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CLINICAL REVIEW

Does obstructive sleep apnea cause endothelial dysfunction? A critical review of the literature

Camilla M. Hoyos [a, *], Kerri L. Melehan [a, b], Peter Y. Liu [c], Ronald R. Grunstein [a, b], Craig L. Phillips [a, d]

[a] NHMRC Centre for Integrated Research and Understanding of Sleep (CIRUS), Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia
[b] Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Sydney, Australia
[c] Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance, CA, USA
[d] Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, Sydney, Australia

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SUMMARY

Endothelial dysfunction is characterized by impaired endothelium-dependent vasodilatation and is an independent predictor of adverse cardiovascular consequences. The ease with which endothelial function can be assessed has led to it becoming a useful marker of cardiovascular diseases in research studies. Obstructive sleep apnea (OSA) has been independently associated with endothelial dysfunction which may explain the increased risk for cardiovascular and all-cause mortality in this population. One possible mechanism for the development of endothelial dysfunction in OSA is through the cyclical pattern of hypoxia and re-oxygenation. This creates a haemostatic imbalance in which nitric oxide bio-availability is reduced and pro-inflammatory and pro-thrombotic forces prevail. Furthermore the repair capacity of the endothelium to protect itself against this increased damage is diminished. All of these pathways contribute to vascular disease which ultimately gives rise to adverse cardiovascular consequences.

This review aims to provide a critical appraisal of the cross-sectional and interventional studies which have investigated micro- and macro-vascular endothelial dysfunction in OSA with emphasis on randomised controlled studies.

Introduction

Obstructive sleep apnea (OSA) is a common condition which is characterised by repetitive occlusion to the upper airway during sleep. The link between OSA and cardiovascular disease (CVD) is becoming increasingly recognised. Several prospective community-based studies have reported an increased risk for all-cause and cardiovascular mortality in men with untreated severe OSA independent of traditional CVD risk factors [1–3]. Increased incident stroke [4,5], coronary heart disease [6] and heart failure [6] have also been shown in individuals with severe OSA. The increased risk for incident stroke and coronary heart disease has been confirmed in two recent meta-analyses [7,8], with the latter analysis also confirming an overall increase in risk in severe OSA compared to no OSA for all-cause mortality [8]. Even though the data from these cohort studies offer credible evidence of a causal association between OSA and CVD, randomised controlled trials assessing the effectiveness of continuous positive airway pressure (CPAP) to reduce these hard endpoints are not yet available. The requirement for long-term follow up in hard endpoint trials has resulted in the majority of research focussing on intermediate markers of CVD risk.

Endothelial dysfunction represents one of the earliest indicators of atherosclerosis development and is a predictive marker of future cardiovascular events [9–11]. Endothelial dysfunction has in particular been proposed as a key mechanism linking OSA with adverse cardiovascular consequences. The association between OSA and endothelial dysfunction is thought to be directly caused by recurrent hypoxia and re-oxygenation (intermittent hypoxia) that occurs as a result of recurrent apneas during sleep [12]. Pathways in which chronic intermittent hypoxia may negatively affect endothelial function include reduced endothelial nitric oxide bioavailability [13–18], increased oxidative stress [19,20], systemic

Abbreviations: AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; EDV, endothelial-dependent vasodilatation; EIV, endothelial-independent vasodilatation; FMD, flow mediated dilatation; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; $TSaO_2 < 90\%$, sleep time spent with arterial oxyhaemoglobin saturation under 90%.

* Corresponding author. PO Box M77, Missenden Road, Camperdown, 2050 NSW, Australia. Tel.: +61 2 9114 0409; fax: +61 2 9114 0010.
E-mail address: camilla.hoyos@sydney.edu.au (C.M. Hoyos).

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inflammation [20] and sympathetic over-activity [21–23]. This impairment in endothelial function is accompanied by the promotion of circulating adhesion molecules [24,25], vascular damaging micro-particles [26,27] and hyper-coagulability [28,29]. Moreover the reduction of repair capacity through diminished numbers of circulating endothelial progenitor cells is another pathway in which endothelial dysfunction may occur in OSA [30]. Recently non alcoholic fatty liver disease has been suggested as a possible mechanism for the endothelial dysfunction in OSA [31]. This review will discuss in detail the current evidence of the causal association between OSA and endothelial dysfunction with emphasis on recent randomised controlled studies of CPAP treatment. Evidence will be presented separately for endothelial dysfunction in the micro- versus macro-vasculature. The underlying mechanisms linking OSA to endothelial dysfunction have been recently reviewed [32,33] and therefore will not be detailed here. A recent review has covered the non-invasive assessment of subclinical cardiovascular disease in OSA including studies investigating the association between OSA and endothelial function as measured by flow mediated-dilatation (FMD) [34]. The current review will provide more detailed information on the association between OSA and endothelial function. It will incorporate endothelial dependent and independent-vasodilation within both the macro and micro-vasculature. It will also include the results of CPAP intervention studies which were not described in the previous review.

