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Review

Relationship between cardio-ankle vascular index and obstructive sleep apnea

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Patients with obstructive sleep apnea (OSA) are susceptible to developing atherosclerosis. Consequently, such patients are at a high risk of developing cardiovascular diseases, leading to poor prognosis. Many physiological parameters have been previously used to predict the development of atherosclerosis. One such parameter, the cardio-ankle vascular index (CAVI), a measure of arterial stiffness, has garnered much attention as it can also predict the degree of atherosclerosis. The CAVI can be calculated based on noninvasive measurements, and is less susceptible to blood pressure variations at the time of measurement. Therefore, the CAVI can assess changes in arterial stiffness and the risk of developing atherosclerosis independent of blood pressure changes. Continuous positive airway pressure (CPAP) is a standard therapy for OSA and can suppress the issue significantly. Several studies have shown that CPAP treatment for OSA could also reduce the CAVI. In this review, we discuss the relationship between OSA and arterial stiffness, primarily focusing on the CAVI. Furthermore, we propose future perspectives for the CAVI and OSA.

Keywords

Arterial stiffness; atherosclerosis; cardio-ankle vascular index (CAVI); continuous positive airway pressure (CPAP); obstructive sleep apnea (OSA)

1. Introduction

Globally, obstructive sleep apnea (OSA) is a common disease. It is caused by repetitive obstruction of the upper airway while sleeping. Moreover, during sleep onset, there is a reduction in the upper airway dilator muscle tone, resulting in an anatomically narrow upper airway. Physiological release of upper airway obstruction is usually accompanied by arousal and snoring that facilitate the resumption of breathing. These repetitive respiratory events lead to frequent episodes of intermittent hypoxia and fragmented sleep. The frequency of such repetitive respiratory events, including partial and complete collapse of the upper airway (i.e., hypopneas and apneas, respectively), generally determines the severity of OSA, which is quantified by the apnea-hypopnea index (AHI). OSA with an AHI $\geq$ 5 affects 20-30% and 10-15% of the general male and female populations, respectively (Peppard et al., 2013; Young et al., 2009). Continuous positive airway pressure (CPAP) therapy, the gold-standard therapy for OSA, can prevent obstructive respiratory events while sleeping.

Cross-sectional studies have suggested a relationship between the presence of OSA and cardiovascular diseases. Moreover, a direct association between the AHI and cardiovascular diseases was shown, even after adjusting for potential confounding factors. Although the latter implies a causal link between OSA and cardiovascular diseases, evidenced by numerous mechanistic studies, it is still unclear whether OSA really causes cardiovascular diseases. Recently, several longitudinal studies have shown that the presence of OSA, particularly in its severe baseline form, is associated with an increased risk of cardiovascular diseases. It can be argued that the increased risk of cardiovascular diseases in OSA patients is due to coexisting obesity, metabolic syndrome, hypertension, or diabetes mellitus. In some longitudinal studies, adjustments for such confounders resulted in the relationship between OSA and cardiovascular diseases to be no longer significant (Gami et al., 2007; Gottlieb et al., 2010; O'Connor et al., 2009). Still, numerous studies have demonstrated the association between OSA and early signs of arteriosclerosis and/or atherosclerosis as a surrogate of cardiovascular diseases. In addition, results from randomized controlled trials suggest that the elimination of OSA by CPAP also eliminates or ameliorates arteriosclerosis/atherosclerosis (Drager et al., 2007).

In this article, we first review and summarize recently developed noninvasive technologies to detect arteriosclerosis/atherosclerosis, primarily focusing on arterial stiffness parameters. These might indicate systemic atherosclerosis and could, consequently, act as a comprehensive indicator of cardiovascular

disease risk. We continue with a specific discussion on the cardio-ankle vascular index (CAVI). This index is a measure of arterial stiffness, generated through noninvasive measurements by simple procedures. We then summarize the relationship between OSA and arteriosclerosis/atherosclerosis while focusing on CAVI data from patients with OSA.

2. Techniques to Detect Arteriosclerosis/Atherosclerosis

Endothelial dysfunction is one of the first symptoms of atherosclerosis. Noninvasive techniques to detect endothelial dysfunction include measurement of flow-mediated vasodilation (FMD) by ultrasonography and evaluation of forearm blood flow changes during reactive hyperemia using plethysmography. The latter technique is more practical and easier to perform, but is not fully validated (Higashi and Yoshizumi, 2003). In contrast, it is difficult to measure the diameter of vessels using the former technique. Nevertheless, a recent meta-analysis on the use of FMD to assess endothelial function found endothelial dysfunction to be a significant predictor of future cardiovascular events (Matsuzawa et al., 2015).

Arteries stiffen as atherosclerosis develops. However, the association between endothelial dysfunction and arterial stiffness is controversial and mild at best. Arterial stiffness is dictated by the structural (e.g., elastin/collagen) and functional (e.g., endothelial function or vascular smooth muscle tone, which can be modulated by the autonomic nervous system) components of the arterial wall. Since arterial stiffness affects blood pressure, blood flow, and the arterial diameter, it may not be the simplest indicator of structural and functional changes in the artery, but it can act as a comprehensive marker for developing arteriosclerosis or cardiovascular diseases (Mattace-Raso et al., 2006; Oliver and Webb, 2003). Indeed, increased arterial stiffness was observed in patients with several conditions known to have a pathophysiological link to cardiovascular diseases.

The most common and well-validated technique to assess arterial stiffness is pulse wave velocity (PWV). PWV is based on the concept that the pressure wave propagates faster in a stiffer artery than a softer artery. Increased stiffness results in an earlier reflection of the wave, and a shorter interval between consecutive pressure increases (Fig. 1). These lead to increased augmenting pressure (AP), which can also be a measure of stiffness. AP is often expressed as a ratio with pulse pressure (PP), a ratio termed the augmentation index (AIx). Although at least one meta-analysis suggested that AIx might be an independent predictor of cardiovascular diseases (Vlachopoulos et al., 2010b), the significance of AP and AIx as predictors for cardiovascular events remains controversial.

