and OSA + HT	*Aortic strain (%)*	Controls *vs.* all groups 0.001
			Controls: 13.7 ± 4.5	OSA + HT *vs.* all groups 0.001
			OSA: 6.1 ± 2.7	
			HT: 6.4 ± 2.4	
			OSA + HT: 4.7 ± 1.8	
			Distensibility (10^{-6}cm^2/dyn)	Controls *vs.* all groups 0.001
			Controls: 6.2 ± 3.2	OSA + HT *vs.* all groups 0.001
			OSA: 2.8 ± 1.6	
			HT: 2.5 ± 0.9	
			OSA + HT: 1.7 ± 0.7	
Tomiyama *et al.*[51]	Patients with OSA, without CVD, pulmonary disease, diabetes and renal disease, and free from medication	Mild OSA, moderate–severe OSA, matched controls with no OSA	*baPWV (m/s)*	<0.01
			Independent association of AHI with baPWV (R^2=0.39, β=0.19)	
Tsioufis *et al.*[42]	Patients with OSA and HT	OSA patients, matched controls with no OSA	*cfPWV (m/s)*	0.001
			Controls: 7.85 ± 0.93	
			OSA: 8.56 ± 0.49	

Abbreviations: AHI, apnea-hypopnea index; AIx, augmentation index; AIx(75), augmentation index corrected to a heart rate of 75 b.p.m.; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; CVD, cardiovascular disease; HT, hypertension; mHT, masked hypertension; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

those without OSA. In addition, a significant independent correlation between OSA and baPWV was noted. Similarly, another study observed that baPWV was higher in OSA compared with OSA-free control patients. This trend was maintained even in individuals free of hypertension and cardiovascular risk factors, indicating that OSA itself may be involved in the causation of stiffening of the arteries.[50] This conclusion is strengthened by the findings of Tomiyama *et al.*,[51] who found AHI to be an independent predictor of baPWV. Furthermore, Kumagai *et al.*[52] compared patients with mild and moderate to severe OSA using the cardio-ankle vascular index. They found cardio-ankle vascular index to be lower in patients with mild OSA as compared to patients with moderate to severe OSA.

Kohler *et al.*[53] evaluated the stiffness of the arteries in minimally symptomatic OSA patients using AIx. They found increased AIx in OSA patients compared with controls. Likewise, Noda *et al.*[54] noted an increased AIx in OSA patients compared with non-OSA controls.

Several studies used ultrasonographic methods to evaluate arterial stiffness in OSA patients. Tanriverdi *et al.*[55] found that the stiffness index of OSA patients was higher as compared to control patients, and that aortic distensibility was lower than in control patients. They also noted a correlation between aortic stiffness and RDI as well as a negative correlation between RDI and distensibility (r=−0.41, P=0.001). Kasikcioglu *et al.*[56] found decreased aortic distensibility and increased stiffness index in OSA patients compared with controls. These findings were furthered by another study that found decreased distensibility in OSA patients compared with controls and a further decrease in OSA hypertensive patients.[57]

Effects of continuous positive airway pressure treatment on arterial stiffness

Kohler *et al.*[58] randomized 102 male OSA patients to 4 weeks of therapeutic or subtherapeutic effects of continuous positive airway

Table 3 Continuous positive airway pressure treatment and arterial stiffness (randomized and nonrandomized studies)

