Sleep Medicine Reviews xxx (2014) 1–13

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Systematic review on noninvasive assessment of subclinical cardiovascular disease in obstructive sleep apnea: new kid on the block!

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ARTICLE INFO

Article history:
Received 11 September 2013
Received in revised form
24 January 2014
Accepted 24 January 2014
Available online xxx

Keywords:
Obstructive sleep apnea
Atherosclerosis
Endothelial dysfunction
Cardiovascular disease
Coronary artery calcium
Intima media thickness
Flow-mediated dilation
Pulse wave velocity

SUMMARY

Patients with obstructive sleep apnea (OSA) have a high burden of cardiovascular disease (CVD) but a causal relationship between OSA and atherosclerotic CVD remains unclear. We systematically reviewed the literature analyzing the relationship. A review of the Medline database for studies noninvasively evaluating subclinical CVD in OSA was conducted. A total of fifty-two studies were included in this review.

Across the studies the prevalence of atherosclerosis, as assessed by coronary artery calcification, carotid intima-media thickness, brachial artery flow-mediated dilation and pulse wave velocity was higher in patients with OSA and correlated with increasing severity and duration of OSA.

This study shows OSA is an independent predictor of subclinical CVD as CVD is more likely to occur in patients with long standing and severe OSA. Further research is however necessary to identify specific OSA populations that would benefit from aggressive screening.

Introduction

Obstructive sleep apnea (OSA) is a clinical disorder characterized by alternating episodes of apnea and hypopnea. OSA is defined as an apnea/hypopnea index (AHI) of ≥5 events/h. The burden is enormous as it affects about 4% of middle-aged men and 2% of middle-aged women [1,2]. OSA affects an estimated 15 million adult Americans [3]. It is estimated that 93% of women and 82% of men with moderate to severe sleep apnea syndrome have not been clinically diagnosed [4]. The prevalence of OSA is slated to increase considerably in concert with the global obesity pandemic. This disorder is associated with high rates of morbidity and mortality [5]. Moderate to severe sleep apnea has been described as an independent predictor of mortality [6] and it is well established that these patients have an increased risk of cardiovascular disease (CVD) and cardiovascular death [5,7–9]. However, whether early accelerated atherosclerosis and endothelial dysfunction are the primary drivers of this phenomenon remains to be clearly established [10].

Early recognition of atherosclerotic changes in these patients may significantly impact risk stratification and subsequent risk factor reduction in these patients. Traditional risk stratification has

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http://dx.doi.org/10.1016/j.smrv.2014.01.004

	Search Terms	Search Items
1	Sleep Apnea	22986
2	Cardiovascular Disease Risk	3782
3	Inflammation	250243
4	Atherosclerosis	76187
5	Atherosclerosis Progression	646
6	Endothelial Function	10286
7	Outcomes Cardiovascular Disease	14
8	Subclinical Atherosclerosis	1233
9	Coronary Artery Calcium	995
10	Carotid Intima Media Thickness	2863
11	CT Angiography	4701
12	Ankle Brachial Index	2528
13	1 and 2	14
14	1 and 3	457
15	1 and 4	245
16	1 and 5	2
17	1 and 6	84
18	1 and 7	0
19	1 and 8	7
20	1 and 9	0
21	1 and 10	23
22	1 and 11	1
23	1 and 12	4
24	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	334904
25	1 and 24	735
26	2 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	95613
27	1 and 26	338
28	Limit 27 to Abstracts, English Language and Humans	264
29	Manual Review of 28	52

Fig. 1. Search flow chart.

relied on scoring systems such as the Framingham risk score [11]. However, newer modalities that assess coronary artery calcium (CAC), carotid intima-media thickness (CIMT), pulse wave velocity (PWV) and flow-mediated dilation (FMD) provide refined assessment of endothelial dysfunction and subclinical atherosclerosis. The presence of a significant association between OSA and markers of early subclinical CVD would warrant the development of a strategy to consider early detection of these changes in these patients and may promote more aggressive therapeutic approaches. Such an association would also provide evidence for pertinent stakeholders to consider whether OSA warrants being included as one of the risk factors in the algorithms for determination of future risk of CVD events. As a result, in this systematic review, we sought to analyze the relationship between OSA and markers of subclinical CVD.

Methods

An electronic search of the Medline database (National Library of Medicine, Bethesda, MD) was carried out through OvidSP (Ovid, New York, NY) (Fig. 1). We included literature published up to December 2013. The keywords employed for the search were “sleep apnea”, “cardiovascular disease risk”, “atherosclerosis”, “atherosclerosis progression”, “endothelial function”, “cardiovascular disease outcomes”, and “subclinical atherosclerosis”. These terms were combined with “coronary artery calcium”, “carotid intima-media thickness”, “computed tomography (CT) angiography”, and “ankle brachial index”. The search was limited to include abstracts and full-text, English language publications from studies in adult human subjects. The search results were reviewed and studies which evaluated the relationship between OSA and markers of

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subclinical cardiovascular disease risk were selected. We also reviewed the references of the selected studies to include additional relevant studies which were not found in the initial electronic search. Fifty-two studies were selected for final review.

Results

Obstructive sleep apnea and coronary artery calcium

Earlier studies have defined coronary calcium as a surrogate marker for coronary atherosclerotic burden and an independent marker for coronary heart disease [12,13]. The studies evaluating the association between OSA and CAC are summarized in Table 1. In a recently published Turkish study, Arik et al. [14] enrolled patients without a history of CVD suspected to have OSA. In their multivariate analysis, age, odds ratio (OR) 1.108, 95% confidence interval (CI) 1.031–1.191, $p = 0.005$ and AHI, OR 1.036, 95% CI 1.003–1.070, $p = 0.033$ were noted to independently predict CAC in patients with OSA with a sensitivity of 88.9% and 77.8% and specificity of 54.3% and 56.5% respectively. Similarly, from the Heinz Nixdorf Recall study, Weinreich et al. [15] showed a significant association between OSA and coronary calcium. This is the largest population-based study evaluating this association. They adjusted for several variables including statin use and also presented gender-dependent results. In the adjusted multivariate linear regression, AHI in men ≤65 y old, was associated with increase in elog CAC (0.25, 95% CI −0.001 to 0.50, $p = 0.05$) and among women of any age (0.23, 95% CI 0.04 to 0.41, $p = 0.02$).The doubling of the AHI was associated with 19% increase in CAC in men ≤65 y and 17% increase in women of any age. In another study, Sorajja et al. [16] demonstrated that patients who underwent polysomnography and subsequent CAC assessment, had more prevalent CAC compared to controls (67% vs. 31%, $p < 0.001$). CAC increased with worsening severity of OSA (trend by AHI quartiles − $p < 0.001$). This association was independent of traditional risk factors in the multivariate analysis. Adjusted odds ratios for CAC increased with AHI quartiles: 1.0 ($p > 0.05$), 2.1 ($p > 0.05$), 2.4 ($p = 0.06$), and 3.3 ($p = 0.03$) respectively.

Kim et al. [17], in a study of Asian males, demonstrated that severe OSA was associated with CAC after adjusting for confounding factors excluding obesity compared to mild OSA (OR 2.21, 95% CI 1.01–4.86). This association was however not significant after adjusting for body mass index (BMI) (OR 1.16, 95% CI 0.49–2.74). Kepez et al. [18] on the other hand, reported that CAC scores increased linearly from the simple snoring group to severe OSA group ($p = 0.046$) in patients who had polysomnography for suspected OSA.

Obstructive sleep apnea and intima-media thickness

Nineteen studies were evaluated for the association between OSA and intima-media thickness, see Table 2. Carotid intima media thickness is an established surrogate marker for atherosclerotic disease and an independent predictor of stroke and myocardial infarction [19]. Silvestrini et al. [20], enrolled 23 males with severe OSA and 23 matched controls, demonstrating increased CIMT in

Table 1
Relationship between obstructive sleep apnea and coronary artery calcium.

