Obstructive Sleep Apnea and Vascular Diseases

Dimitrios Baltzis,[1] Jessie P. Bakker,[2] Sanjay R. Patel,[2] and Aristidis Veves[*1]*

ABSTRACT

Obstructive sleep apnea (OSA) affects a large proportion of adults, and is as an independent risk factor for cerebrovascular and cardiovascular disease. The repetitive airway obstruction that characterizes OSA results in intermittent hypoxia, intrathoracic pressure swings, and sleep fragmentation, which in turn lead to sympathetic activation, oxidative stress, inflammation, and endothelial dysfunction. This review outlines the associations between OSA and vascular diseases and describes basic mechanisms that may be responsible for this association, in both the micro- and macrocirculation. It also reports on interventional studies that aim to ameliorate OSA and thereby reduce vascular disease burden. © 2016 American Physiological Society. *Compr Physiol* 6:1519-1528, 2016.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder affecting 13% and 6% of adult males and females in the United States, respectively (92), characterized by partial or complete collapse of the upper airway during sleep. The repeated occurrence of obstructive respiratory events is associated with a predictable pattern of intermittent hypoxemia/hypercapnia associated with reduced inspiratory airflow, and an increase in respiratory effort in an attempt to breathe against an occluded airway. Obstructive events usually terminate with an arousal allowing the airway to open and normal gas exchange to be restored. There are a number of risk factors predisposing to OSA, such as male gender, older age, menopause in women, and obesity. A variety of craniofacial and oropharyngeal abnormalities can also contribute to OSA pathogenesis, including a large neck circumference, retrognathia or micrognathia, nasal obstruction, enlarged tonsils/adenoids, macroglossia, and a low-lying soft palate (26, 44, 108, 112). Genetic and environmental factors may also adversely affect airway size explaining the increased incidence of sleep apnea in some families or races (112, 132). Obesity is a particularly strong risk factor; a 10% increase in weight is associated with a sixfold greater risk of developing OSA (93).

Numerous studies have established OSA as an independent risk factor for hypertension, diabetes, heart failure, stroke, and mortality (42, 99, 101, 131). Investigation of the mechanisms linking OSA and vascular complications have focused on the pathophysiological sequence of events described above: intermittent hypoxemia, intrathoracic pressure swings resulting from increased respiratory effort, and sleep fragmentation resulting from repeated arousals, each of which will be discussed in turn below (Fig. 1). The first-line treatment for OSA, continuous positive airway pressure (CPAP), has demonstrated efficacy in improving surrogate markers of cardiovascular disease, as well as reducing cardiovascular morbidity and mortality.

Possible Mechanisms Linking OSA and Vascular Complications

Intermittent hypoxia

OSA is characterized by intermittent episodes of either complete (apnea) or partial (hypopnea) breathing cessation for periods of 10 s or more (5), both of which can lead to temporary drops in oxyhemoglobin saturation. These drops are more severe in obese individuals who have lower functional residual capacity, and therefore reduced oxygen stores during the respiratory event (91). Data from both animal and human studies support links between intermittent hypoxia and its adverse impact at the tissue level. Intermittent hypoxia increases systemic and vascular inflammation, promotes oxidative stress by increased production of reactive oxygen species, increases sympathetic activation (27) and contributes to diverse multiorgan chronic morbidity and mortality through endothelial dysfunction. Data from observational studies in large population groups support the role for hypoxemia in the pathogenesis of OSA comorbidities including cardiovascular, metabolic, and neurocognitive disease as well as cancer (26, 27, 86).