PWV can be measured using several techniques. Devices that use a probe, a transducer, or a tonometer record the pulse wave, and devices that use cuffs placed around the limbs record the pulse wave by the oscillometric method. As PWV can be measured noninvasively, it has been clinically used for several decades. In particular, the PWV measured between the carotid and femoral arteries (carotid-femoral [cf] PWV) is well-validated and acts as a surrogate marker of mortality in various diseases. For instance, in 2,232 participants from the Framingham cohort, it was found that the higher the cfPWV, the greater was the risk for a cardiovascular event (Mitchell et al., 2010). In addition, a meta-analysis of more than 15,000 patients demonstrated that higher cfPWV was associated with worse clinical outcomes (Vlachopoulos et al., 2010a). When measuring brachial-ankle [ba] PWV, the cuffs are placed around the limbs so that an oscillometer can record the arrival of the pulse waves. Generally speaking, baPWV can be measured more easily than cfPWV. As to the segments of the arteries, cfPWV represents the stiffness of the aorta, while baPWV represents the stiffness of the arteries in the extremities and that of the aorta (Yamashina et al., 2002). However, the reproducibility of PWV measurements (cfPWV and baPWV) is a problem, because cfPWV depends highly on the observer's skill, and both cfPWV and baPWV depend on the blood pressure at the time of measurement. Thus, arterial stiffness parameters that are highly reproducible and independent of blood pressure at the time of measurement were sought for. Blood pressure at the time of measurement affects all arterial stiffness parameters except β. About 15 years ago, the CAVI, a novel blood pressure-independent stiffness index that links the stiffness parameter β with PWV, was introduced to clinical use (Shirai et al., 2006). The CAVI will be further discussed later.

Progression of arteriosclerosis/atherosclerosis leads to the development of visually detectable morphological changes, including arterial wall thickening, plaque formation, and calcification. An intima-media thickening and plaque formation can be detected by ultrasonography. As such, the carotid arteries intima-media complex thickening is often used as an indicator of early-stage arteriosclerosis/atherosclerosis. The carotid intima-media thickness (IMT) has been widely used to predict the risk of future cardiovascular events, independently of other traditional risk factors. In a meta-analysis that included 14 studies, the carotid IMT was a predictor for myocardial infarction and stroke in asymptomatic individuals (Den Ruijter et al., 2012). Computed tomography (CT) can be used to detect and quantify aortic and coronary artery calcification. Coronary artery calcification is known to be a risk factor for cardiovascular events, including myocardial infarction (Taylor et al., 2001). Atherosclerotic plaques in the carotid arteries and the aorta can also be viewed using high-resolution magnetic resonance imaging (MRI). In fact, in an interventional trial, changes in carotid and aortic atherosclerotic plaque burden due to statins were identified by high-resolution MRI (Raggi et al., 2005; Underhill et al., 2008). Viewing coronary plaques by MRI is more challenging. For a review on the various emerging techniques to estimate atherosclerosis severity, see Noguchi et al. (2013).

In summary, the manifestations or consequences of the arteriosclerotic process can be measured in both elastic or muscular arteries in cross-section and longitudinally (Fig. 2).

3. The CAVI, a novel blood pressure-independent index as a measure of arterial stiffness

The CAVI is a measure based on a technique similar to that used to measure baPWV. Placing the cuffs around the limbs and recording the pulse wave by an oscillometer is simple and independent of the observer's skill. More specifically, the heart-ankle PWV (haPWV), rather than the baPWV, is used to measure the