Study	Population (age, %male)	Results	Comments
Sorajja et al., 2008 [16]	$N = 202$ (Median: 50 y, 70%) OSA: 154 (Median: 51 y, 72%) Controls: 48 (Median: 46 y, 63%)	OSA vs. controls: CAC >0: 67% vs. 31%; $p < 0.001$ CAC vs. AHI: odds ratios for AHI quartiles with 1st quartile as reference: 2nd quartile: 2.1 (0.8–5.4), $p = 0.12$[a] 3rd quartile: 2.4 (1.0–6.4), $p = 0.06$[a] 4th quartile: 3.3 (1.2–9.4), $p = 0.03$[a]	CAC directly correlated with the severity of OSA.
Kim et al., 2010 [17]	$N = 258$ (45 ± 3 y, 100%)	CAC >0: 4th quartile vs. the 1st quartile of AHI severity: Unadjusted: OR 2.98 (1.44–6.20); Adjusted[b]: OR 2.21 (1.01–4.86) No longer significant after adjusting for BMI: OR 1.16 (0.49–2.74)	Study population comprised only of Asians. No independent association between severity of OSA and CAC after adjusting for BMI. No control group used.
Kepez et al., 2011 [18]	$N = 97$ (49 ± 1 y, 66%) Simple snoring: 17 (47 ± 5 y, 59%) Mild OSA: 22 (47 ± 10 y, 73%) Moderate OSA: 21 (52 ± 7 y, 76%) Severe OSA: 37 (50 ± 11 y, 59%)	CAC scores increased linearly from simple snoring group to severe OSA groups ($p = 0.046$).	No control group used.
Arik et al., 2013 [14]	$N = 73$ (50 ± 10 y, 59%) Mean AHI: 22.8 ± 19.8 events/h (Range: 1–95)	In multivariate analysis, AHI associated with CAC: OR 1.036, 95% CI 1.003–1.070, $p = 0.033$ [c]	Turkish population.
Weinreich et al., 2013 [15]	$N = 1604$ (50–80 y, 49%) OSA prevalence Men-29% Women-16%	In an adjusted multiple linear regression analysis AHI was associated with CAC: men ≤65 y elog CAC:0.25 (−0.001–0.50) $p = 0.05$ women any age elog CAC:0.23 (0.04–0.41) $p = 0.02$ Doubling of the AHI associated with 19% increase in CAC in men ≤65 y and 17% increase in women of any age	Cross-sectional analysis of the Heinz Nixdorf Recall study

AHI: apnea–hypopnea index; BMI: body mass index; CAC: coronary artery calcium; OR: odds ratio; OSA: obstructive sleep apnea.
[a] Adjusted for age, gender and traditional risk factors [16].
[b] Adjusted for age, heart rate, hypertension, diabetes mellitus, total cholesterol, triglyceride, HDL (High-density liprotein) cholesterol, smoking, alcohol, and AHI quartiles [17].
[c] Adjusted for age, body mass index, hypertension, diabetes mellitus, oxygen desaturation index and basal oxygen saturation [14].

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Table 2
Relationship between obstructive sleep apnea and intima media thickness.

Study	Population (age, %male)	Results	Comments
Silvestrini et al., 2002 [20]	$N = 46$ OSA: 23 (62 ± 9 y, 50%) Controls: 23 (63 ± 5 y, 50%)	OSA: 1.429 ± 0.34 mm vs. controls: 0.976 ± 0.17 mm, $p < 0.0001$	Study population consists only of male patients with severe OSA.
Kaynak et al., 2003 [21]	$N = 114$ (49 ± 7 y) Habitual Snorers: 37 Mild to moderate OSA: 41 Severe OSA: 36	CIMT (mm): Habitual snoring: 1.37 ± 0.46 Mild-moderate OSA: 1.78 ± 0.57 Severe OSA: 1.91 ± 0.39 One way variance analysis: $F = 12.08$, $p < 0.001$	Study of males referred to the sleep laboratory for evaluation.
Suzuki et al., 2004 [22]	$N = 167$ (47 ± 13 y, 83%)	Correlation of IMT vs. AHI: $r = 0.327$, $p < 0.001$; MR: $\beta = 0.114$, $p = 0.1134$ IMT vs. T90: $r = 0.354$, $p < 0.001$; IMT vs. Mean nadir oxygen saturation: $r = -0.331$, $p < 0.001$	No control group used.
Schulz et al., 2005 [23]	$N = 70$ OSA: 35 (56 ± 1 y, 97%) Controls: 35 (56 ± 1 y, 97%)	CCA-IMT: OSA: 1.04 ± 0.04 mm vs. controls: 0.79 ± 0.02 mm, $p < 0.01$ Plaque score: OSA: 1.43 ± 0.14 vs. controls: 0.96 ± 0.13, $p < 0.05$ IMT vs. T90: $r = 0.49$, $p < 0.01$; IMT vs. Mean SaO_2: $r = -0.51$, $p < 0.01$	Low number of patients in both groups and predominantly male sex limit the scope of generalization.
Baguet et al., 2005 [24]	$N = 83$ (48 ± 11 y, 89%)	Mean CIMT: 0.67 ± 0.13 mm IMT >0.8 mm: 30% of patients Logistic regression analysis shows association of mean nocturnal SaO_2 <92% (OR 3.9, 95% CI 1.1 −12.7, $p = 0.04$) with carotid wall hypertrophy. Correlation of IMT vs. Mean nocturnal SaO_2: $r = -0.30$, $p = 0.006$; IMT vs. T90: $r = 0.19$, $p = 0.090$; IMT vs. minimal nocturnal SaO_2: $r = -0.12$, $p = 0.290$	No control group used.
Minoguchi et al., 2005 [25]	$N = 52$ Mild OSA: 13 (49 ± 4 y, 100%) Moderate to severe OSA: 23 (48 ± 2 y, 100%) Obese (BMI: 28 ± 1 kg/m^2) controls: 16 (47 ± 4 y, 100%)	CIMT: Moderate to severe OSA: 1.16 ± 0.05 mm Mild OSA: 0.92 ± 0.07 mm Controls: 0.71 ± 0.03 mm, $p < 0.0001$ Carotid Plaque *(Presence of focal, severe wall thickening IMT>1.2 mm, wall irregularity and calcification)*: Moderate to severe OSA: 30%, Mild OSA: 23%, Controls: 12% ($p < 0.001$)	The population sample is small and consists only of male patients. The percentage of time with SaO_2 <90% (T90) is the strongest predictor of CIMT ($p = 0.036$).
Yun et al., 2010 [26]	$N = 124$ OSA = 82 (42 ± 10 y, 92%) Control = 22 (39 ± 11 y, 86%)	CIMT (mm): OSA vs. control 0.62 ± 0.096 vs. 0.55 ± 0.08, $p = 0.01$ AHI correlated with CIMT: $r = 0.71$, $p < 0.001$	OSA led to the over production of endothelial microparticles (EMPS)
Drager et al., 2010 [27]	$N = 81$ MS + OSA: 51 (47 ± 7 y, 76%) MS − OSA: 30 (45 ± 7 y, 57%)	CIMT (mm): MS + OSA: 767 ± 140 microm MS − OSA: 661 ± 117 microm, $p < 0.001$ OSA correlated with IMT: $r = 0.34$, $p = 0.002$	81 consecutive patients with MS defined by the ATP III
Altin et al., 2005 [28]	$N = 70$ Severe OSA: 30 (46 ± 8 y, 100%) Mild OSA: 20 (47 ± 9 y, 100%) Controls: 20 (45 ± 6 y, 100%)	Mean IMT values are higher across the levels of OSA severity than controls (RCCA 0.81 vs. 0.63 vs. 0.58, $p < 0.01$; LCCA 0.97 vs. 0.78 vs. 0.67, $p < 0.01$	Classical risk factors (i.e., hypercholesterolemia, diabetes mellitus, and hypertension) were excluded and other factors (i.e., smoking, age and obesity) were controlled in this study.
Drager et al., 2005 [29]	$N = 42$ Mild to moderate OSA: 15 (43 ± 1 y, 93%) Severe OSA: 15 (44 ± 1 y, 84%) Controls: 12 (42 ± 2 y, 93%)	IMT in severe OSA was higher than in both mild-to-moderate and control groups ($p < 0.05$). IMT correlated significantly only with AHI ($r = 0.44$, $p = 0.004$)	Classical cardiovascular risk factors were excluded. Narrow range of age was studied excluding elderly patients.
Saletu et al., 2006 [30]	$N = 147$ (NA, 69%) Controls: 44 (50 ± 14 y, NA) Mild OSA: 27 (55 ± 12 y, NA) Moderate OSA: 25 (55 ± 10 y, NA) Severe OSA: 51 (54 ± 11 y, NA)	Correlation of AHI vs. Common CIMT, $\beta = 0.005$, $p \leq 0.001$ Plaque Score: control vs. Severe OSA, $p < 0.001$	No adjusted analysis presented.
Tanriverdi et al., 2006 [31]	$N = 64$ OSA: 40 (51 ± 9 y, 80%) Controls: 24 (52 ± 5 y, 79%)	IMT: OSA vs. controls; 0.85 ± 0.13 vs. 0.63 ± 0.11 mm, $p = 0.0001$ Plaque scores were similar between both groups. Correlation of RDI vs. IMT; $r = 0.69$, $p = 0.0001$ T90 vs. IMT: $r = 0.54$, $p = 0.002$	Subjects with history of smoking, hypertension, and hypercholesterolemia were excluded.
Szaboova et al., 2007 [33]	$N = 49$ (NA, 100%) OSA with CVD: 33 (52 ± 8 y, 100%) Controls with CVD: 16 (48 ± 11 y, 100%)	*Patients with CVD:* IMT_{max}: OSA vs. controls (0.91 ± 0.21 mm vs. 0.77 ± 0.18 mm, $p < 0.05$)	The population sample is relatively small and subject