Repeated arousals

Most apneas/hypopneas result in cortical arousal to increase tone in the upper airway dilator muscles and reestablish airway patency (19). Fluctuations in ventilation in the form of cyclic apnea or periodic breathing cause oscillations in blood gases, and sympathetic nervous system activation. During

[*]Correspondence to aveves@bidmc.harvard.edu

[1]Microcirculation Lab and Joslin-Beth Israel Deaconess Foot Center, Harvard Medical School, Boston, USA

[2]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

Published online, July 2016 (*comprehensivephysiology.com*)

DOI: 10.1002/cphy.c150029

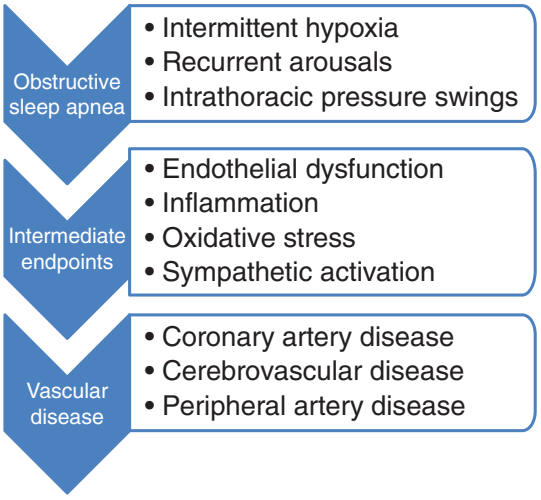

Figure 1 Possible mechanisms linking OSA with vascular disease.

the early period of apnea, blood pressure and heart rate are decreased; however, as oxygen saturation decreases, blood pressure, heart rate, and pleural pressure swings increase until the occurrence of an arousal. The initial decrease in heart rate has been linked with an increase in parasympathetic activity as seen in the diving reflex (27, 36). Left ventricular stroke volume is reduced due to the negative intrathoracic pressure (increased left ventricular afterload) alongside a decrease in pulmonary venous return (decreased left ventricular preload), accounting for a decrease in cardiac output. Hypoxia may influence blood pressure control through a number of different mechanisms (36). The local vascular effect of severe hypoxia tends to reduce arterial blood pressure by vasodilatation. Vasoactive substances derived from the vascular endothelium including nitric oxide, adenosine and eicosanoids may be implicated as early mechanisms in this response.

Arousal from sleep, as a discontinuance of the apnea/hypopnea, is an important protective mechanism for airway reopening (19, 32). However, the physiological events that accompany the arousal response might contribute to the pathophysiology of the syndrome. The continual repeated arousals that appear in patients with OSA result in sleep fragmentation, reduced sleep quality, and diminished amounts of slow wave and rapid eye-movement sleep (82). Sleep fragmentation leads to an increase in sympathetic nervous system activation, causing inflammation, and reduces glucose tolerance, all of which can contribute to the development of vascular disease (17, 20, 52, 109, 118).

Intrathoracic pressure swings

Forced inspiratory efforts against an occluded airway during an obstructive event leads to excessive negative intrathoracic pressure to levels approaching −60 mmHg or even −80 mmHg. These pressure swings can produce extensive shear and wall stresses on intrathoracic blood vessels including the aorta, leading to an increased venous return and therefore overload of the right ventricle (60). The negative intrathoracic pressure also leads to an increased transmural pressure of the left atrium, left ventricle, and aorta, and disrupts ventricular function resulting in aortic dilation (107). Thus, these mechanical effects and the contribution of surges in blood pressure result in diastolic dysfunction, reduced stroke volume, and cardiac output in accordance with increased left ventricular preload and afterload. Some studies suggest that intrathoracic pressure changes in patients with OSA might play a role in the pathogenesis of aortic dilatation (60).

Sympathetic activation

Acute hypoxemia has been found to cause reflex vasoconstriction, an increase in heart rate, and activation of the sympathetic nervous system (27). Muscle sympathetic nerve traffic is inhibited during the beginning of an obstructive apnea episode, gradually increases, and is followed by a strong inhibition during the late phase. These changes in sympathetic nerve traffic are associated with similar changes in vascular resistance and may therefore have implications for the increase in blood pressure observed during the apneic/hypopneic episodes. The postapneic blood pressure elevation correlates with the severity of hypoxia during the obstructive episode.