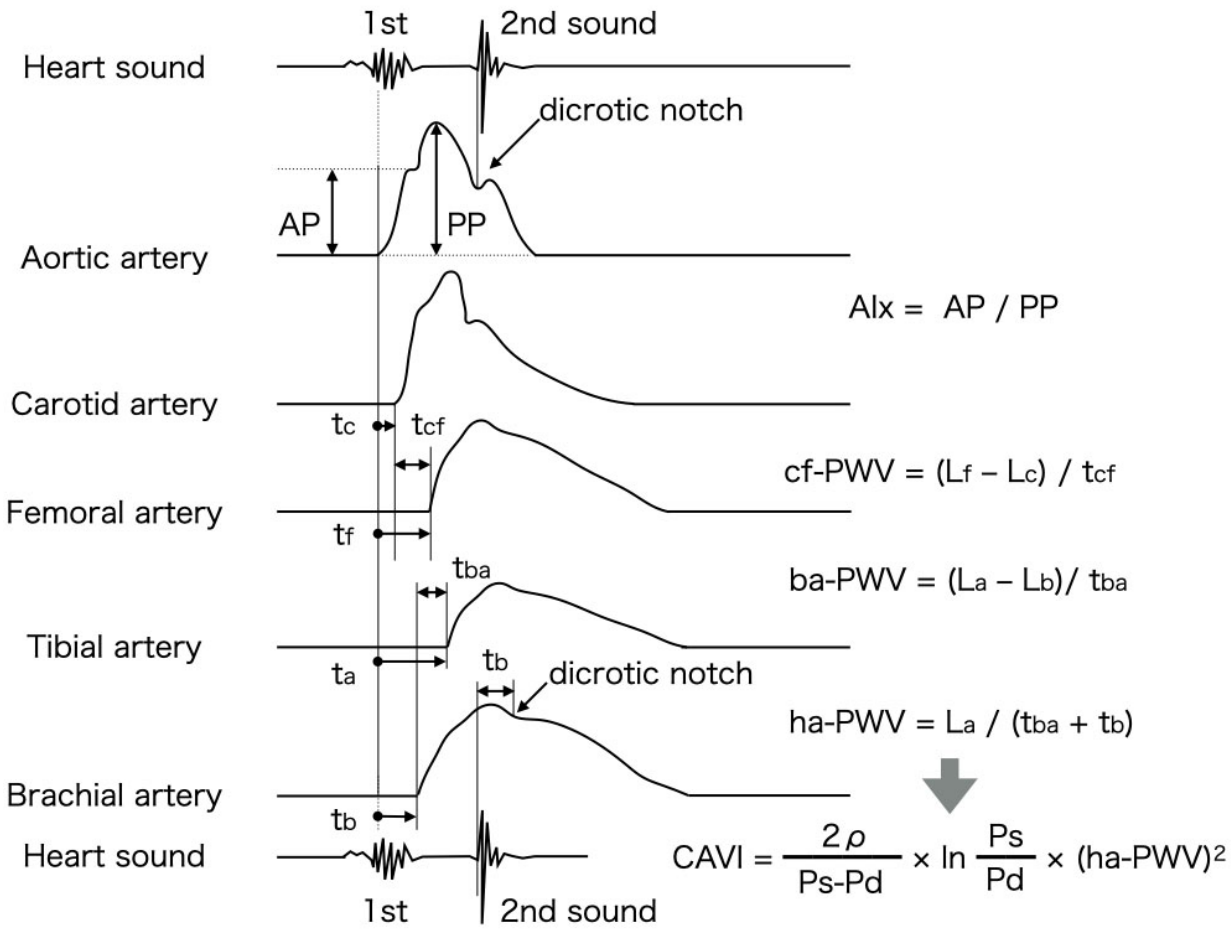

Fig. 1. Arterial pressure waveforms at each point are shown on the same timeline. Aortic pressure starts rising at the time of the first heart sound and has two peaks. The first peak is called augmenting pressure (AP), and the second peak is called pulse pressure (PP). The augmentation index (AIx) is calculated as AP divided by PP. Since the dicrotic notch in the aorta coincides with the second heart sound, the time between the dicrotic notch at the brachial artery and the second heart sound indicates the propagation time from the heart to the brachial artery. Pulse wave velocity (PWV) can be calculated using the propagation time between two points if the distance between them is known. Lf is the distance from the upper margin of the sternum to the navel, and from there to the groin. Lc is the distance from the upper margin of the sternum to the neck. La is the distance from the upper margin of the sternum to the navel, and from there to the ankle. Lb is the distance from the upper margin of the sternum to the elbow. The cardio-ankle vascular index (CAVI) is calculated using the heart-ankle PWV (haPWV). Ps and Pd are the systolic and diastolic blood pressure values, respectively, and ρ is the blood density.

values needed to calculate the CAVI. haPWV is calculated by dividing the distance from the aortic origin to the ankle by the time it takes for a pulse wave to propagate over this distance (Fig. 1). Besides, the CAVI is less dependent on blood pressure at the time of measurement because it is calculated using systolic and diastolic blood pressures measured simultaneously. In this section, we will discuss several aspects related to the CAVI.

First, since arterial stiffening is part of the aging process, arterial stiffness and its related parameters are predominantly affected by age. This also applies to arterial stiffness expressed by the CAVI. In healthy subjects, the CAVI is reported to be higher in the elderly than in younger subjects. Moreover, the CAVI was reported to increase linearly with age in individuals aged 20 to 70 years, at an increasing rate of approximately 0.5 units per decade (Shirai et al., 2011a). Besides, the CAVI was reported to be 0.2 units higher in men than in women of the same age groups.

Second, lifestyle habits also have an effect. Smoking is one of the leading causes of arteriosclerosis/atherosclerosis progression. In fact, the CAVI was shown to be higher in smokers than in non-smokers (Kubozono et al., 2007). Furthermore, the CAVI in smokers has improved after complete cessation of smoking (Noike et al., 2010). Warm footbath was reported to reduce systemic arterial stiffness in women, as indicated by the CAVI (Hu et al., 2012). The authors speculated that this reduction was the effect of the increased nitric oxide release on the vascular smooth muscle.

The effect of bodyweight reduction on the CAVI is controversial. A calorie restriction diet and exercise therapy resulted in a CAVI decrease, along with a decrease in the visceral fat area, as viewed on CT images (Nagayama et al., 2013). After a weight decrease, metabolic dysfunctions, including dyslipidemia and hyperglycemia, tend to improve. However, reduction in the visceral fat area, as viewed on CT images, was the only parameter associated with a decrease in the CAVI. Therefore, the authors speculated that the visceral fat area is associated with arterial