Table 2 (*continued*)

Study	Population (age, %male)	Results	Comments
	OSA without CVD: 11 (41 ± 6 y, 100%) Controls without CVD: 7 (49 ± 2 y, 100%)	IMT_{max} vs. AHI: $r = 0.31$, $p < 0.05$ IMT_{max} vs. SaO_2 <90%: $r = 0.42$, $p < 0.01$ *Patients without CVD:* IMT_{max} vs. controls (0.83 ± 0.14 mm vs. 0.63 ± 0.08 mm, $p < 0.01$) IMT_{max} vs. AHI: $r = 0.56$, $p < 0.05$ IMT_{max} vs. SaO_2 <90%: $r = 0.63$, $p < 0.05$ ($\beta = 0.71$, $p < 0.005$)	population consists only of male patients.
Wattanakit et al., 2008 [38]	$N = 985$ (62 y, 45%)	*Observed CIMT by Quartiles of RDI*: 0.80, 0.84, 0.86, 0.89 OR (95% CI) for presence of carotid plaque by quartiles of RDI: Unadjusted: 1.0, 1.14 (0.80−1.63), 1.27 (0.88−1.82), 1.48 (1.03−2.13) Adjusted: 1.0, 1.04 (0.71−1.54), 1.07 (0.71−1.61), 1.25 (0.81−1.95)	No control group used. No association with CIMT and carotid plaques found with increasing RDI.
Protogerou et al., 2008 [32]	$N = 74$ (57 ± 1 y, 59%) Moderate OSA: 20 (59 ± 2 y, 57%) Severe OSA: 31 (55 ± 2 y, 65%) Very severe OSA: 23 (53 ± 2 y, 48%)	CIMT: Moderate OSA: 0.724 ± 0.04 mm; Severe OSA: 0.809 ± 0.03 mm; Very severe OSA: 0.879 ± 0.04 mm; $p < 0.037$ RDI was an independent predictor of IMT: $\beta = 0.371$, $p = 0.007$	IMT measurements are adjusted for age, gender, BMI, heart rate, mean blood pressure, smoking and diabetes mellitus. The studied population had a high burden of cardiovascular risk factors. No control group used.
Drager et al., 2009 [34]	$N = 94$ (46 ± 6 y, NA) OSA alone: 25 (46 ± 5 y, 80%) HTN alone: 20 (44 ± 4 y, 80%) OSA & HTN: 27 (47 ± 5 y, 81%) Normotensive Controls: 22 (45 ± 7 y, 68%)	IMT: Normotensive controls: 0.597 ± 0.082 mm; HTN: 0.713 ± 0.182 mm; OSA: 0.713 ± 0.117 mm OSA & HTN: 0.837 ± 0.181 mm; $p < 0.01$.	OSA and HTN have additive effects on the progression of carotid atherosclerosis.
Baguet et al., 2009 [37]	$N = 130$ (49 ± 10 y, 84%) RDI <37 (A): 65 (48 ± 10 y, 80%) RDI >37 (B): 65 (49 ± 10 y, 88%)	Group A IMT (RDI < 37): 0.64 ± 0.16 mm Group B IMT (RDI > 37): 0.66 ± 0.13 mm, p = NS CIMT vs. Mean nocturnal SaO_2: $r = -0.21$, $p = 0.017$ Prevalence of carotid hypertrophy higher when mean SaO_2 <93.5% (29.5% vs. 16%, $p = 0.05$).	No control group used. Prospective study.
Ciccone et al., 2012 [35]	$N = 156$ (60 ± 11 y, 80%) IMT <0.9 mm: 85 (56 ± 11 y, 81%) IMT >0.9 mm: 71 (64 ± 11 y, 79%)	Among those with IMT values <0.9 mm, significant proportion of patients had low-moderate forms of OSAS ($p < 0.05$); whereas more patients with IMT values ≥0.9 had severe form.	No control group used.
Özdemir et al., 2013 [36]	$N = 90$ Severe OSAS: 35 (47 ± 6 y, 94%) Mild-moderate OSAS: 35 (45 ± 7 y, 91%) Control: 20 (42 ± 5 y, 75%)	AHI: severe vs. mild-moderate OSAS vs. control 65.00 ± 24.14 vs. 14.05 ± 7.65 vs. 2.09 ± 1.39, $p < 0.001$ ODI: severe vs. mild-moderate OSAS vs. control 58.81 ± 24.72 vs.12.68 ± 7.81 vs. 2.19 ± 2.34, $p < 0.001$ IMT: severe vs. mild-moderate OSAS vs. control 0.95 ± 0.14 vs. 0.83 ± 0.15 vs. 0.77 ± 0.13, $p < 0.001$ FRS: severe vs. mild-moderate OSAS vs. control 11.26 ± 5.13 vs. 9.97 ± 4.59 vs. 5.95 ± 3.38, $p < 0.001$	Regression analysis showed AHI and ODI were independent predictors of IMT. ODI independently affected the progression of atherosclerosis.

Apnea is defined as complete or almost complete cessation of airflow and hypopnea as a decrease in airflow of approximately 30% of baseline for 10s or more, accompanied by a 3% or more decrease in oxygen saturation.
AHI (apnea−hypopnea index) is obtained by dividing the total number of apneas and hypopneas by the total sleep time.
A plaque is defined by a localized thickening of >1.2 mm, not involving the whole circumference of artery. Plaque score is calculated by summing all the plaque thickness measurements in both carotid arteries.
OSA is defined as respiratory disturbance index (RDI) above or equal to 10, with a percentage of obstructive and mixed apneas above 50% of the total number of apneas.
BMI: body mass index; CCA−IMT: common carotid artery−intima media thickness; CIMT: carotid IMT; FRS: Framingham risk score; HTN: hypertension; IMT_{max}: largest value of intima media thickness; NS: not significant; ODI: oxygen desaturation index; RDI (respiratory disturbance index): number of apneas and hypopneas per hour of recording; T90: the duration of oxygen saturation below 90% expressed as a percentage of total sleeping time.

patients with severe OSA (1.429 ± 0.34 vs. 0.976 ± 0.17 mm, $p < 0.0001$). There was however, no association found between OSA and the prevalence of atherosclerotic plaques. In another study, Kaynak et al., [21] studied a population of male patients referred to a sleep laboratory for evaluation. In this study there were no significant differences among sleep disordered breathing (SDB) severity groups with respect to age, prevalence of hypertension and diabetes, smoking, total cholesterol and total triglyceride levels. The CIMT was highest among severe OSA subjects (1.91 ± 0.39 mm), compared to mild to moderate OSA (1.78 ± 0.57) and habitual snorers (1.37 ± 0.46 mm). The one way variance analysis to show differences was significant, $F = 12.08$, $p < 0.001$. Suzuki et al. [22] demonstrated that AHI, duration of oxygen saturation below 90% and the mean nadir oxygen saturation were all significantly associated with CIMT, even after adjustment for confounding factors. OSA-related hypoxemia was associated with CIMT independent of the AHI, indicating that hypoxemia may be more strongly associated with atherosclerosis than obstructive episodes. In a study of

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Table 3
Relationship between obstructive sleep apnea and pulse wave velocity.