The surges of sympathetic activity triggered by obstructive respiratory event are in part due to hypoxia and activation of carotid and/or aortic chemoreceptors (51). Enhanced chemoreflex activity could play a role in the pathogenesis of chronic sympathoexcitation and hypertension in OSA (106, 119), a concept which is supported by animal models demonstrating enhanced chemoreflex responses to chronic intermittent hypoxia (43). At the conclusion of the obstructive event, heart rate and blood pressure are both elevated to reach a peak within the immediate postapneic breaths. Arousal from sleep, at the third phase of an apneic event, may cause further peripheral resistance by increasing sympathetic nerve activity (20). Of note, OSA patients also have increased sympathetic activity during the day, as indicated by microneurography and elevated catecholamine levels both in plasma and urine (18). Indeed, increased and variable heart rate and blood pressure has been demonstrated in OSA patients compared to healthy people during wakefulness (20). Morbidity and mortality in patients with heart failure, diabetes, and coronary artery disease are predicted by the dysfunction of autonomic cardiovascular regulation, probably by causing cardiac beta-adrenoreceptor desensitization, myocyte injury and necrosis, and hypertension. This dysfunction also exists in OSA and may contribute to cardiovascular disease (20, 37).

The carotid body has been the subject of recent investigation, due to its role maintaining oxygen homeostasis. Hypoxic stimulation of the carotid body increases chemosensory discharge, which in turn elicits reflex sympathetic, cardiovascular, and ventilatory adjustments (87). Chronic intermittent

hypoxia with OSA can lead to upregulation of vascular endothelial growth factor, nitric oxide synthase, proinflammatory cytokines, angiotensin-II, and endothelin-1 in the carotid body; endothelin-1, in particular, has been proposed as a mediator of carotid body chemosensory potentiation induced by chronic intermittent hypoxia, and thus may contribute to the resulting hypertension in OSA (53). The carotid body has been a focus of recent research in OSA due to its potential role in cardiovascular disease; indeed, some investigators have suggested denervation or surgical removal of the carotid body as a treatment to resistant hypertension (87, 88).

Inflammation

OSA is associated with systemic inflammation, which is demonstrated by increased levels of circulating inflammatory biomarkers such as C-reactive protein, leptin, interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α), intercellular cell adhesion molecule, vascular endothelial growth factor (1), and macrophage migration inhibitory factor (3, 33). OSA is considered a chronic low-grade inflammatory disease, similar to atherosclerosis, and chronic inflammation is related to the pathogenesis of cardiovascular diseases. (6, 45, 46, 54). One of the strongest predictors of cardiovascular risk is c-reactive protein (6, 69, 100), which alongside other inflammatory markers such as IL-6 and TNF-α, is correlated with carotid intima-media thickness in OSA patients (23). Changes in inflammatory markers are correlated with OSA severity, suggesting a contribution to the development of atherosclerosis in OSA patients (3).

Beyond systemic inflammation, airway inflammation also exists in OSA and seems to be directly affected through mechanical stress, snoring-induced airway vibration, and/or local oxidative stress (1). One study found that airway inflammation, assessed by exhaled IL-8 and TNF-α levels, was related to proximal airway resistance independently of body mass index (2). To eliminate possible confounding by obesity, various studies have measured the effect of intermittent hypoxia in otherwise healthy humans. The results from these studies consistently show that OSA has an independent effect on autonomic system, but no definitive results are available regarding inflammation (1, 69, 100). Fourteen nights of experimentally induced intermittent hypoxia in healthy subjects has been shown to elevate blood pressure and sympathetic activity, but not systematic inflammatory markers (117).

