Arterial Stiffness in Obstructive Sleep Apnea

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INTRODUCTION

Obstructive sleep apnea (OSA)—also referred to as obstructive sleep apnea-hypopnea—is a sleep disorder that involves cessation or significant decrease in airflow in the presence of breathing effort. It is the most common type of sleep-disordered breathing and characterized by recurrent episodes of upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturations and arousals from sleep. OSA patients frequently have several risk factors for cardiovascular disease development, such as obesity, hypertension, and diabetes. 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 [1,2]. OSA has been linked to the development of atherosclerosis. In a study of 36 subjects [3] with OSA and 16 matched controls, all without comorbidities, subjects with moderate-to-severe OSA were found to have increased carotid intima-media thickness, increased pulse wave velocity, and increased carotid diameter, all of which are consistent with atherosclerosis. Abnormalities in these parameters were predicted by either the apnea-/hypopnea index or the degree of nocturnal desaturation.

DEFINITION

Arterial stiffness is an early marker of atherosclerosis, as it sets in at an earlier stage than a change in intima-media thickness (IMT) in patients with vascular disease. It increases chronically with age, with the development of chronic conditions (e.g., hypertension), and with the presence of vascular risk factors (e.g., smoking) [4,5]. Arterial stiffness determines how quickly the pulse wave generated by the contracting heart travels to the periphery and is reflected from there. 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 may depend 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 [6,7]. 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 [8-11]. The way in which arterial stiffness leads to heart failure is depicted in Figure (1).

Arterial stiffness can be measured noninvasively by applanation tonometry, echotracking, and Doppler ultrasound. These techniques have very good reproducibility and have been widely applied [12]. 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 [13] and the European Society of Hypertension and the European Society of Cardiology [14] (Figure 2). PWV is inversely related to arterial distensibility [13] 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 [14,12].

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 in the diseased populations. Measurements of arterial stiffness are believed to reflect global arterial endothelial function [15,16]. A strong correlation between arterial stiffness and the development of atherosclerosis at various sites in the arterial tree has been noted [17-19].
These observations have prompted researchers investigating OSA-cardiovascular interactions to study the role of OSA in increasing arterial stiffness.

**PATHOPHYSIOLOGY**

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 patients with OSA [20,21]. Intermittent hypoxia is associated with increased production of reactive oxygen species and, therefore, increases oxidative stress [21,22]. Increased inflammation may play a role in the pathogenesis of OSA, increasing arterial stiffness and contributing to the early atherosclerosis found in OSA patients. Several reports consistently showed that OSA is independently associated with endothelial dysfunction [23,24] and that treatment of OSA with CPAP also significantly improved endothelial function [25,26]. Figure (3) shows a summary of the multiple causes and locations of arterial stiffness [27].

Recent studies have shown that patients with OSA have elevated serum levels of tumor necrosis factor-α, IL-6, IL-8, C-reactive protein, and adhesion molecules [e.g., pentraxin-PTX-3] which are markers of systemic inflammation with proatherogenic properties [28]. In addition, Ciccone et al. found a correlation between these inflammatory markers and carotid intima-media thickness (cIMT) in a sample of OSA patients [29]. In particular, hsCRP, TNF-α, and PTX-3 were independent predictors of cIMT values in this study. Pathophysiologically, it is widely accepted that the role of both OSA and hypertension (HTN) on the progression of endothelial damage is mediated by inflammation. A relationship could be demonstrated between the presence of OSA/HTN and increased values of inflammatory markers such as interleukin 6 and PTX-3 [30].

A systematic analysis of endothelial dysfunction in obese patients with and without OSA was performed. Jelic et al. [31], measured brachial artery flow-mediated dilation, an indirect marker of endothelial nitric oxide (NO)-mediated reactivity, in 71 subjects with a BMI ranging from normal to obese who underwent polysomnography. Proteins that regulate basal NO production and inflammation and markers of oxidative stress were quantified in venous endothelial cells. The investigators reported that expression of endothelial NO synthase (eNOS), phosphorylated eNOS, and flow-mediated dilation were significantly lower whereas expression of nitrotyrosine (a marker of oxidative stress) was significantly higher in patients with OSA than in OSA-free subjects, regardless of central adiposity. Expression of nuclear factor kB, a marker of inflammation, was greater in obese patients with OSA than in obese OSA-free subjects.