Study	*Inclusion criteria*	*Comparison*	*Outcome*	P-*value*
Drager *et al.*[43]	Nonsmoking patients with untreated, severe OSA with no cardiovascular or renal conditions, diabetes and not on medication	CPAP or no CPAP; Repeated measures after 4 months	*cfPWV (m/s)*	NS
			Controls baseline: 10.1 ± 1.3	
			Controls 4 months: 10.3 ± 1.3	
			CPAP baseline: 10.4 ± 1.0	<0.001
			CPAP 4 Months: 9.3 ± 0.9	
			Controls *vs.* CPAP 4 months	<0.001
Keles *et al.*[60]	Patients referred for overnight polysomnography to diagnose OSA with no cardiovascular or pulmonary conditions	Healthy controls; Repeated measures after 6 months of CPAP treatment	*Aortic strain (%)*	<0.001
			Controls: 12.4 ± 3.1	0.007
			OSA: 6.7 ± 2.1	
			After Treatment: 7.3 ± 1.7	
			Sig. correlation with AHI: $r=-0.63$	<0.001
			Aortic distensibility (cm^2/dyn)	<0.001
			Controls: $5.5 \pm 1.7 \times 10^{-6}$	0.01
			OSA: $2.8 \pm 0.9 \times 10^{-6}$	<0.001
			After Treatment: $3.1 \pm 0.9 \times 10^{-6}$	
			Sig. correlation with AHI: $r=-0.62$	
			Aortic systolic diameter (mm)	0.48
			Controls: 32.1 ± 2.2	NS
			OSA: 32.6 ± 2.0	
			After treatment: 32.2 ± 2.1	
			Aortic diastolic diameter (mm)	0.001
			Controls: 28.1 ± 2.3	<0.001
			OSA: 30.3 ± 1.7	0.001
			After treatment: 29.8 ± 1.8	
			Sig. correlation with AHI: $r=0.496$	
			Pulsatile diameter change (mm)	<0.001
			Controls: 4.0 ± 1.0	0.01
			OSA: 2.2 ± 0.8	<0.001
			After treatment: 2.36 ± 0.6	
			Sig. correlation with AHI: $r=-0.58$	
Kitahara *et al.*[62]	Patients with newly diagnosed untreated OSA	Repeated measures after 2 and 4 months of CPAP treatment	*baPWV (m/s)*	0.01
			Start: 15.6 ± 0.6	0.027
			2 months: 15.0 ± 0.5	
			4 months: 14.9 ± 0.6	
			Correlation between baPWV and arousal index: $r=0.596$	0.012
Kohler *et al.*, 2008	Patients referred for overnight polysomnography to diagnose OSA with ODI $>$ 10	Subtherapeutic and therapeutic CPAP after 4 months	*AIx (%)*	
			Subtherapeutic baseline: 12.2 ± 13.6	
			Subtherapeutic 4 months: 14.2 ± 14.9	
			Therapeutic baseline: 14.5 ± 11.3	
			Therapeutic 4 months: 9.1 ± 13.8	
			Therapeutic CPAP decreased AIx compared with subtherapeutic CPAP	0.001
Phillips *et al.*[61]	*Intervention study:* male, 20–65-year-old, untreated OSA patients with RDI $>$ 25	None—repeated measures after 2 months of CPAP treatment	*Peripheral systolic BP (mm Hg)*	0.3 (NS)
			Pre-intervention: 126.8 ± 12	
			Post-intervention: 123.8 ± 13	
			Central systolic BP (mm Hg)	0.043
			Pre-intervention: 115.1 ± 12	
			Post-intervention: 110.9 ± 12	
			Aix75 (%)	0.015
			Pre-intervention: 14.4 ± 9.3	
			Post-intervention: 11.9 ± 8.6	
	Withdrawal study: 18- to 75-year-old patients, on CPAP for at least 1 year, with RDI $>$ 15 events per hour at diagnosis and AHI $<$ 10 after CPAP treatment	None—repeated measures after 7 nights of CPAP withdrawal	*Peripheral systolic BP (mm Hg)*	NS
			No significant change	
			No exact values provided	
			AIx75 (%)	
			No significant change	
			No exact values provided	

Table 3 Continued

Study	*Inclusion criteria*	*Comparison*	*Outcome*	P-*value*
Saito *et al.*[64]	Normotensive or hypertensive patients with moderate–severe OSA who had been on CPAP treatment for 2 years, and had hypertension	Repeated measures after 6, 12 and 24 months of CPAP treatment	*baPWV (m/s)* Baseline: 14.6 ± 2.1 6 months: 14.1 ± 2.1 12 months: 14.3 ± 2.2 24 months: 14.5 ± 2.3	<0.001 <0.05 NS
Shiina *et al.*[63]	Patients referred for treatment of OSA, no history of heart disease or diabetes	Repeated measures after 3 months of CPAP treatment	*baPWV (m/s)* Pre-intervention: 15.4 ± 0.3 Post-intervention: 14.5 ± 0.3	0.001

Abbreviations: AHI, apnea-hypopnea index; AIx, augmentation index; AIx(75), augmentation index corrected to a heart rate of 75 b.p.m.; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; HT, hypertension; mHT, masked hypertension; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

pressure (CPAP). They noted a decrease in AIx in the therapeutic group compared with a slight, nonsignificant increase in the subtherapeutic group.[58] They also tested the sensitivity of the baroreflex at these time points, and found significant improvements following only therapeutic CPAP. The authors hypothesized that CPAP may improve arterial stiffness by acting upon baroreflex sensitivity. Drager *et al.*[59] performed a similar study with 4 months of CPAP, examining cfPWV, which is the 'gold standard' for arterial stiffness measurements. The CPAP group had a decrease in cfPWV, C-reactive protein and catecholamines, whereas changes in the non-CPAP control group were not significant.[59]