Study	Population (age, %male)	Results	Comments
Nagahama et al., 2004 [40]	$N = 208$ OSA: 104 (53 ± 9 y, 88%) 48 cases free from HTN Controls: 104 (53 ± 8 y, 88%) 90 cases free from HTN	baPWV: OSA vs. controls: 1645 ± 349 cm/s vs. 1436 ± 278 cm/s; $p < 0.0001$ *Among cases free from HTN:* OSA vs. controls: 1453 ± 216 cm/s vs. 1374 ± 213 cm/s; $p < 0.05$ *Among cases entirely free from risk factors:* OSA vs. controls: 1400 ± 200 cm/s vs. 1198 ± 79 cm/s; $p < 0.05$	OSA significantly associated with higher PWV even among normotensives and those with no other risk factors.
Drager et al., 2005 [29]	$N = 42$ Mild to moderate OSA: 15 (43 ± 1 y, 93%) Severe OSA: 15 (44 ± 1 y, 84%) Controls: 12 (42 ± 2 y, 93%)	Controls: 8.7 ± 0.2 m/s Mild to Moderate OSA: 9.2 ± 0.2 m/s Severe OSA: 10.3 ± 0.2 m/s PWV vs. AHI: $r = 0.61$, $p < 0.0001$ PWV vs. SaO_2 <90%: $r = 0.44$, $p = 0.005$ PWV vs. SaO_2min: $r = -0.42$, $p = 0.005$	Classical cardiovascular risk factors were excluded. Narrow range of age was studied excluding elderly patients. OR not given.
Shiina et al., 2006 [41]	$N = 94$ OSA + MS = 41 (51 ± 2 y) OSA − MS = 53 (52 ± 2 y)	PWV (cm/s): OSA + MS vs. OSA-MS 1562 ± 19 vs. 1432 ± 21, $p < 0.05$ A general linear model analysis demonstrated an independent association between OSA and MS with PWV	Presence of MS may constitute an additive cardiovascular risk factor in subjects with OSAS.
Tsioufis et al., 2007 [43]	$N = 99$ OSA = 46 (49 ± 8 y, 76%) Control = 53 (49 ± 5 y, 75%)	Carotid-femoral pulse wave velocity (c-fpwv) m/s: OSA vs. control 8.56 ± 0.49 vs. 7.85 ± 0.93, $p = 0.001$ c-fpwv correlated with log AHI $r = 0.389$, $p = 0.0001$	Greek study population. Patients were newly diagnosed stage I–II essential hypertension who had OSA. Controls were matched for age sex and smoking status.
Protogerou et al., 2008 [32]	$N = 74$ (57 ± 1 y, 59%) Moderate OSA: 20 (59 ± 2 y, 57%) Severe OSA: 31 (55 ± 2 y, 65%) Very severe OSA: 23 (53 ± 2 y, 48%)	PWV measured in 38 patients. Moderate OSA: 8.5 ± 0.6 m/s Severe OSA: 8.7 ± 0.4 m/s Very Severe OSA: 10.2 ± 0.7 m/s; $p = 0.227$ PWV vs. RDI: $\beta = 0.359$, $p = 0.016$	No control group used. PWV was measured only in a limited number of patients because pulse wave analysis was difficult in patients with severe obesity.
Baguet et al., 2009 [37]	$N = 130$ (49 ± 10 y, 84%) RDI <37 (A): 65 (48 ± 10 y, 80%) RDI >37 (B): 65 (49 ± 10 y, 88%)	Group A (RDI < 37) PWV: 8.9 ± 1.6 m/s Group B (RDI > 37) PWV: 9.2 ± 1.4 m/s Total PWV: 9.1 ± 1.5 m/s; p = NS	No control group used. Prospective study.
Tomiyama et al., 2009 [46]	$N = 164$ (48 ± 11 y, 9)	AHI independently associated with baPWV [a] $R(2) = 0.39$, beta = 0.19, $p < 0.01$	Japanese study population. No Controls
Chung et al., 2010 [44]	$N = 112$ Mild to moderate OSA: 39 (44 ± 9 y, 100%) Severe OSA: 44 (44 ± 6 y, 100%) Controls: 29 (44 ± 6 y, 100%)	PWV: Controls: 8.8 ± 1.2 m/s; mild to moderate OSA: 9.0 ± 1.4 m/s; Severe OSA: 9.8 ± 1.6 m/s; $p < 0.01$ PWV vs. AHI: $r = 0.31$, $p < 0.01$ PWV vs. T90: $r = 0.26$, $p < 0.01$, $\beta = 0.34$	The study population consists only of male patients which limit the applicability of the results.
Drager et al., 2010 [45]	$N = 61$ OSA = 43 Control = 18	PWV (m/s) Controls :8.7 ± 0.7 OSA alone :9.4 ± 1.0 OSA + masked HTN :10.6 ± 1.1 $p < 0.001$	All male participants. Controls were matched for age and BMI
Drager et al., 2010 [42]	$N = 81$ MS + OSA = 51 (47 ± 7 y, 76%) MS − OSA = 30 (45 ± 7 y, 57%)	PWV (m/s): MS + OSA vs. MS-OSA 10.6 ± 1.6 vs. 9.6 ± 1.0, $p < 0.001$ AHI correlated with PWV $r = 0.32$, $p = 0.004$	MS was defined by the Adult Treatment Panel III
Korcarz et al., 2010 [47]	$N = 153$ SDB = 83 (62 ± 8 y, 57%) Control = 70 (60 ± 7 y, 57%)	Aortic-PWV (m/s): SDB vs. control 9.06 ± 2.15 vs. 8.51 ± 1.88, $p = 0.112$ AHI correlated with aortic-PWV $R = 0.18$, $p = 0.032$	Nested cross-sectional study of the Wisconsin sleep cohort.

AHI: apnea–hypopnea index; baPWV: brachial–ankle pulse wave velocity; HTN: hypertension; MS: metabolic syndrome; NA: not available; OR: odds ratio; OSAS: obstructive sleep apnea syndrome; PWV: pulse wave velocity; SaO_2min: minimal SaO_2; T90: percentage of time <90% O_2 saturation.
OSAS:at least 10 to 15 apneas and hypopneas per hour of sleep associated with symptoms of sleep apnea, including loud snoring, restless sleep, nocturnal dyspnea, morning headaches and excessive daytime sleepiness.
[a] Adjusted for age, gender, CVD risk factors [46].