Taken together, these findings suggest that OSA has an independent effect on endothelial dysfunction, surrogate markers of atherosclerosis, and arterial stiffness in obesity and the metabolic syndrome.

**Figure 1** Schematic outlining proposed pathophysiological components of OSA and cardiovascular disease mechanisms.

**Figure 2** Schematic outlining the pulse waves of the carotid and the femoral artery. Pulse wave velocity is determined by the distance (D) divided by the time (t).

**Figure 3** Vascular changes in arterial stiffness.
Dates of arterial stiffness in obstructive sleep apnea

Namtvret et al., reported a positive association between severity of OSA and impaired endothelial function, independent of obesity and other cardiovascular risk factors [32]. Regarding surrogate markers of atherosclerosis and arterial stiffness, a previous investigation found that patients with both metabolic syndrome and OSA had higher values of pulse wave velocity. The apnea-hypopnea index was independently associated with impairments in pulse wave velocity (PWV) [33]. Several studies evaluated central arterial stiffness by measuring cfPWV. Tsiousif et al.[34], found a higher cfPWV in OSA patients compared to controls. Drager et al.[35], noted that although cfPWV was higher in OSA patients than in controls, it was even more elevated in OSA patients with hypertension. Another study by the same group compared the cfPWV of non-OSA controls with that of a mild-to-moderate OSA group and with a severe OSA group [36]. 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 patients with severe OSA and non-OSA participants. A further study by Drager et al.[37], examined the effect of the presence of OSA on arterial stiffness in patients with metabolic syndrome. 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 AIH [37].

Protogerou et al.[38], determined carotid intima-media thickness (IMT), carotid diameter and plaques, carotid-femoral pulse wave velocity (cfPWV), central augmentation index (AI), and central blood pressures in mild, moderate and severe OSA patients. It was found that the severity of OSAS, expressed as respiratory disturbance index (RDI), was a predictor of two of the most commonly used and well-established markers of cardiovascular risk: carotid IMT and carotid-femoral PWV. This relation was independent of age and cardiovascular risk factors. As far as the other parameters are concerned, e.g. carotid plaques, carotid diameter, AI, central blood pressures, they were not significantly associated with the severity of OSAS as expressed by RDI or other nocturnal hypoxaemias. Several studies used ultra sonographic methods to evaluate arterial stiffness in OSA patients. Tanriverdi et al.[39], 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. Kasikcioglu et al.[40], found decreased aortic distensibility and increased stiffness index in OSA patients compared to controls. Table (1) lists the various studies investigating the association between OSA and arterial stiffness.

Effects of continuous positive airway pressure treatment on arterial stiffness

The effects of CPAP therapy on the early signs of atherosclerosis are multi factorial and associated with improvements in inflammation and sympathetic activity. Kohler et al.[41], randomized 102 male OSA patients to 4 weeks of therapeutic or sub therapeutic effects of continuous positive airway pressure (CPAP). They noted a decrease in augmentation index (Aix) in the therapeutic group compared to a slight, non-significant increase in the sub therapeutic group. They also tested the sensitivity of the baroreflex, 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.[42], 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, compared to the control group.

### Table 1: Studies investigating the association between OSA and arterial stiffness.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Compared groups</th>
<th>Arterial stiffness – analyzed parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drager et al. [36]</td>
<td>OSA: sleep clinic control: hospital staff</td>
<td>severe OSA vs. mild/moderate OSA vs. control</td>
<td>c-f PWV</td>
<td>severe OSA&gt; mild/moderate OSA &gt; control</td>
</tr>
<tr>
<td>Drager et al. [35]</td>
<td>OSA: sleep clinic control: staff/relatives</td>
<td>OSA with htn vs. OSA without htn</td>
<td>c-f PWV</td>
<td>OSA with htn &gt; OSA without htn</td>
</tr>
<tr>
<td>Drager et al. [37]</td>
<td>heart institute</td>
<td>MS with OSA vs. MS without OSA</td>
<td>c-f PWV</td>
<td>MS with OSA &gt; MS without OSA</td>
</tr>
<tr>
<td>Kasikcioglu et al. [40]</td>
<td>sleep clinic</td>
<td>OSA vs. control</td>
<td>aortic stiffness index, aortic distensibility</td>
<td>OSA &gt; control OSA &lt; control</td>
</tr>
<tr>
<td>Kohler et al. [41]</td>
<td>OSA: sleep clinic control: GP database</td>
<td>OSA vs. control</td>
<td>AIX</td>
<td>OSA &lt; control</td>
</tr>
<tr>
<td>Protogerou et al. [38]</td>
<td>sleep clinic</td>
<td>very severe OSA (RDI&gt;50/h) vs. severe OSA (RDI 31-50/h) vs. mild OSA (RDI 10-30/h)</td>
<td>c-f PWV</td>
<td>No group differences</td>
</tr>
<tr>
<td>Tanriverdi et al. [39]</td>
<td>sleep clinic</td>
<td>OSA vs. control</td>
<td>aortic stiffness index, aortic distensibility</td>
<td>OSA &gt; control OSA &lt; control</td>
</tr>
<tr>
<td>Tsiousif et al. [34]</td>
<td>htn with OSA symptoms</td>
<td>htn with OSA vs. htn without OSA</td>
<td>c-f PWV</td>
<td>htn with OSA &gt; htn without OSA</td>
</tr>
</tbody>
</table>