Oxidative stress

Oxidative stress is defined as a disturbance in the balance between the production of free radicals and antioxidant defenses (10); this means either a decreased antioxidant capacity or an overproduction of free radicals, or both, leading to a state of oxidative stress (5). Free radicals play an important role in regulation of signal transduction and cellular function, but their overproduction can damage lipids, proteins, and DNA, thus affecting many cellular and physiological mechanisms. This can contribute to pathological situations including cardiovascular disease (5). Oxygen metabolism during normal cellular respiration generates reactive oxygen species as by-products, and their elimination occurs through enzymatic and nonenzymatic antioxidant systems, such as superoxide dismutase, erythropoietin, glutathione, and thioredoxin (67). When reactive oxygen species generation exceeds the capacity of antioxidants, oxidative stress occurs, and causes damage to cells and tissues. When superoxide anions react with nitric oxide, an important endothelium-derived vasodilator, reactive nitrogen species are produced. Thus, nitric oxide bioavailability decreases and the vasodilator ability of blood vessels is compromised.

In the current literature, numerous studies link oxidative stress with cardiovascular disease in patients with OSA (5, 56, 68, 73, 96, 133). In OSA, the increasing oxidative stress caused by hypoxia-related free radicals leads to increased reactive oxygen species production in monocytes and polymorphonuclear neutrophils, overexpression of adhesion molecules, and cytotoxicity of monocytes. These mechanisms further reduce nitric oxide bioavailability and increase monocyte and platelet adhesion, thus aiding in the progression of atherosclerosis and vascular dysfunction (38).

Mitochondrial dysfunction also plays a crucial role in producing oxidative stress. In OSA, periods of hypoxia are associated with elevated reactive oxygen species production and many of these reactive species are generated in the mitochondria. Mitochondria are a major source of superoxide anions during oxidative phosphorylation (41). Moreover, there are other sources of reactive oxygen species including enzymes such as xanthine oxidase, endothelial nitric oxide synthase, NADPH oxidase, and superoxide dismutase (66). In a study that exposed mice to 30 days of chronic intermittent hypoxia, fasting plasma insulin was elevated compared to controls, while the glucose levels were comparable between the two groups, indicating insulin resistance. Insulin content was decreased in β-cells exposed to intermittent hypoxia, and this effect was associated with increased proinsulin levels. More importantly, glucose-stimulated insulin secretion was impaired in the mice exposed to intermittent hypoxia. Mitochondrial levels of reactive oxygen species were also elevated, suggesting a potential contribution to the development of type 2 diabetes (67, 123).

Lipid peroxidation, a marker of oxidative stress, is increased in OSA patients, while treatment with CPAP can reverse this effect (66). Prior studies have demonstrated increased levels of thiobarbituric acid (a marker of lipid peroxidation), nitrotyrosine, and cyclooxygenase-2 expression in OSA patients (5,56). Antioxidant capacity is impaired in OSA patients, in a positive linear relationship with OSA severity defined by the apnea hypopnea index (22). However, total antioxidant status before and after sleep has been shown to be significantly lower in patients with mild/moderate OSA compared with severe OSA. These results could be explained by differences between the acute effects of hypoxia, resulting from apneic sleep, and chronic oxidative stress that may

be sustained in severe OSA patients even during the daytime (58).

Endothelial dysfunction

The endothelium regulates the balance of circulating cells and mediators involved in tissue metabolism, inflammation and repair, all of which are impaired in patients with OSA (76). The endothelium reacts to physiological challenges, such as stress, alterations in cardiac output, or hypoxemia, and releases various vasoactive substances including nitric oxide, and endothelin that regulate vasodilation and vasoconstriction (25). The endogenous endothelial repair mechanism, comprising bone marrow-derived endothelial progenitor cells, helps maintain the integrity of the natural blood-tissue barrier in the face of vascular injury and physiological stress (4). Disruption of this well-regulated vascular homeostasis is believed to lead to a sequence of pathological events, including excessive vasoconstriction, upregulation of adhesion molecules, inflammatory cytokine amplification, enhanced lipoprotein oxidation, prothrombotic states, and the formation of atherosclerotic plaque (14, 72).