OSA matched controls, Schulz et al. [23] reported, CIMT was increased in OSA and significantly related to the degree of nocturnal hypoxia. The degree of plaque formation was also more pronounced as compared to the controls. Baguet et al. [24], in their study, demonstrated that mean nocturnal oxygen saturation <92% was associated with carotid hypertrophy (OR 3.9, 95% CI 1.1–12.7) and carotid plaque formation (OR 3.1, 95% CI 1.0–9.4) even after adjustment for high blood pressure. Minoguchi et al. [25], in a study of 36 patients with OSA and 16 obese controls, demonstrated that CIMT was higher in patients with OSA as compared to controls. It also showed that CIMT was significantly correlated with the duration of OSA-related hypoxia ($r = 0.60$, $p = 0.0001$), and severity of OSA ($r = 0.50$, $p = 0.002$). The duration of hypoxia during total sleep time was the strongest independent predictor of CIMT in patients with OSA and obese control subjects ($p = 0.036$). This study also noted that inflammatory markers such as C-reactive protein, interleukin-6 and interleukin-8 were higher in patients with OSA and that these markers correlated well with CIMT ($r = 0.61/p = 0.0001$, $r = 0.41/p = 0.01$ and $r = 0.45/p = 0.005$, respectively). Similarly, Yun et al., [26] in a study of 82 OSA subjects and 22 controls, reported that OSA led to the over production of endothelial microparticles (EMPS). They showed that OSA subjects

Please cite this article in press as: Ali SS, et al., Systematic review on noninvasive assessment of subclinical cardiovascular disease in obstructive sleep apnea: new kid on the block!, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.01.004

Table 4
Relationship between obstructive sleep apnea and flow-mediated dilation.

Study	Population (age, %male)	Results	Comments
Kato et al., 2000 [48]	$N = 17$ OSA (44 ± 4 y) Control (48 ± 3 y)	FMD%: OSA vs. control 3.7 ± 0.7 vs. 4.7 ± 1.4	OSA subjects have an impairment of resistance vessel endothelium-dependent vasodilation.
Ip et al., 2004 [49]	$N = 40$ OSA = 28 Control = 12	FMD%: OSA vs. control 5.3 ± 1.7 vs. 8.3 ± 1, $p < 0.001$	All men. Treatment with CPAP reversed the dysfunction.
Nieto et al., 2004 [50]	$N = 1037$ (68–96 y, 44%)	FMD vs. AHI: $r = -0.11$, $p < 0.001$ Correlation of FMD vs. AHI[a]: $r = -0.038$ (without HTN), $r = -0.095$ (with HTN) FMD vs. hypoxemia index[a]: $r = -0.003$ (without HTN), $r = -0.107$ (with HTN); $p < 0.05$	Study population is a subset of a cohort study.
Tanriverdi et al., 2006 [31]	$N = 64$ OSA: 40 (51 ± 9 y, 80%) Controls: 24 (52 ± 5 y, 79%)	FMD: OSA vs. controls; 4.57 ± 1.3 vs. 6.34 ± 0.83, $p = 0.0001$ FMD vs. RDI: $r = -0.52$, $p = 0.0001$ FMD vs. T90: $r = -0.62$, $p = 0.001$	Subjects with history of smoking, hypertension, and hypercholesterolemia were excluded.
Kohler et al., 2008 [52]	$N = 79$ OSA: 64 (58 ± 7 y, 89%) Controls: 15 (58 ± 7 y, 87%)	FMD: OSA vs. controls; 5.0 ± 2.7 vs. 7.5 ± 3.3 (95% CI −4.1 to −0.9%; $p = 0.003$).	The study population consisted of patients with minimally symptomatic OSA.
Jelic et al., 2008 [53]	$N = 45$ OSA = 30 (38 ± 11 y, 67) Control = 15 (39 ± 7 y, 60)	FMD%: OSA vs. control 4.01 ± 2.99 vs. 9.52 ± 2.79, $p < 0.001$	CPAP therapy significantly increased FMD in patients who adhered to CPAP ≥4 h daily.
Jelic et al., 2010 [54]	$N = 71$ OSA = 38 (38 ± 11 y, 61%) Control = 33 (37 ± 11 y, 55%)	FMD%: OSA vs. control 2 (0.5–4) vs. 9.5 (9–11), $p = 0.03$	Untreated OSA rather than obesity is a major determinant of vascular endothelial dysfunction.
Chung et al., 2009 [55]	$N = 161$ Middle-aged: 117 (46 ± 6 y, 100%) Elderly: 44 (66 ± 5 y, 100%)	FMD vs. AHI: middle-aged $r = -0.11$, $p =$ NS; Elderly $r = -0.24$, $p =$ NS FMD vs. T90: middle-aged $r = -0.23$, $p < 0.05$; Elderly $r = -0.13$, $p =$ NS FMD vs. lowest SaO_2: middle-aged $r = 0.26$, $p < 0.01$, $\beta = 0.25$; Elderly $r = 0.04$, $p =$ NS FMD vs. ODI: middle-aged $r = -0.20$, $p < 0.05$; Elderly $r = -0.18$, $p =$ NS	The study subjects were all male, limiting the generalization of the results.
Patt et al., 2010 [57]	$N = 14$ OSA = 7 (36 ± 2 y) Control = 7 (39 ± 5 y)	FMD: OSA vs. control (mean ± SEM) 5.7 ± 0.5 vs. 9.5 ± 0.6; $p = 0.02$ After adjusting for BMI, age and sex, the difference between OSA and control remained significant. (3.2 ± 1.1, $p = 0.02$)	Participants recruited from the Ohio State University (OSU) Sleep Disorders Center. Controls were matched for age and weight. OSA subjects with low CVD risk had increased oxidant production in the microcirculation and endothelial dysfunction that improved with treatment.
Yoshihisa et al., 2010 [56]	$N = 129$ Group A: 93 (59 ± 14 y, 77%) Moderate-severe OSA Group B: 36 (58 ± 15 y, 58%) Mild OSA	FMD: Group A vs. Group B: 3.5 ± 1.6 vs. 7.8 ± 3.1, $p < 0.01$	No adjusted analysis presented. Japanese population.
Chung et al., 2010 [44]	$N = 112$ Mild to moderate OSA *(AHI ≥5, AHI <30)*: 39 (44 ± 9 y, 100%) Severe OSA *(AHI ≥30)*: 44 (44 ± 6 y, 100%) Controls *(AHI <5)*: 29 (44 ± 6 y, 100%)	FMD: Severe OSA vs. controls; 6.1 ± 2.1 vs. 8.1 ± 2.6, $p < 0.01$ FMD vs. AHI: $r = -0.32$, $p < 0.01$ FMD vs. Respiratory Arousal Index: $r = -0.22$, $p = 0.03$ FMD vs. Av. SaO_2: $r = 0.29$, $p < 0.01$ FMD vs. lowest SaO_2: $r = 0.30$, $p < 0.01$, $\beta = 0.25$, Adjusted $R^2 = 6\%$ FMD vs. T90: $r = -0.31$, $p < 0.01$; FMD vs. ODI: $r = -0.31$, $p < 0.01$	The study population consists only of male patients.
Yim-Yeh et al., 2010 [51]	$N = 72$ OSA: 38 (44 ± 10 y, 53%) Controls: 34 (32 ± 12 y, 26%)	FMD: OSA vs. controls; 5.7 ± 3.8 vs. 8.3 ± 0.1, $p = 0.005$ *In subjects younger than 50 y of age:* OSA status only independent predictor of FMD; $p = 0.04$ ($n = 59$).	Odds ratios not given.
Namtvedt et al., 2012 [58]	$N = 71$ OSA = 37 (47 ± 5 y, 70%) Control = 34 (43 ± 5 y, 59%)	FMD%: OSA vs. control 6.4 ± 3.2 vs. 10.1 ± 6.3, $p = 0.003$ FMD correlated with AHI, $r = -0.33$, $p = 0.004$ Multivariate analysis: AHI predicted FMD $\beta = -0.29$, $p = 0.01$	Norwegian cross-sectional study. OSA associated with endothelial dysfunction independent of obesity and conventional risk factors.

CPAP: continuous positive airway pressure; CV Risk score: cardiovascular risk score estimates the risk of death (in percent) in the next five years due to a cardiovascular event; FMD: percentage flow-mediated dilation; NS: not significant; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; SAS: sleep apnea syndrome; T90: duration of oxygen saturation below 90% expressed as a percentage of total sleeping time.

[a] Adjusted for age, sex, race and BMI [50].

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had a high CIMT and that AHI was correlated with CIMT, $r = 0.71$, $p < 0.001$. Drager et al. [27] demonstrated that the association of OSA and intima-media thickness (IMT) was independent of the presence of the metabolic syndrome (MS). They enrolled 81 consecutive patients with the MS and showed that subjects with OSA had a higher CIMT compared to subjects without OSA, 767 ± 140 microm vs. 661 ± 117 microm, $p < 0.001$. They also showed a correlation between OSA and CIMT, $r = 0.34$, $p = 0.002$.