Furthermore, we identified five nonrandomized clinical observational studies. Keles *et al.*[60] measured aortic elastic parameters, aortic strain and aortic distensibility using echocardiography in 24 patients with newly diagnosed, previously untreated, moderate or severe OSA and 17 healthy controls. Following 6 months of CPAP treatment, measurements were repeated in the OSA group, and a significant improvement in aortic elastic parameters was found. Similarly, Phillips *et al.*[61] found that 2 months of CPAP treatment significantly decreased AIx, but not peripheral blood pressure. In the same study, withdrawing CPAP for a week in patients who had undergone CPAP treatment for at least 1 year did not significantly affect AIx, but led to an increase in peripheral blood pressure in the morning as compared to the late evening.[61] A study by Kitahara *et al.*[62] found that 4 months of CPAP treatment significantly decreased baPWV. Furthermore, they found a significant correlation between the severity of sleep apnea, as measured by arousal index, and baPWV. Similarly, Shiina *et al.*[63] found 3 months of CPAP to lead to a significant decrease in baPWV but not peripheral blood pressure. Saito *et al.*,[64] however, found 6 months of CPAP treatment to decrease both baPWV and peripheral blood pressure in both hypertensive and normotensive patients. Interestingly, following the significant decrease observed after the first 6 months of treatment, baPWV gradually increased in both groups over the following 18 months under study, whereas peripheral blood pressure did not.

DISCUSSION

This systematic review has presented data from 24 studies evaluating the effect of OSA on arterial stiffness. The results indicate that arterial stiffness is increased in OSA patients, and the majority of the studies point to an association between the severity of OSA and the magnitude of the effect on arterial stiffness. The consistency of the literature is of note. All studies presented in this review found an association of OSA and arterial stiffness. As to the association between the severity of OSA and arterial stiffness, the literature is somewhat less consistent. Out of the seven studies investigating the association between severity of OSA and arterial stiffness,[45,47,48,51,52,60,62] six provided full support for the association[45,47,51,52,60,62] and one provided mixed results.[48] More specifically, the study by Protogerou *et al.*[48] did not find a direct association between OSA severity categories (moderate, severe and very severe) and arterial stiffness. However, they did find RDI to predict cfPWV significantly, the gold standard of arterial stiffness measurements. This is in line with findings by Keles *et al.*,[60] who found a significant correlation between AHI and aortic elastic parameters. Clearly, more research is needed to further our understanding of this association.

The results presented in this review are in keeping with previous studies evaluating endothelial function of OSA patients using flow-mediated dilation. Numerous studies noted that flow-mediated dilation, measured locally in the brachial artery, was decreased in OSA patients compared with non-OSA controls,[2,53,65–67] indicating that endothelial dysfunction occurs in OSA. However, here we discuss the available literature that furthers our understanding of the effect of OSA on arterial function, showing that not only local, but also global arterial function is impaired in OSA.

One of the strongest lines of evidence supporting an independent effect of OSA on arterial stiffness is the finding of the two randomized, controlled studies performed to date, which found that CPAP treatment of OSA significantly improved arterial stiffness.[58,59] Similar findings have also been reported from other studies evaluating OSA treatment effects on arterial stiffness which did not meet our inclusion criteria.[68] Also of note, Phillips *et al.*[61] found that 8 weeks of CPAP treatment lead to reductions in AIx and central systolic blood pressure without a concomitant decrease in peripheral blood pressure. Thus, although the numbers are relatively small in the randomized studies to date, and further larger studies are required with longer follow-up of both arterial stiffness and cardiovascular event outcomes, the current literature points to an independent association between OSA and arterial stiffness. However, as only two randomized trials have been performed to date, more randomized trials are needed to further explore this relationship.

Importantly, it should be noted that arterial stiffness was found to be elevated throughout the day, in the awake state. This implies a carryover effect of OSA on arterial stiffness. More specifically, arterial stiffness is not only elevated acutely at night, when the respiratory disturbance occurs, as shown by Jelic *et al.*,[69] but also during the awake state.