Endothelial dysfunction is a primary contributor to the development of atherosclerosis (11) and importantly, even with atherosclerotic changes, endothelial dysfunction has been shown to be reversible (13). This endothelial damage impacts the balance of different endothelium-derived substances responsible for maintaining vascular tone (110). Although the origin of the endothelial injury is not well understood, studies suggest this may be related to intermittent hypoxemia, which perpetuates the generation of reactive oxygen species and proinflammatory molecules (98). Some of the mechanisms involved in endothelial dysfunction observed in OSA patients are the following: oxidative stress, inflammation, disturbances on circulating endothelial cells, endothelial progenitor cells and circulating microparticles (98), lipid peroxidation (55, 110), endothelial repair capacity (71), hypercoagulability, genetics (14), and endothelial cell apoptosis (Fig. 2) (35).

Flow-mediated dilation (FMD) in the brachial artery, is considered the standard noninvasive test for the assessment of macrovascular endothelial function and is reduced in patients with OSA as suggested by the majority of the studies (Fig. 3) (129). The largest study to date, the Cardiovascular Health Study component of the Sleep Heart Health Study, showed a dose-dependent association between OSA severity and reduced FMD after adjustment for age, gender and race (89). In contrast, the Framingham Heart Study component of the Sleep Heart Health Study showed no adjusted association between FMD and OSA severity. One reason for this discrepancy may be that the majority of participants in the Framingham/Sleep Heart Health Study had mild OSA (63%