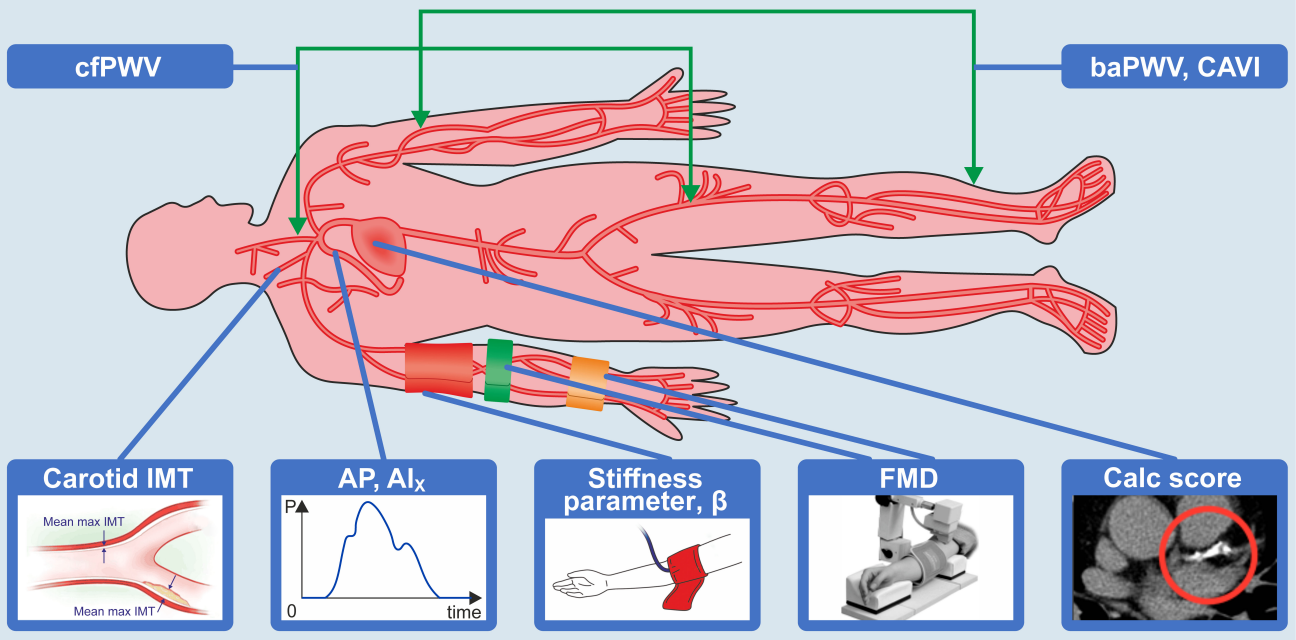

Fig. 2. Using probes or a tonometer, the pulse wave velocity (PWV) can be measured between the carotid and femoral arteries (cfPWV) or brachial and ankle arteries (baPWV). The cardio-ankle vascular index (CAVI) can be obtained from blood pressure and heart-ankle PWV (haPWV) measurements. The carotid intima-media thickness (IMT) is measured using ultrasonography. The augmenting pressure (AP) and the augmentation index (AIx) are derived from the central arterial waveforms. The arterial stiffness parameter β is calculated using systolic and diastolic pressure values and the variation in the aortic diameter. Flow-mediated vasodilation (FMD) is a technique that uses ultrasonography and plethysmography to analyze changes in the forearm blood flow. Coronary artery calcification is assessed by computed tomography (CT).

stiffness, and thus, a decrease in the visceral fat area might contribute to preventing atherosclerosis progression. A three-month weight-loss program improved both metabolic dysfunction and the CAVI in obese patients. These changes might be due to increased adiponectin production, which promotes improvement in endothelial function. Such an improvement leads to a lower CAVI (Satoh et al., 2008). However, in healthy non-obese and obese subjects without metabolic disorders, the CAVI was negatively associated with body mass index (BMI) (Nagayama et al., 2017). The authors suggested that systemic accumulation of adipose tissue *per se* might lead to a linear decrease of the CAVI.

Third, numerous reports have shown that the CAVI is linked to various diseases that play an essential role in arteriosclerosis/atherosclerosis pathogenesis. It is also linked to other diseases, including cardiovascular diseases (Shirai et al., 2011a). Hypertension, dyslipidemia, diabetes mellitus, and metabolic syndrome were all shown to be associated with a higher CAVI (Shirai et al., 2011a). Furthermore, higher CAVI indicates impaired kidney function, the degree of atherosclerosis/arteriosclerosis, and cardiovascular disease risk in patients with renal insufficiency (Kubozono et al., 2009). Several studies have shown that kidney function markers such as estimated glomerular filtration rate and serum cystatin C level are associated with the CAVI (Kubozono et al., 2009; Nakamura et al., 2009). Moreover, it was shown that the CAVI is higher in hemodialysis patients than in healthy controls (Ueyama et al., 2009). Vascular impairment in chronic kidney disease, which can be caused by chronic inflammation and uremic toxins, plays an important role in the development of cardiac dysfunction (Zanoli et al., 2019). Consequently, high CAVI might also indicate a risk of developing cardiovascular diseases such as angina pectoris, myocardial infarction, and stroke. The severity of coronary artery disease, assessed by the number of stenosed vessels on angiography, was related to a higher CAVI (Nakamura et al., 2008). It was also shown that patients with cerebral infarction have a higher CAVI than healthy controls. Moreover, the CAVI clearly relates to the carotid ultrasonographic plaque score (Suzuki et al., 2013).

Lastly, medical treatment for several diseases, including diabetes mellitus, hypertension, and hyperlipidemia, can decrease the CAVI. Blood glucose control by either insulin or oral hypoglycemic agents decreases the CAVI (Nagayama et al., 2010; Ohira et al., 2011). Since CAVI improvement is associated with improved postprandial hyperglycemia, reduced insulin resistance might contribute to a reduction in arterial stiffness. Blood pressure control by anti-hypertensive agents, particularly angiotensin II receptor antagonists, was found to decrease the CAVI (Kinouchi et al., 2010). Another study, in which the CAVI was assessed in 12 healthy male volunteers, demonstrated that the systolic blood pressure and the baPWV value were lowered by both β1- and α1-adrenoceptor blockers, but only the α1-adrenoceptor blocker decreased the CAVI (Shirai et al., 2011b). Lipid-lowering agents used for lipid profile control, including statin and non-statin drugs, also decrease the CAVI (Miyashita et al., 2009). It is possible that improving the lipid profile by such drugs reduces the CAVI by suppressing oxidative stress (Miyashita et al., 2009).