From other studies, Altin et al. [28] and Drager et al. [29] demonstrated that CIMT was significantly increased in patients with severe OSA compared to controls and patients with mild OSA. Saletu et al. [30] demonstrated that AHI was an independent predictor of common CIMT ($p = 0.001$) and combined IMT ($p = 0.001$) in OSA patients and the percentage of total sleep time with an oxygen saturation below 90% was associated with bulb-internal CIMT ($p = 0.018$).

Tanriverdi et al. [31] demonstrated that OSA patients exhibited increased CIMT and IMT correlated positively with the severity of OSA as assessed by the respiratory disturbance index (RDI). In a similar study, Protogerou et al. [32] demonstrated that severity of OSA expressed as RDI positively correlated with CIMT ($\beta = 0.371$, $p = 0.007$) independent of CVD risk factors. Also, oxygen desaturation index (ODI) was shown to be an independent predictor of CIMT. The presence of carotid plaques was not associated with the severity of OSA and other indices of nocturnal hypoxemia. In a study of male subjects, Szaboova et al. [33] demonstrated that untreated OSA, with or without CVD risk factors, increased atherosclerotic changes in the carotid arteries (0.91 ± 0.21 mm vs. 0.77 ± 0.18 mm, $p < 0.05$). This is affected by severity of OSA and nocturnal hypoxemia relatively independent of traditional CVD risk factors after multivariate analysis.

Drager et al. [34] reported that OSA and hypertension have additive effects on the progression of carotid atherosclerosis. CIMT was positively related to systolic blood pressure and AHI ($p < 0.05$). Ciccone et al. [35] on the other hand demonstrated that the duration and severity of OSA correlates with higher values of CIMT ($r = 0.34$, $p < 0.001$ and $r = 0.51$, $p < 0.001$, respectively). In a recent study, Özdemir et. al [36], evaluated the IMT and the 10-y risk of coronary heart disease, Framingham risk score (FRS) in a population of 90 consecutive patients referred for a polysomnography test. This study showed IMT and FRS were found to be statistically significantly increased in the severe OSAS group compared to the controls and mild OSAS groups. CIMT was found to be significantly positively correlated with AHI, oxygen desaturation index (ODI) and time duration with oxygen saturation (SpO_2) <90%, and negatively correlated with minimum oxygen saturation at sleep (minimum SpO_2) and mean SpO_2. In the regression analysis AHI and ODI were found to be an independent predictor of CIMT. ODI was found to have an independent effect on the progression of atherosclerosis. Interestingly, Baguet et al. [37] reported that in newly diagnosed OSA patients without clinically diagnosed CVD, there were no significant differences in CIMT between groups based upon severity of OSA, however the prevalence of carotid hypertrophy was higher when mean SaO_2 was below 93.5% ($p = 0.05$). Only one study showed no association between OSA, CIMT and carotid plaques after adjusting for CVD risk factors. Wattanakit et al. [38] in a cross-sectional study of 985 participants in the Sleep Heart Health Study with no history of CHD and stroke concluded that the association between SBD and subclinical atherosclerosis can be attributed to confounding by CVD risk factors.

Obstructive sleep apnea and pulse wave velocity

Table 3 presents the results of the eleven studies evaluating the association between OSA and PWV. Arterial stiffness (AS) is now considered as a marker for cardiovascular event [39].The gold standard noninvasive measure for AS is the vessel pulse wave velocity. Nagahama et al. [40] reported that brachial–ankle PWV was higher in OSA patients compared to controls matched for age, sex and body mass index. However, no correlation was observed between AHI or percentage of time spent below 90% SaO_2 and brachial–ankle PWV. Similarly, Drager et al. [29] demonstrated that severity of OSA influences PWV ($r = 0.61$, $p < 0.0001$). They also showed that the minimal saturation of oxygen ($r = -0.42$, $p = 0.005$) and the percentage of time spent with oxygen saturation below 90% ($r = 0.44$, $p = 0.005$) correlate with the PWV. Among a population of subjects with MS, Shiina et al. [41]reported that the presence of MS may constitute an additional cardiovascular risk in individuals with OSA. In their general linear model analysis, OSA was associated with PWV independent of the MS. Similarly, Drager et al. [42]showed AHI correlated with PWV in a cohort of subjects with MS. In a Greek study, matched for age, sex and smoking status, Tsioufis et al. [43], showed the carotid-femoral PWV (C-fpwv) was 8.56 ± 0.49 m/s in OSA subjects and 7.85 ± 0.93 m/s in controls. There was a correlation between the log AHI and the c-fpwv. In a similar study, Protogerou et al. [32] demonstrated that severity of OSA expressed as RDI positively correlated with carotid-femoral PWV ($\beta = 0.359$, $p = 0.016$) independent of CVD risk factors. Also ODI and nocturnal hypoxemia were shown to be independent predictors of carotid-femoral PWV. The degree of association was influenced by the severity of the OSA. Both Chung et al. [44] and Drager et al. [45] in studies limited to male subjects showed OSA subjects had higher PWV compared to their controls. Chung et al. demonstrated that the PWV was significantly higher in patients with severe OSA as compared to those with mild to moderate degree of OSA or normal control subjects. From a Japanese study population, Tomiyama et al. [46] reported an independent association between AHI and brachial–ankle PWV, $R(2) = 0.39$, beta = 0.19, $p < 0.01$. From a nested cross-sectional study of the Wisconsin sleep cohort, Korcarz et al. [47] reported that individuals with severe disorders of breathing have a higher aortic-PWV compared to controls, 9.06 ± 2.15m/s vs. 8.51 ± 1.88m/s, $p = 0.112$. They summed that AHI correlated with the aortic-PWV.

One study however, did not show a significant correlation between OSA and PWV. Baguet et al. [37] reported that in newly diagnosed OSA patients without clinically diagnosed cardiovascular diseases, there were no significant differences in carotid-femoral PWV between groups based upon severity of OSA.

Obstructive sleep apnea and flow-mediated dilation

Impaired endothelium-dependent vascular relaxation is a prognostic marker of atherosclerosis and cardiovascular disease. Table 4 presents the results of fourteen studies evaluating the association between OSA and FMD. Kato et al. [48] showed that OSA subjects had impairment of resistance vessel endothelium-dependent vasodilatation. Similarly Ip et al. [49], in a study of male subjects reported that the FMD of subjects with OSA was significantly lower than in controls. In this study, treatment with continuous positive airway pressure (CPAP) reversed the dysfunction. Nieto et al. [50] demonstrated that OSA is associated with impaired FMD and this association was stronger in patients <80 y of age and hypertensive. Increased severity of OSA, as assessed by AHI and the hypoxemia index (percentage of time spent <90%), was associated with decreased brachial artery FMD. This association is shown to be attenuated after adjustment for cardiovascular risk factors, particularly body mass index. Yim-Yeh et al. [51] reported that OSA has a premature aging effect on the vasculature in obesity. They showed that OSA is associated with impaired FMD compared with controls; this association is

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Table 5
Relationship between obstructive sleep apnea and plaque burden by other modalities.