Methods

An electronic search using PubMed database was conducted. We included literature published up to April 2014. The keywords utilised in the search were 'sleep apnea' with 'endothelial function' and then these terms combined with 'continuous positive airway pressure (CPAP)'. The search was limited to include full-text and English language publications. References of the selected studies were reviewed to identify additional relevant studies that were not found in the initial search. We specifically included all population-based studies ($n = 4$), case-controlled studies ($n = 40$) and interventional CPAP studies both observational ($n = 22$) and randomised ($n = 9$) which assessed a measurement of vascular reactivity. Cross-sectional studies that examined the effect of OSA on endothelial function with or without another condition (e.g., OSA + metabolic syndrome vs OSA − metabolic syndrome) were not included [31,35,36].

Endothelial dysfunction

The vascular endothelium is an active mono-layer of cells which line the internal vasculature. Endothelial cells produce nitric oxide, which protects vessels against atherosclerosis through the promotion of local vasodilatation and the inhibition of platelet aggregation, monocyte adhesion and vascular smooth muscle proliferation [37]. Endothelial dysfunction has therefore been implicated as one of the earliest detectable and possibly reversible abnormalities during atherosclerosis and the development of CVD. Endothelial dysfunction commonly refers directly to impaired endothelium-dependent vasodilatation (EDV) which is generally related to decreased nitric oxide bioavailability. In contrast, endothelium-independent vasodilatation (EIV) can also be assessed and generally represents further structural damage related to smooth muscle dysfunction in the arterial wall. Both EDV and EIV can be measured in either the macro- and micro-vasculature.

Endothelial function within the macro-vasculature can be assessed by several methods. FMD is the most common and measures change in the diameter of the brachial artery using non-invasive ultrasound, before and after ischaemia brought about by occluding blood flow to the arm. The subsequent reactive hyperaemia response, after the release of the cuff, stimulates endothelial nitric oxide release which causes vascular smooth muscle relaxation and dilatation [38,39]. Hand vein compliance is another technique which measures the maximum venodilation after the intra-venous administration of an endothelium-dependent vasodilator (e.g., bradykinin, or acetylcholine). EIV can be assessed using brachial artery ultrasound or hand vein compliance after the administration of an endothelium-independent vasodilator (e.g., nitroglycerin, a nitric oxide donor or sodium nitroprusside, a nitric oxide releasing drug). Studies have also implemented pulse wave analysis after inhaled salbutamol or sublingual nitroglycerin to assess endothelium dependent and independent responses respectively [40].

In contrast to the macro-vasculature, endothelial function within the micro-vasculature can be assessed by venous occlusion plethysmography of the forearm [41] or cutaneous blood flow by laser Doppler flowmetry [42]. Both methods can measure EDV by determining the response to an endothelium-dependent mediator including either reactive hyperaemia or the administration of acetylcholine either by direct infusion or by skin iontophoresis. EDV can also be measured using peripheral arterial tonometry, a non-invasive assessment that measures the changes of the pulse wave amplitude before and during reactive hyperaemia [37,39]. EIV can be examined using venous occlusion plethysmography or laser Doppler flowmetry to measure the response after the administration of nitro-glycerin.

Interestingly, several methods of macro- and micro-endothelial dysfunction measurement have been shown to be poorly correlated [43] which questions whether the predictive power of one is the same as the other. The Framingham Heart Study ($n = 1023$) reported that there was no association between assessments of macro- (FMD) and micro-vascular (peripheral arterial tonometry) function and that each measure had varying correlations with cardiovascular risk factors [44]. This suggests that the mechanisms which promote damage in the different vascular beds may vary between the macro- and micro-vasculature. Hence in this review we will differentiate between assessments of endothelial dysfunction in the macro- and micro-vascular beds.

Evidence linking OSA to macro-vascular endothelial dysfunction

Population and clinical cross-sectional studies

Nested-case controlled studies within population-based cohorts have reported OSA subjects to have impaired FMD compared to controls (apnea hypopnea index [AHI] < 5) [45,46]. The role of gender in these two studies was inconsistent. The first reported an association between male gender and FMD in uni-variate analyses but this was lost in multi-variate analyses and only AHI remained significant. On the other hand the second study reported female gender modulated the association between OSA and FMD. In all participants ($n = 193$) there was a significant association between increasing OSA severity and worsening FMD, however after stratification by sex the association remained only in women ($n = 111$) and therefore the study concluded that women may be more vulnerable to OSA related CVD than men [46]. In addition, the largest study to date, the Sleep Heart Health/Cardiovascular Health Study ($n = 1032$), showed dose-dependent associations between OSA severity (AHI and sleep time spent with arterial oxyhaemoglobin saturation under 90% [$TSaO_2 < 90\%$]) with a reduction of FMD after adjustment with age, gender and race [47]. This association however, was reduced and lost significance after body mass index was added into the model. Furthermore these findings were consistent in both men and women after stratification. In contrast the Framingham/Sleep Heart Health Study ($n = 682$) [48] showed no