As discussed above, the CAVI can be used as an indicator of some conditions, including atherosclerotic diseases. However, it is still unclear whether the CAVI is a prognostic indicator in pa-

tients with and without atherosclerotic diseases. Analysis of the follow-up data of 194 hemodialysis patients found that neither the CAVI nor baPWV could predict mortality (Kato et al., 2010). In a recent study (Kim et al., 2019), the association between several arterial stiffness parameters and cardiovascular disease incidence and all-cause mortality was examined in older adults aged 66-90 years. The study found no association between the CAVI and cardiovascular events or all-cause mortality. The prognostic value of the CAVI seems to be limited in older adults. In a meta-analysis (Matsushita et al., 2019) of nine prospective and 17 cross-sectional studies, a modest association between the CAVI and the risk of cardiovascular diseases was found. The author mentioned as a limitation the fact that most of the included studies were conducted in Asia and that relatively high-risk patients for cardiovascular diseases were included. Although many studies have shown that cf-PWV has a prognostic value (Vlachopoulos et al., 2010a), blood pressure at the time of measurement acts as a confounder. Thus, studies that assess whether the CAVI *per se* is associated with clinical outcomes are warranted.

4. Relationship between OSA and Arteriosclerosis/Atherosclerosis

4.1 Pathogenesis, definition, and diagnosis of OSA

In the general population, obesity is a significant risk factor for OSA, probably because of the associated neck thickening and narrowing of the pharynx lumen by fat pads adjacent to it. In fact, the pharynx is generally narrowed in patients with OSA (Nichols et al., 1988). The loss of pharyngeal dilator muscle tone at sleep onset causes the pharynx to completely or partially collapse, leading to obstructive apnea and hypopnea, respectively.

Apnea is defined as an absence of tidal volume for $\geq$ 10 s while hypopnea is a reduction in tidal volume by $>$ 50% (but not completely absent) for $\geq$ 10 s, accompanied by a 3 to 4% decrease in oxyhemoglobin saturation or terminated by arousal from sleep (Berry et al., 2015). The respiratory effort generated to overcome the narrowed upper airway in an apnea or hypopnea condition causes the rib cage and abdomen to distort and move out of phase. The standard OSA diagnosis method is by attended overnight polysomnography in a sleep laboratory, during which sleep architecture, cardiac rhythm, arterial oxyhemoglobin saturation, airflow, and respiratory movements of the rib cage and abdomen are recorded continuously (Berry et al., 2015). OSA is generally diagnosed based on the presence of $\geq$ 5 apnea or hypopnea events per hour of sleep (i.e., AHI $\geq$ 5), accompanied by symptoms such as associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea or associated medical or psychiatric disorder (hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder). Alternatively, an AHI $\geq$ 15 satisfies the criteria for diagnosis, even in the absence of associated symptoms or disorders (Sateia, 2014). In general, OSA is classified as mild for AHI of 5-15, moderate for AHI of 15-30, and severe for AHI $>$ 30. These thresholds, however, are arbitrary.

4.2 Mechanisms linking OSA and arteriosclerosis/atherosclerosis

Repetitive intermittent hypoxia and post-apneic reoxygenation, in association with OSA, lead to increased oxidative stress and the production of reactive oxygen species (ROS) (Lavie, 2003). ROS decrease the bioavailability of nitric oxide, which has antiatherogenic properties, including inhibition of platelet aggregation and adhesion, smooth muscle cell proliferation, leucocyte adhesion, and vascular permeability. In addition, decreased bioavailability of nitric oxide results in impairment of the vascular endothelium vasodilatory effects (Moncada and Higgs, 1993). Hypoxia and production of ROS increase the release of inflammatory mediators such as serum amyloid A and C-reactive protein (Punjabi and Beamer, 2007; Svatikova et al., 2003) by activated transcription factors, leading to exacerbated endothelial dysfunction (Garvey et al., 2009). Endothelial dysfunction leads to the production of various factors that regulate cellular adhesion, smooth muscle cell migration and proliferation, and focal inflammation (Libby et al., 2002; Ross, 1999). Endothelial cells prevent thrombosis by numerous mechanisms, including inhibition of platelet aggregation and the release of fibrinolytic mediators. Fibrinogen concentration and plasminogen activator inhibitor type-1 level were shown to be elevated in patients with OSA (von Känel et al., 2006). Thus, patients with OSA have a higher risk for thrombosis, which can, however, be reversed by treating the OSA (Chin et al., 1996; von Känel et al., 2006). Endothelial dysfunction also triggers the recruitment of proinflammatory circulating cells, which results in increased vascular permeability for plasma lipids, and, consequently, promotes plaque formation.

In patients with OSA, these processes cause FMD impairment, increased arterial stiffness, and IMT (Monneret et al., 2010). These effects are reversible by OSA treatment (i.e., CPAP) (Drager et al., 2007; Hui et al., 2012). In a meta-analysis (Ning et al., 2019) of 15 randomized controlled trials that assessed the efficacy of several biomarkers, subgroup analysis showed that CPAP was particularly effective in improving FMD in severe OSA patients and patients with effective CPAP use for $\geq$ 4 h/night. These findings support the cause and effect relationship between OSA and arteriosclerosis/atherosclerosis.

Nevertheless, the indirect impact of OSA on arteriosclerosis/atherosclerosis should also be considered. It is well-recognized that OSA causes daytime and nighttime hypertension and insulin resistance. Hypertension and insulin resistance are risk factors for the development and progression of arteriosclerosis/atherosclerosis and cardiovascular diseases. In fact, randomized controlled trials and meta-analyses have found that CPAP treatment reduces systemic blood pressure in patients with OSA. In a meta-analysis of 15 studies that evaluated the effect of CPAP treatment on insulin resistance, CPAP did not induce glycemic control changes but improved insulin resistance in 12 of the studies with non-diabetic patients (Yang et al., 2013). In another meta-analysis of six diabetic studies, CPAP treatment significantly improved insulin resistance (Chen et al., 2014). Further large-scale randomized controlled trials are needed to evaluate the effect of CPAP on diabetes because the aforementioned meta-analyses included only a few randomized controlled trials. CPAP was shown to have a favorable effect on cardiovascular diseases in a non-

randomized clinical trial. A prospective cohort study, which followed 449 patients with OSA for a median of six years (Buchner et al., 2007), showed that, compared with no treatment, CPAP therapy was associated with a reduction in the likelihood of developing cardiovascular events such as myocardial infarction, stroke, or acute coronary syndrome that required a revascularization procedure. An observational study (Marin et al., 2005) that followed 1,651 men recruited from a sleep clinic, and a population-based sample of healthy men, demonstrated that severe OSA significantly increased the risk of fatal and non-fatal cardiovascular events and that CPAP treatment reduced this risk.