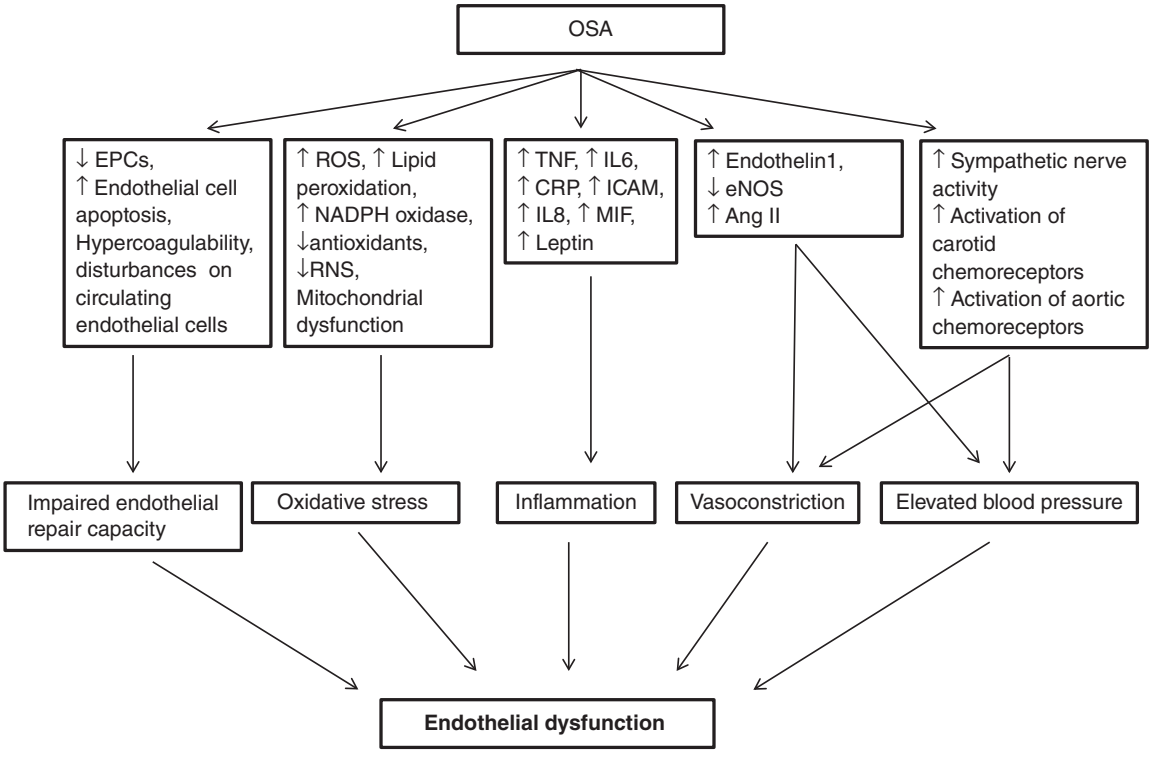

Figure 2 Pathways linking OSA to endothelial dysfunction. ↑, upregulation; ↓, downregulation; Angio II, angiotensin II receptor; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthetase; EPCs, endothelial progenitor cells; HIF, hypoxia-inducible facto; ICAM, intercellular adhesion molecule; IL 6, interleukin 6; IL 8, interleukin 8; NADPH, nicotinamide adenine dinucleotide phosphate; NF-KB, nuclear factor- kB; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

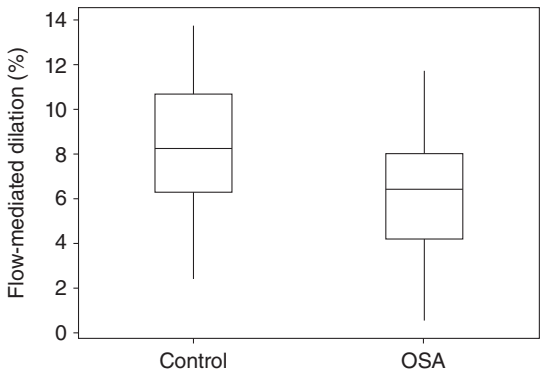

Figure 3 Endothelial function, as measured by flow-mediated dilation of the brachial artery, is impaired in subjects with OSA, as compared with control subjects, in a subgroup of subjects younger than 50 years of age. The box encompasses the 25% to 75% quartiles, and the median is represented by the horizontal line within the box. The whiskers extend to the highest and lowest values within the higher and lower limits, respectively (129).

had an apnea hypopnea index between 5 and 15 events/h) and therefore may have been less likely to have any significant hypoxemia (48). In another study, it was shown that OSA impairs endothelial function in the brachial artery to a similar degree as type 2 diabetes (130). Interestingly, preliminary data presented recently, reported that OSA and DM exert a synergistic detrimental effect on endothelial function (9).

Associations between OSA and Vascular Disease

Coronary artery disease

There is growing awareness that OSA is related to the development and progression of cardiovascular disease, as evidenced by the prevalence of OSA being about twofold greater in patients with coronary artery disease compared to those without (40). OSA appears in approximately 60% to 70% of patients with stroke or ischemic heart disease, and is also significantly associated with all-cause mortality in these conditions (126). Published studies have shown that severe OSA is associated with an increased risk of fatal and nonfatal cardiac events, although exact mechanisms remain unclear (70). It was found that more than 50% of sudden cardiac deaths in patients with OSA occur during sleep (61). In a subset of the Multi-Ethnic Study of Atherosclerosis, a prospective cohort of 2603 participants followed for 8 years, OSA was associated with coronary artery calcification, a risk factor for atherosclerosis, after adjustment for confounders including obesity (63). In a study with hard endpoints (death from any cause, stroke or transitory ischemic attack, and myocardial infarction), it was found that sleep-disordered breathing in patients with coronary artery disease was associated with a 60% to 70% increase in the risk of death and cardiovascular morbidity during long-term follow-up (83).