Study	Population (age, %male)	Results	Comments
Friedlander et al., 1998 [59]	$N = 938$ OSA: 47 (Mean: 59 y, 100%) Controls: 891 (Mean: 58 y, 100%)	Calcified carotid artery atheromas: OSA: 21.3%; controls: 2.5%; $p < 0.000001$	Cephalometric radiographs used to assess plaque burden.
Friedlander et al., 1999 [60]	$N = 108$ OSA: 54 (Mean: 60 y, 100%) Controls: 54 (Mean: 60 y, 100%)	Calcified carotid artery atheromas: OSA: 22%; controls: 3.7%; $p = 0.0079$	Panoramic radiographs used to assess plaque burden.
Kaynak et al., 2003 [21]	$N = 114$ (49 ± 7 y) Habitual snoring = 37 Mild to moderate OSA = 41 Severe OSA = 36	Presence of plaque (%) Habitual snoring = 28% Mild-Moderate OSA = 59% Severe = 89% Significant between group differences, $p < 0.001$ Logistic regression analysis: RDI predicted Plaque β=0.04, $p < 0.05$	
Wattanakit et al., 2008 [38]	$N = 985$ (62 y, 45%) Quartiles of RDI I = 254 II = 257 III = 244 IV = 230	Odds ratio of carotid plaque by quartiles of hypoxemic index: [c]Quartiles: 1: ref 2: 1.08 (0.68–1.71) 3: 1.14 (0.80–1.63) 4: 1.17 (0.78–1.75)	The median RDI = 8.7 events/h
Kylintireas et al., 2012 [61]	$N = 97$ OSA: 42 (56 ± 2 y, 21%) Controls: 39 (59 ± 2 y, 23%)	Carotid wall thickness: OSA vs. controls: 1.47 ± 0.03 mm vs. 1.26 ± 0.05 mm, $p < 0.01$ Aortic wall thickness: OSA vs. controls: 2.95 ± 0.09 mm vs. 2.05 ± 0.07 mm, $p < 0.001$ Carotid plaque prevalence: OSA: 50% vs. controls: 23%, $p < 0.05$ ODI vs. carotid wall thickness: $r = 0.44$, $p < 0.005$; ($\beta = 0.3 \pm 0.09$, $p < 0.005$)[a]; Multivariate analysis: $\beta = 0.41 \pm 0.15$, $p < 0.01$ ODI vs. aortic wall thickness: $r = 0.38$, $p < 0.01$; ($\beta = 0.63 \pm 0.2$, $p < 0.005$)[a]; Multivariate analysis: $\beta = 0.61 \pm 0.21$, $p < 0.01$	CMR scans used to assess plaque burden. 58 OSA patients recruited. 42 were matched for age, gender, height and weight, and CV risk factors to 39 control subjects.
Sharma et al., 2012 [62]	$N = 81$ OSA: 49 (60 ± 12 y, 63%) Controls: 32 (54 ± 13 y, 43%)	Non-calcified/mixed plaques: OSA: 63% vs. controls: 16%; $p < 0.0001$ Adjusted[b] OR: 7.0; 95% CI: 1.9–26.5, $p < 0.05$ Non-calcified/mixed plaques vs. AHI[b]: Mild OSA (AHI 10–20): OR: 3.2; 95% CI: 0.2–43.7 Moderate-to-severe OSA (AHI>20): OR: 14.2; 95% CI: 1.3–158.5 Multiple vessel involvement: OSA: 85.7% vs. controls: 34.5%; OR[b]: 8.5; 95% CI: 2.3–30.8 Vascular stenosis (≥70%): OSA: 22.5% vs. controls: 6%; $p < 0.05$	Coronary CT angiography used to assess plaque burden. Broad CI most likely due to small sample size.
Kent et al., 2013 [63]	$N = 29$ (45 ± 8 y) High AHI = 14 (45 ± 6 y) Low AHI = 15 (45 ± 9 y)	Coronary plaque volume (mm^3): High AHI vs. low AHI 2.6 ± 0.7 vs. 0.8 ± 0.2, $p = 0.017$ Plaque volume correlated significantly with AHI Spearman's $r = 0.433$, $p = 0.0019$. Stepwise multivariate regression analysis adjusting for FPG and HDL-C: $\beta = 0.424$, $p = 0.027$	All male subjects. Subjects with an AHI above the median (15.5 events/h) were categorized as high AHI, with the remainder categorized as low AHI. Severity of OSA may predict occult coronary atherosclerosis in otherwise healthy overweight or obese males.
Tan et al., 2013 [64]	$N = 93$ (54 ± 9 y, 87%) Moderate to severe 32 (58 ± 7 y, 81%) No to mild 61 (53 ± 9 y, 90%)	Atheroma volume: moderate-severe vs. no-mild OSA 461.3 ± 250.4 mm^3 vs. 299.2 ± 135.6 mm^3, $p < 0.001$ Relative mean diff: 1.73, 95% CI 1.38–2.15	All patients were recruited with angiographically proven coronary artery disease. Atheroma was evaluated with VH-IVUS.

AHI: apnea hyponea index; CI: confidence interval; CT: computed tomography; FPG: fasting plasma glucose; HDL-C: high density lipoprotein cholesterol; LDL: low density lipoprotein; OSA: obstructive sleep apnea; RDI: Respiratory disturbance index; VH-IVUS: virtual histology intravascular ultrasound.

[a] After adjustment for Framingham risk score; ODI: oxygen desaturation index; Carotid plaque: Carotid atheroma class III and above [61].

[b] Adjusted for age, sex, race, smoking history, and hypercholesterolemia [62].

[c] Adjusted for age, sex, BMI, hypertension, smoking, diabetes, fibrinogen, LDL (Low-density lipoprotein) and HDL (High-density lipoprotein) [38].

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influenced by older age. Among subjects <50 y of age, FMD was predicted by OSA status and not by age or BMI ($p = 0.04$); however this was not true of older patients.

Tanriverdi et al. [31] reported a lower FMD in subjects with OSA than in the controls. RDI was negatively correlated with FMD ($r = -0.52$, $p = 0.0001$, $\beta = -0.86$). Kohler et al. [52], in a study of patients with minimally symptomatic OSA, demonstrated that FMD was impaired compared to controls. There was no significant correlation found between FMD and RDI. In two different studies, Jelic et al. and Jelic et al. [53,54], reported significant reductions in the FMD of OSA subjects compared to controls. In the latter, untreated OSA rather than obesity was a major determinant of vascular endothelial dysfunction [54]. Chung et al. [55] in their study showed that FMD was significantly lower in elderly patients. Minimal oxygen saturation was found to be a significant determinant of FMD ($\beta = 0.25$, $p < 0.01$) in middle-aged patients. Yoshihisa et al. [56] demonstrated that FMD impairment was related to the severity of OSA; mild, moderate and severe. In a similar study, Chung et al. [44] demonstrated that FMD was significantly impaired with the severity of OSA ($p < 0.01$). It also showed that the lowest oxygen saturation was a significant determinant for FMD ($\beta = 0.25$, adjusted $R^2 = 6\%$, $p < 0.01$). In a study of participants with controls matched for age and weight, Patt et al. [57], reported that the differences in the FMD of OSA and controls remained significant after adjusting for BMI, age and sex. Namtvedt et al. [58], reported that the association of OSA and endothelial dysfunction was independent of obesity and conventional risk factors. FMD correlated inversely with AHI, $r = -0.33$, $p = 0.004$ and in the multivariate analysis, AHI predicted FMD, $\beta = -0.29$, $p = 0.01$.

Obstructive sleep apnea and plaque burden by other modalities

Table 5 presents the results of studies evaluating the association between obstructive sleep apnea, atheroma and plaque burden. The oldest of the studies, Friedlander et al. [59] demonstrated that subjects with OSA have a higher prevalence of calcified carotid artery atheromas as compared to healthy, age-matched controls. In another study, Friedlander et al. [60] again reported increased prevalence of carotid atheromas in patients with OSA as compared to age-matched controls. They showed that type 2 diabetes was more prevalent in individuals with both OSA and calcified atheromas in the study ($p = 0.035$).

Kaynak et al. [21] reported a higher prevalence of plaque among severe OSA subjects compared to mild to moderate OSA or habitual snorers. In their study, RDI predicted plaque, $\beta = 0.04$, $p < 0.05$. A similar study, Wattanakit et al. [38], using a large cohort showed that the odds of carotid plaque increased with the quartiles of the hypoxemic index. Kylintireas et al. [61] demonstrated that there is an increased atheroma burden in OSA patients compared to controls matched for known cardiovascular risk factors ($p < 0.05$). This study suggested that OSA is an independent contributor to CVD risk. Sharma et al. [62] demonstrated that the frequency of non-calcified/mixed plaques is higher in patients with OSA than in non-OSA patients ($p < 0.0001$). In a recently published study, Kent et al. [63] demonstrated that plaque volume correlated significantly with AHI, spearman's $r = 0.443$, $p = 0.0019$ in an all male population. They concluded that the severity of OSA may predict occult coronary atherosclerosis in otherwise healthy overweight or obese subjects. Tan et al. [64], reported a similar relationship in their study of patients with angiographically proven coronary artery disease recruited for virtual-histology intravascular ultrasound (VH-IVUS) examination and home-based sleep study. In this study, moderate to severe OSA was independently associated with a larger total atheroma volume in the target coronary artery.