Mechanisms

A number of mechanisms could explain the role of OSA in increasing arterial stiffness. Inflammation, oxidative stress and sympathetic

activity affect endothelial function and are all altered in OSA.[9,10] Intermittent hypoxia is associated with increased production of reactive oxygen species, and therefore, increases oxidative stress.[70,71] Prolonged oxidative stress disturbs cellular function, promotes endothelial dysfunction and increases inflammation, which can further increase the metabolic and cardiovascular complications of OSA such as atherosclerosis.[70] Oxidative stress also reduces the activity of nitric oxide synthase and thus leads to decreased production of nitric oxide, increasing arterial stiffness.[72] Various studies have also found that C-reactive protein, tumor necrosis factor-α, interleukin-6 (IL-6), IL-8 and cell adhesion molecules such as intercellular adhesion molecule-1 are increased in the circulation in OSA patients independent of obesity.[10,15,73,74] Increased inflammation may have a role in the pathogenesis of OSA, increasing arterial stiffness and contributing to the early atherosclerosis found in OSA patients.[3] Furthermore, it also appears that endothelial dysfunction in OSA is partially mediated through apoptotic dysregulation; circulating apoptotic endothelial cells were found to be associated with AHI (r=0.56, P=0.004). This was partially reversed after 8 weeks of CPAP treatment.[2]

Therapeutic and clinical implications

It has been well established that OSA is an independent risk factor for hypertension, myocardial infarction and stroke.[2–7] Arterial stiffness is independently associated with cardiovascular risk[19–24,26,28–31,75–78] and may therefore provide a potential explanation for the increased risk of cardiovascular events in OSA patients. Furthermore, a strong correlation between arterial stiffness and the development of atherosclerosis at various sites in the arteries has been noted.[35,36] Therefore, measuring arterial stiffness can be an important clinical tool for the monitoring of disease progression and treatment efficacy, as recommended by the European Network for Non-invasive Investigation of Large Arteries[25] and the 2007 European guidelines for the management of arterial hypertension.[26] The use of arterial stiffness measurements may be particularly useful in assessing the endothelial damage induced by certain cardiovascular risk factors, such as OSA. However, not all parameters of arterial stiffness are equal; cfPWV is the best measure of arterial stiffness. It is considered the 'gold standard' for the assessment of aortic stiffness,[25,26] and cfPWV and AIx have the greatest amount of evidence to support their predictive value for cardiovascular events in healthy and diseased populations.[26,28–30,75,79,80] Therefore, other parameters of arterial stiffness, such as local distensibility or compliance, may not be as valuable to assess the vascular effects of OSA and are not as useful clinical parameters.

Limitations

This review has a number of limitations. First, the studies use slightly different protocols and methods; the time of day and the conditions under which the studies took place (for example, fasting) were not standardized between studies or not reported. Furthermore, the age groups of subjects, severity of OSA, body mass index, renal function, lipid profile, menopausal status, medication use, including statin use, were not uniform between studies or subject groups. Furthermore, studies were typically cross-sectional, with small sample sizes, and links to long-term outcomes (for example, cardiovascular events or progression of sleep apnea) have yet to be investigated. Moreover, studies examining the effect of CPAP on arterial stiffness have had short follow-ups, thereby not providing information about long-term outcomes.

These factors were also often not reported or corrected for; clearly, future studies should recruit more homogeneous populations. The methods of assessing arterial stiffness also differed between studies; however, it is encouraging that eight studies used cfPWV, AIx or both as parameters of arterial stiffness.[42–45,47,48,53,54] Furthermore, limiting our search to English language publications may have led to an omission of potentially relevant studies. Owing to methodological constraints, a meta-analysis of studies aiming to also quantify the overall magnitude of the effect of OSA on arterial stiffness could not be conducted.

Many studies did not report the time of the day at which arterial stiffness measurements were performed. A study by Phillips *et al.*[81] demonstrated circadian variation of arterial stiffness in OSA patients. More specifically, arterial stiffness was found to be higher in the morning as opposed to the evening. Although Phillips *et al.* did not recruit healthy controls to compare this effect in both healthy and OSA patients, other studies have shown this circadian effect also in healthy populations.[82] Furthermore, a study in healthy individuals by Papaioannou *et al.*[82] suggested that the aforementioned circadian effect is at least in part due to increased blood pressure in the morning. As to OSA patients, it may represent a carryover effect from increased stiffness as well as blood pressure observed during respiratory disturbances at night.[69] Nevertheless, it should be noted that this effect still bears importance, as most cardiovascular events take place in the morning.[83,84]

CONCLUSION

To the best of our knowledge this is the first systematic review on the effect of OSA on arterial stiffness. We have reviewed results from 24 studies evaluating the effect of OSA on arterial stiffness. Arterial stiffness is increased in OSA patients compared with non-OSA control patients. The magnitude of the increase in arterial stiffness appears to be greater in more severely affected OSA patients and in those with other cardiovascular risk factors, such as hypertension. Therefore, arterial stiffness may have a role in the increased risk of cardiovascular complications in OSA. Interestingly, the use of CPAP was found to improve arterial stiffness in patients with OSA. Assessment of arterial stiffness in OSA patients by means of currently available, convenient and noninvasive methods may be an effective method to also monitor disease progression and treatment efficacy.

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