Stroke

Large-scale studies and meta-analyses have established moderate-to-severe untreated OSA as an independent risk factor for stroke (28, 40, 78, 83, 123), which may be partly due to the development of atrial fibrillation. Of five studies with ischemic stroke and OSA (84, 102, 104, 128), only one did not report the presence of atrial fibrillation (70). Increased risk of stroke in OSA patients may also be associated with hypertension and/or changes in cerebral blood flow (105). It was found that a significant decline in blood flow occurred in 76% of obstructive hypopneas and in 80% of obstructive apneas in the central cerebral artery (85). In a study with 214 patients with ischemic stroke, OSA was identified as an independent risk factor for atherosclerotic artery disease, with 42% of patients with OSA having atherosclerotic lesions—significantly greater than what was observed in non-OSA patients (31). Another longitudinal study of 166 patients with stroke found that the presence of moderate-to-severe OSA was associated with an increased incidence of nonfatal cardiovascular events (78). Finally, an analysis of the Sleep Heart Healthy Study found that in a total of 5422 participants without a history of stroke and untreated for OSA at baseline, 193 ischemic strokes occurred within the median follow-up time period of 8.7 years (102). In conclusion, OSA is related with many risk factors pathogenetic for stroke; atheromatosis, hypertension, and hemodynamic changes during episodes of apnea, atrial fibrillation, and decreased cerebral flow are contributing. All of them increase risk of stroke, creating a link between the two situations (128).

Peripheral artery disease

Peripheral arterial disease represents a severe atherosclerotic event with high mortality risk. Patients with severe peripheral arterial disease undergoing lower-extremity bypass surgery (revascularization) have a poor prognosis, with a 5-year mortality of almost 30%, which is mostly caused by cardiac complications (24, 65). The prevalence of OSA in patients with severe peripheral arterial disease requiring surgery has been estimated at 85% (121). This percentage is higher than in any other previously reported population with manifestations of atherosclerosis, such as studies showing 30% to 58% prevalence of OSA in coronary artery disease and 30% to 80% prevalence in arterial hypertension (12, 128). In another study that followed 84 patients for a median period of 52 months following revascularization, it was found that 17 of 39 patients with OSA (44%), and 6 of 45 patients (13%) without significant OSA, suffered from major adverse cardiovascular and cerebrovascular events. After a multivariate analysis, OSA was a significant independent predictor of events [hazard ratio (HR) 5.1; 95% confidence interval (CI): 1.9–13.9; $P = 0.001$] and was associated with poor long-term outcome in patients with peripheral arterial disease following revascularization (120); however, more studies are warranted to clarify the relationship between OSA and peripheral arterial disease.

Microvascular diseases

The literature regarding microvascular endothelial dysfunction in OSA is more limited than the data on its macrovascular counterpart (89). In a study of 72 participants, although flow-mediated dilation was impaired in patients with OSA suggesting endothelial dysfunction of the microvasculature, no correlation was found between OSA and vascular reactivity in the skin microcirculation (129). Interestingly there are data suggesting that OSA and type 2 diabetes have a synergistic role in endothelial dysfunction (9).

The pathogenesis of microvascular complications in diabetes, such as diabetic nephropathy or diabetic peripheral neuropathy, is similar; hyperglycemia and hypertension are fundamental to its development, as they promote increased oxidative and nitrosative stress (30). OSA is also associated with increased oxidative and nitrosative stress, and patients with both OSA and type 2 diabetes are at increased risk of developing microvascular complications (115, 116). In studies of patients with OSA and type 2 diabetes, OSA has been identified as an independent risk factor for the development of both diabetic nephropathy (115) and peripheral neuropathy (116).

Interventional Studies

The first-line treatment for OSA is CPAP, which eliminates upper airway collapse during sleep by pneumatically splinting the upper airway (Fig. 4) (6, 45). The majority of studies and meta-analyses published to date suggest that CPAP therapy reduces cardiovascular morbidity and mortality in patients with moderate/severe OSA (103, 127); however, the impact of CPAP in mild OSA is unclear (111).