Discussion

In this comprehensive review of fifty-two studies there is strong evidence that patients with OSA carry a very high burden of CVD risk. While these patients have a high prevalence of risk factors such as obesity, hypertension (HTN) and type 2 diabetes mellitus, we have shown in this review that these patients have accelerated atherosclerosis and endothelial dysfunction independent of other factors.

The vast majority of studies demonstrate that markers of subclinical atherosclerosis are altered in patients with OSA. Seventeen of nineteen studies that used CIMT to assess for atherosclerosis showed a positive correlation between the degree of CIMT and OSA severity. The two main physiologic disturbances that occur in patients with OSA are obstructive episodes and hypoxemia. The repetitive desatuaration–reoxygenation leads to the generation of reactive oxygen radicals that enhance lipid perioxidation which damages the vascular endothelium [31]. Most studies in this review showed a correlation between obstruction (as demonstrated by the AHI or the RDI) and hypoxemia (mean nocturnal O_2 <92%, mean nadir O_2 saturation). Suzuki et al. [22] demonstrated that hypoxemia correlated with CIMT even after adjusting for AHI, suggesting that hypoxemia may be associated with atherosclerosis independent of obstruction.

It is important to note that one study reported no association between OSA and IMT. This was a large cross-sectional study, a subset of the Sleep Heart Study [38].In contrast to the other studies, subjects were recruited from the general community rather than just the referred patients to the sleep clinics. The limitation of this study was that most participants were middle-aged Caucasians who had only mild-moderate degree of SDB as the median RDI was 8.7 events per hour. The authors acknowledged that this might explain the different results seen. In contrast to this study, a recent study of a cohort of over 1600 subjects including men and women from the Heinz-Nixdorf Recall study, demonstrated AHI was associated with atherosclerosis after adjusting for conventional risk factors. [15]

The PWV, an important maker of arterial stiffness, was also found to be increased in patients with OSA. The only paper that did not show an association was a study that enrolled patients with newly diagnosed OSA who were relatively young (mean age 49 ± 10 y) and had mild OSA [37]. The authors recognized that this finding was not consistent with other studies and suggested that increased arterial stiffness may occur with prolonged duration and increased severity of OSA.

All fourteen studies that evaluated FMD showed a positive correlation between endothelial dysfunction and increasing severity of OSA. Interestingly, Yim-Yeh [51] showed that FMD (but not age or obesity) was associated with OSA status in patients who were younger than 50 y of age. These findings echo results from Chung et al. [55] who showed that FMD was associated with hypoxemia in younger (<60 y of age) but not in older patients. What this may indicate is that endothelial dysfunction testing may be useful in younger patients to look for early atherosclerotic changes.

CAC assessment is thought to be the cornerstone of atherosclerosis evaluation. Of the six studies reviewed, four studies showed that AHI independently correlated to the CAC score. While Kim et al. [17] and Kepez et al. [18] showed that CAC did not independently correlate with OSA after adjusting for BMI and age, respectively, Weinreich et al. [15] from the largest population-based study demonstrated significant associations after adjusting for relevant conventional risk factors independent of gender. CAC, can be described as a later step in the atherosclerosis pathway explaining why endothelial dysfunction is much more consistently noted in these patients.

Please cite this article in press as: Ali SS, et al., Systematic review on noninvasive assessment of subclinical cardiovascular disease in obstructive sleep apnea: new kid on the block!, Sleep Medicine Reviews (2014), http://dx.doi.org/10.1016/j.smrv.2014.01.004

From a pathophysiological stand point, endothelial dysfunction and chronic systematic inflammation, both integral drivers of atherosclerosis, result in accelerated development of atherosclerotic plaques in the vasculature in patients with OSA [65]. The alternating cycles of hypoxemia and reoxygenation that occur in OSA result in over-production of reactive oxidative species and a down-regulation of intrinsic anti-oxidant activity [66,67]. Increased oxidative stress is also thought to suppress the nitric oxide synthase pathway, leading to a blunting of the physiologic endothelial function. Similar dysfunction is noted in patients with sleep deprivation, which is frequently present in patients with OSA [68,69]. There is increasing evidence that the effects of OSA on the cardiovascular system are reversible with treatment [3]. The use of the continuous positive airway pressure to treat has been shown to reverse or slowed the progression of atherosclerosis [70]. A few studies in this review have shown a reversal of these processes with treatment of OSA with CPAP [49,53,57,71]. In addition, there is over expression and activation of inflammatory markers and immune cells in patients with OSA, through up-regulation of the nuclear factor kappa B (NF-KB) pathway [72]. This results in further activation of Reactive Oxygen Species (ROS) providing an alternative pathway for endothelial damage. A reliable marker of systemic inflammation is C-reactive protein (CRP), frequently elevated in patients with OSA and proportional to the degree of severity [73], has also been shown to respond to CPAP.

Our extensive review of all studies assessing relationship of OSA with subclinical CVD identified several important questions that require further explanation. The role of systemic inflammation in the association between OSA and subclinical atherosclerosis needs to be clarified in future studies. Assessing markers of systemic inflammation e.g., CRP in conjunction with noninvasive measurement of subclinical CVD would help elucidate this relationship in these patients. Another important consideration is that to date all the studies have been cross sectional and as a result causality cannot be determined. Existing data is limited by the lack of any prospective, population-based studies that establish a causal relationship between endothelial dysfunction and subclinical atherosclerosis with OSA. Several studies consisted of consecutive patients with OSA without a control group. Due to lack of prospective data, relationship between markers of subclinical CVD and morbidity and mortality data in this population could not be ascertained. Finally, our systematic review raises the question whether individuals with OSA ought to be screened for subclinical CVD, or whether certain subpopulations e.g., patients with long standing or severe disease etc, would demonstrate greater benefit from screening for subclinical CVD. Some studies also did not adjust for statin use which would help illustrate the role of preventive strategies in this population and whether presence of OSA should be an indication for lower treatment thresholds.

Conclusions

As the prevalence of OSA rises, preventing CVD in these patients becomes increasingly important. In this systematic review, we have shown that patients with OSA have an increased burden of endothelial dysfunction and atherosclerosis, independent of other CVD risk factors regardless of which noninvasive modality is employed. Targeting younger patients with severe OSA as assessed by the AHI or nocturnal hypoxemia might be higher yield than screening all patients with OSA though prospective data is required to assess which patients would benefit most from aggressive treatment for CVD prevention. Identification of subclinical CVD might be an additional indication for treating patients with OSA with CPAP, given that the severity of OSA is independently associated with worsening subclinical atherosclerosis.

Practice points

1) Patients with OSA have a high burden of CVD.
2) There is a significant association between OSA and markers of subclinical CVD.
3) Early detection of endothelial dysfunction and subclinical atherosclerosis in OSA patients may promote more aggressive therapeutic approaches.
4) Traditional risk stratification has relied on scoring systems such as Framingham risk score, however, OSA warrants consideration to be included as one of the risk factors in the algorithms for determination of future risk of CVD events.

Research agenda

1) The role of systemic inflammation in the association between OSA and subclinical atherosclerosis needs to be clarified in future studies.
2) There is a need of prospective, population-based studies that establish a causal relationship of endothelial dysfunction and subclinical atherosclerosis with OSA.
3) Future studies should use adequate control groups.
4) There is a need to establish relationship between markers of subclinical CVD and morbidity and mortality in OSA population.
5) Future studies need to adjust for statin use which would help illustrate the role of preventive strategies.

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