4.3 OSA and arterial stiffness measured by parameters other than the CAVI

According to a recent meta-analysis (Wang et al., 2015) that included five cross-sectional studies, arterial stiffness, determined by cfPWV or AIx, was significantly higher in patients with OSA than in healthy controls. Another meta-analysis of 15 articles (n = 615 patients) assessing the effect of CPAP treatment on arterial stiffness in patients with OSA, showed that CPAP treatment improves various indices of arterial stiffness, regardless of the proportion of compliant patients or the duration of CPAP use (Vlachantoni et al., 2013). However, most of the included studies had no control group or had a non-randomized control group. To date, seven randomized controlled trials (Drager et al., 2007; Hoyos et al., 2015; Jones et al., 2013; Kohler et al., 2013, 2008; Litvin et al., 2013; Paz et al., 2016) have assessed the effectiveness of CPAP treatment in reducing arterial stiffness. Three (Hoyos et al., 2015; Jones et al., 2013; Litvin et al., 2013) of the seven studies were designed as crossover trials. The number of participants in these studies was small. Only three (Kohler et al., 2013, 2008; Paz et al., 2016) of the studies included more than 100 participants. The control groups received standard care without CPAP or a subtherapeutic CPAP (with insufficient pressure to treat OSA). Moreover, the severity of OSA varied between studies from mild to severe. The AHI cut-off or oxygen desaturation index (ODI) ranged from 7.5 to 30. Two (Kohler et al., 2013, 2008) of the seven studies included mild OSA. The duration of CPAP use ranged from three weeks to six months. Arterial stiffness was assessed using the AIx and/or cfPWV. The results of these studies were inconsistent with respect to the reduction in arterial stiffness. Four of the seven studies (Drager et al., 2007; Kohler et al., 2008; Litvin et al., 2013; Paz et al., 2016) succeeded in showing that CPAP treatment was significantly effective in reducing arterial stiffness compared with the control, while the other three studies did not. One of the important differences among these studies was the usage of CPAP. In all studies that failed to demonstrate the effectiveness of CPAP treatment, it was used for less than 4 h/day, while it exceeded 4 h/day in all other studies. Since patients with OSA are known to experience an overnight increase in arterial stiffness (Phillips et al., 2005), the results can change depending on measurement timing. One of the above randomized controlled trials has demonstrated this time-of-day measurement difference. CPAP treatment improved arterial stiffness as measured by the AIx only if measured in the morning, while the treatment reduced blood pressure independent of when it was measured through the day (Hoyos et al., 2015). The other studies did not refer to the timing of arterial stiffness measurement.

4.4 CAVI and OSA

Some studies have suggested an association between OSA and white coat hypertension (García-Río et al., 2004; Li et al., 2015). Therefore, the CAVI is considered superior to other arterial stiffness parameters because it is highly reproducible and does not vary with blood pressure changes at the time of measurement.

Several studies measuring the CAVI in patients with OSA concluded that the CAVI increases with OSA severity. Kumagai and colleagues (2009) investigated the clinical utility of the CAVI in 543 consecutive patients with OSA (AHI $\geq$ 5) in whom the CAVI was measured on the day after overnight polysomnography. They, first, measured the CAVI three times on different days for 25 of the patients to evaluate the CAVI reproducibility. The study found that reproducibility of the CAVI was higher than baPWV. In 74 of their patients, IMT was assessed in addition to the CAVI, finding a significant correlation between them (r = 0.487). This correlation suggests that a higher CAVI in patients with OSA might be associated with more severe atherosclerosis/arteriosclerosis based on the IMT. Although there was a significant correlation between the blood pressure and the simultaneously measured baPWV, a correlation with the CAVI was less pronounced, suggesting that baPWV was affected by blood pressure whereas the CAVI was not. Finally, they divided the patients into two groups using an AHI of 15 as a cut-off value. Patients with moderate to severe OSA (AHI $\geq$ 15/h) had a higher CAVI (7.7 $\pm$ 1.4) than those with mild OSA (AHI $<$ 15; 7.3 $\pm$ 1.2, P = 0.034). Furthermore, similar to other populations, the CAVI increased with age and in men (compared to women), even among patients with OSA. However, the CAVI increased with OSA severity regardless of age or sex. Alberto et al. (2014) demonstrated a relationship between OSA severity (determined by pulse oximetry) and the CAVI level in overweight subjects. In their study, multivariate-adjusted odds ratio (OR) of severe OSA, defined as 3% ODI $\geq$ 15/h, indicated that the CAVI was significantly higher only in subjects with BMI $>$25 kg/m^2 (OR = 2.53, 95% confidence interval, 1.08-5.96; P= 0.03). A study by Iguchi and colleagues (2013) that included overweight and obese participants showed a good correlation between the CAVI and AHI, which was measured by a portable polygraph (r = 0.351, $P < 0.001$). Taken together, these studies suggest that BMI affects the CAVI-OSA relationship; a correlation between the CAVI and OSA severity is more prominent in obese subjects.

Although data from elderly patients is limited, a cross-sectional study (Kim et al., 2015) on elderly patients ($\geq$ 60 years) investigated the relationship between the CAVI and OSA severity. They found a significant association between OSA severity and the CAVI only in patients without comorbid medical conditions and those not under medication treatment. Older people usually have a more advanced form of atherosclerosis than younger ones, and thus, probably due to a ceiling effect, a change in the CAVI was revealed only in those without advanced atherosclerosis. These studies suggest a relationship between the severity of OSA and arterial stiffness, although the causal relationship remains unknown.