**Abbreviations:** OSA: Obstructive Sleep Apnea; htn: Hypertension; GP: General Practitioner; MS: Metabolic Syndrome; AIX: Augmentation Index; c-fPWV: Carotid-Femoral Pulse Wave Velocity; RDI: Respiratory Disturbance Index.
Table 2: Continuous positive airway pressure treatment and arterial stiffness.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study group</th>
<th>Post treatment follow-up</th>
<th>Arterial Stiffness Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drager et al. [42]</td>
<td>OSA randomized to CPAP or control</td>
<td>4 months</td>
<td>c-f PWV</td>
<td>CPAP: decreased by 1.1 +/- 0.6 m/s. control: no change.</td>
</tr>
<tr>
<td>Kato et al. [23]</td>
<td>moderate vs. severe OSA</td>
<td>1 month</td>
<td>c-a VI</td>
<td>decreased at 1 mo</td>
</tr>
<tr>
<td>Kohler et al. [41]</td>
<td>moderate to severe OSA randomized to therapeutic vs. sub-therapeutic CPAP</td>
<td>1 month</td>
<td>AIX</td>
<td>decreased on therapeutic CPAP. No change on sub-therapeutic CPAP.</td>
</tr>
<tr>
<td>Ciccone et al. [44]</td>
<td>OSA randomized to CPAP therapy started less and more than 3 months before vs. no CPAP therapy</td>
<td>3 months</td>
<td>FMD of the brachial artery</td>
<td>significant reversibility of FMD in patients treated with CPAP therapy for more than 3 months</td>
</tr>
</tbody>
</table>

Abbreviations: c-f PWV: Carotid-Femoral Pulse Wave Velocity; c-a VI: Carotid Artery Vasodilation Index; AIX: Augmentation Index; FMD: Flow Mediated Dilation

C-reactive protein, and catecholamines, whereas changes in the non-CPAP control group were not significant [43]. Interestingly, there were parallel decreases in blood pressure with therapeutic CPAP, which may have accounted for the improvement in arterial stiffness. Furthermore, effective treatment of OSA with CPAP significantly increased flow-mediated dilation and expression of eNOS and phosphorylated eNOS, whereas expression of nitrotyrosine and nuclear factor kB significantly decreased [31]. The study of Ciccone et al. showed the effect of CPAP on endothelial function. A non-invasive method to assess endothelial function is flow-mediated vasodilation. Data obtained from this study demonstrate the significant reversibility of flow-mediated vasodilation in patients treated with CPAP for more than 3 months [44]. Finally, in a preliminary single-arm study, Oyama et al.[45], reported that CPAP therapy improved endothelial dysfunction and decreased markers of oxidative stress in patients with the metabolic syndrome and OSA. The results of the studies that examined the influence of CPAP on arterial stiffness are given in Table (2).

CONCLUSION

Arterial stiffness is an established independent risk factor for cardiovascular disease. Many of the risk factors and pathophysiological mechanisms linking arterial stiffness to cardiovascular disease (including obesity and hypertension) are present in OSA patients. Most of the cross-sectional studies examining arterial stiffness in OSA have attempted to control for these known confounders. To the best of our knowledge, arterial stiffness is increased in OSA patients compared with non-OSA control patients. The extent 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. Although there are relatively few interventional studies that have incorporated a control group, there are two randomized trials showing short-term improvements in arterial stiffness with CPAP treatment. 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.

REFERENCES

13. Hayward CS, Kraikly M, Webb CM, Collins P. Assessment of endothelial...