Our retrospective study included 574 OSA patients who underwent assessment for the CAVI and overnight polysomnography. The mean age was 53 $\pm$ 13 years, 87% were male, and the mean BMI was 26 $\pm$ 4 kg/m^2. The relationship between the AHI and the CAVI varied with sex. Based on a CAVI threshold of 7, the AHI

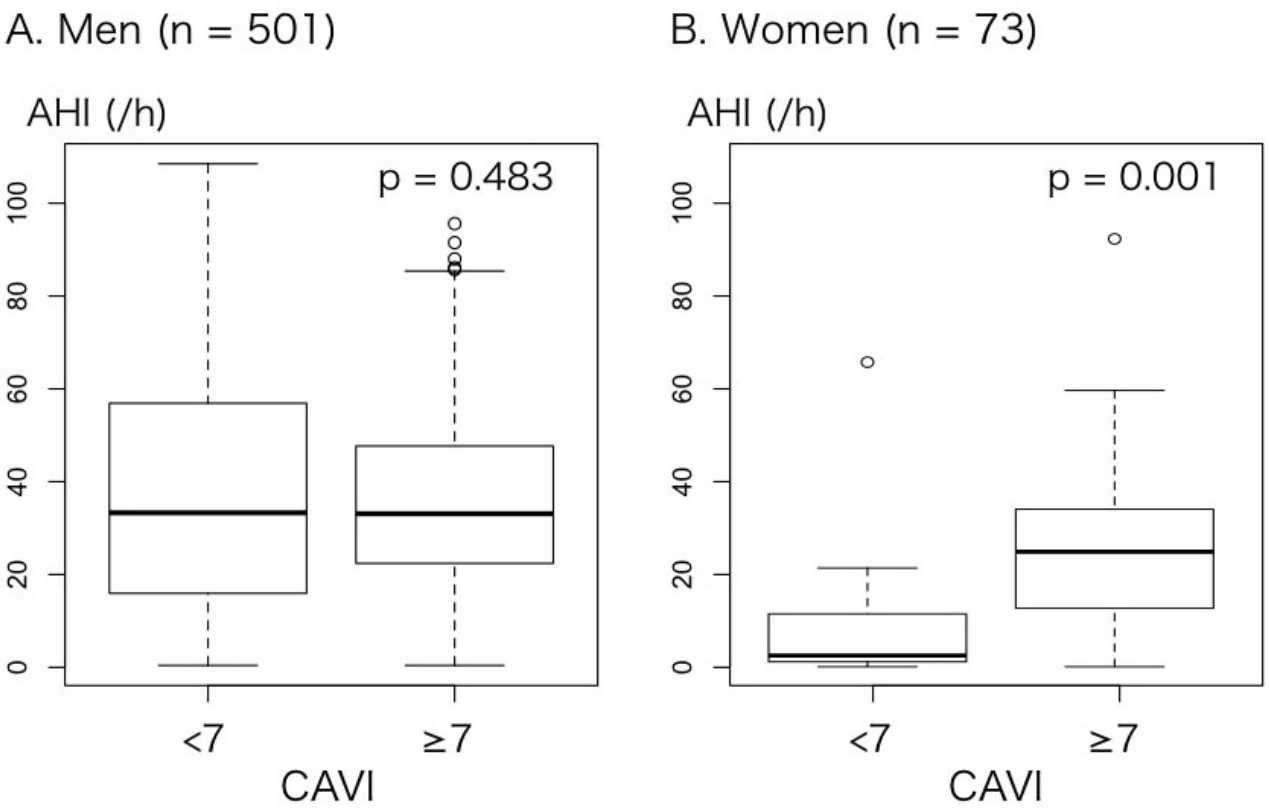

Fig. 3. Patients were divided based on a cardio-ankle vascular index (CAVI) cut-off value of 7. In men, the apnea-hypopnea index (AHI) was similar in both groups (37.1 vs. 35.6, $P = 0.483$). In women, the AHI was higher in the CAVI $\geq$ 7 group (26.1 vs. 9.0, $P = 0.001$).

was higher in the CAVI $\geq$ 7 group than in the CAVI $<$ 7 in women, but was similar in men (Fig. 3). Moreover, a multivariate regression analysis revealed that CAVI $\geq$ 7 was an independent predictor for AHI $\geq$ 20/h in the polysomnography ($\beta = 0.18$, $P < 0.001$). An AHI $\geq$ 20/h is a cut-off value for initiating CPAP treatment according to the Japanese health insurance system, in addition to a higher BMI, older age, more rapid heart rate, and male sex. These findings suggest that CAVI $\geq$ 7, without other risks, can be indicative of moderate to severe OSA. Besides, the results suggest when CPAP should be initiated for patients and when should they be referred to a sleep clinic. These data are unpublished, but the ethics committee of the Toranomon Hospital approved this study (No. 787).

The CAVI can measure changes in arterial stiffness that are less dependent on changes in blood pressure. Non-hypertensive patients with OSA and matched controls without either hypertension or OSA were compared for overnight change in the CAVI based on measurements performed before and after sleep (Lü et al., 2008). After sleep, the CAVI was significantly higher than before in patients with OSA (8.3 $\pm$ 1.2 vs. 7.3 $\pm$ 1.0, P= 0.001), but not in the controls. These findings suggest that OSA induced an overnight increase in arterial stiffness. In other words, these findings support the causal relationship between OSA severity and the increase in the CAVI. Several other studies assessed OSA treatment-induced changes in the CAVI, such as following CPAP treatment (Table 1). In a study that assessed a short-term change in the CAVI in non-hypertensive OSA patients (Lü et al., 2008), 22/60 patients were treated by CPAP. In the morning following the first night of treatment, the CAVI and blood pressure significantly decreased. Moreover, following a three-night treatment, the CAVI decreased even further. Such reductions in the CAVI due to CPAP treatment were replicated in other studies in which the change in the CAVI was evaluated after CPAP treatment for one month in patients with moderate to severe OSA (Kasai et al., 2011; Kato et al., 2011). These short-term reductions in the CAVI might be mediated by suppressing the sympathetic nerve overactivity and improving the inflammation. However, 12 months after CPAP initiation, the CAVI was actually higher than that measured after one month of treatment (Kato et al., 2011). This increase could be explained by the natural progression of arterial stiffness due to the aging process. In support of this, the CAVI at 12 months after CPAP treatment initiation was lower than expected based on predictions of the natural progression of the CAVI (Kato et al., 2011; Shirai et al., 2011a). This finding suggests that CPAP treatment for OSA might retard arterial stiffness progression. In the same study, reduction in the CAVI was related to the use of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB), reduction in hemoglobin A1c levels, and change in nightly CPAP usage from the first month to the last. Thus, long-term CPAP treatment for OSA might be more beneficial in delaying arterial stiffness progression in patients taking ACE-I/ARB, those with controlled blood glucose levels, and those with good adherence to CPAP usage.

Table 1. Change in the CAVI after intervention for sleep disordered breathing

Author, year	Participants	n	Intervention	Duration	Results
Lü et al., 2008	Hypertensive patients with OSA	22 (of 60)	CPAP	1 day 3 days	CAVI↓, BP↓ CAVI↓
Kato et al., 2011	Moderate to severe OSA	30	CPAP	1 month 1 year	CAVI↓ No change
Kasai et al., 2011	Moderate to severe OSA	27 (of 50)	CPAP	1 month	CAVI↓ Pentraxin 3↓
Iguchi et al., 2013	Overweight or obese patients	60	Weight reduction	3 months	CAVI↓ AHI↓
Yoshihisa et al., 2013	HFpEF with moderate to severe SDB	18 (of 36)	ASV	6 months	CAVI↓ NYHA↓ BNP↓

AHI, apnea-hypopnea index; ASV, adoptive servo-ventilation; BNP, brain natriuretic peptide; BP, blood pressure; CAVI, cardio-ankle vascular index; CPAP, continuous positive airway pressure; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association functional classification; OSA, obstructive sleep apnea; SDB, sleep disordered breathing.

Weight reduction as an intervention for OSA was assessed in overweight or obese subjects (Iguchi et al., 2013). Although the study included a small number of OSA patients (average AHI, 18), subjects who successfully reduced their weight during the three months of the study, defined as >3% reduction from the baseline, had significantly lower CAVI (from 8.49 ± 0.3 to 7.98 ± 0.3, $P<0.05$), in addition to a significantly reduced AHI (from 18.0 ± 2.9 to 9.61 ± 1.9, $P < 0.05$).

It should be noted that the aforementioned studies included patients with no cardiovascular disease other than hypertension, and therefore whether the CAVI can act as an indicator of disease condition or prognosis for the secondary prevention of cardiovascular diseases remains to be investigated. There is only one study (Yoshihisa et al., 2013) that included heart failure patients with moderate to severe sleep apnea. All patients had preserved left ventricular function of $>$ 50%, received optimal medication, and were in a stable condition. They were randomly assigned to two groups: 18 patients were treated with adaptive servo-ventilation (ASV), an effective treatment for sleep apnea in heart failure patients, and the remaining 18 patients were not treated with ASV. Several clinical parameters, including the CAVI, were measured at baseline and six months after randomization. The most important finding in this small randomized controlled trial was that the event-free rate of the patients in the ASV group was significantly higher than that in the control group. Moreover, after six months of treatment, the CAVI in the ASV group was significantly lower than the control. The levels of the New York Heart Association (NYHA) functional class and B-type natriuretic peptide were also lower in the ASV group. Therefore, heart failure patients with moderate to severe sleep apnea might have a better prognosis when treated with ASV, possibly thanks to the drop in the CAVI.

5. Conclusions

OSA can promote arteriosclerosis/atherosclerosis and lead to cardiovascular events. Various physiological parameters have been used to predict the onset of cardiovascular events and mortality (Den Ruijter et al., 2012; Kato et al., 2010; Matsuzawa et al., 2015; Mattace-Raso et al., 2006; Mitchell et al., 2010; Oliver and Webb, 2003; Shirai et al., 2011a; Taylor et al., 2001; Vlachopoulos et al., 2010a,b). Arterial stiffness is one such parameter. Compared with other parameters such as FMD, IMT, and inflammatory markers, arterial stiffness can reveal systemic arteriosclerosis/atherosclerosis and provide hints to the functional properties of the arteries. Although cfPWV is the gold-standard parameter for arterial stiffness evaluation, the CAVI is a promising emerging parameter that is easy to measure, highly reproducible, and represents changes in the central arteries and resistance in the peripheral arteries. In patients with OSA, who are more likely to have blood pressure variations at the time of measurement (Shiina et al., 2016), the CAVI might be a useful parameter of arterial stiffness assessment because it is less affected by blood pressure variations at the time of measurement. To evaluate changes in arterial stiffness following interventions that might change blood pressure, the CAVI appears superior to other parameters. In studies evaluating changes in the CAVI before and after CPAP treatment initiation (Drager et al., 2007; Hoyos et al., 2015; Jones et al., 2013; Kohler et al., 2013, 2008; Litvin et al., 2013), longer nightly CPAP usage was associated with improvement of the CAVI. Therefore, the CAVI can be used as a parameter of compliance or adherence to CPAP usage in patients with OSA. Further epidemiological studies are needed to elucidate the CAVI prognostic value in OSA patients by comparing it to cfPWV.

Authors' contributions

Yasuhiro Tomita and Takatoshi Kasai drafted the article; Takatoshi Kasai revised it critically.

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Conflict of interest

Drs. Kasai and Tomita are affiliated to a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi.

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