CPAP treatment leads to a reduction in 24-h ambulatory blood pressure (7, 8), improves resistant hypertension in OSA patients, and leads to reduced sympathetic nerve activation. These findings suggest that OSA contributes to blood pressure elevations partly via sympathetic excitation (57, 79). Hypertension has been consistently shown to increase arterial stiffness and vice versa arterial stiffness contributes to the development of hypertension (39, 94, 97). Given the high prevalence of hypertension in patients with OSA, several studies have examined the association between OSA and arterial stiffness independently from the effects of hypertension. Interestingly, these studies proposed that OSA is associated with increased arterial stiffness independent of blood pressure (95), while numerous studies have reported a favorable effect of CPAP treatment on arterial stiffness (29, 59, 64, 122). Additionally, conflicting are the effects of CPAP on systemic inflammation. The majority of the studies and meta-analyses show that CPAP therapy reduces cardiovascular morbidity and inflammation (103, 127). However, in the Multi-Center Obstructive Sleep Apnea Interventional Cardiovascular trial recruiting patients with minimally symptomatic OSA, no consistent changes were found in the markers of systemic inflammation (IL-6, IL-10, C-reactive protein, and tumor necrosis factor) (111).

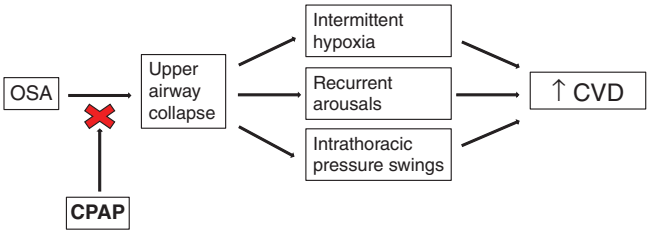

Figure 4 Intervention of CPAP on OSA pathway. ↑, increase; OSA: obstructive sleep apnea; CPAP, continuous positive airway pressure; CVD, cardiovascular disease.

Several studies have demonstrated that CPAP can reduce the risk of fatal and not fatal cardiovascular events (47, 49, 74) in both middle age and older patients (77), with one study demonstrating substantial risk reduction particularly in females (16). Evidence to date suggests that rates of hard end points, such as stroke or myocardial infarction are reduced in OSA patients who use CPAP (75) with one study demonstrating that long-term CPAP treatment in patients with moderate to severe OSA and ischemic stroke was associated with a reduction in mortality risk (80).

Although CPAP is markedly efficacious in treating OSA, suboptimal adherence is a major challenge which limits effectiveness of therapy (21). It is estimated that at least 50% of patients are use CPAP for under four hours per night (124) with many patients abandoning therapy within the first 4 weeks of treatment (50). Thus, although observational trials suggest OSA treatment with CPAP reduces cardiovascular event rates; randomized trials to definitively assess the effectiveness of CPAP have not yet been completed. Currently, there are several trials underway that should provide clearer evidence in the near future (81, 90). The first few weeks of treatment are crucial to determining long term compliance and studies reinforce the idea that any extra support at this stage such as behavioral interventions (frequent contact and follow-up with the health care provider, intensive patient support and reinforcement, cognitive behavioral therapy) and education will have a positive impact on compliance (125). If patients cannot tolerant CPAP therapy, alternative treatments such as bilevel positive airway pressure, mandibular advancement devices, and surgical procedures are potential therapeutic options (15, 34, 62, 108, 113, 114).

Conclusions

The role of OSA as an independent risk factor for cardiovascular disease is well established by numerous studies. Mechanisms linking OSA with vascular complications include intermittent hypoxia, intrathoracic swings, repeated arousals, and sympathetic system activation, mostly via inflammation,

endothelial dysfunction, and oxidative stress. Intermittent hypoxia increases systemic and vascular inflammation, promotes oxidative stress by increased production of reactive oxygen species, and through endothelial dysfunction contributes to diverse multiorgan chronic morbidity and mortality. CPAP is the first-line treatment for OSA and is associated with improvements in surrogate markers of cardiac risk, as well as reducing cardiovascular morbidity and mortality. Randomized trials assessing the impact of CPAP on vascular outcomes are currently underway.

Acknowledgements

This work was partly supported by National Institutes of Health R01 NS066205 (A. Veves), R01 DK076937 (A. Veves), and R01 HL110350 (A. Veves and S. R. Patel), the American Heart Association 14SDG20160000 (J. P. Bakker), and the American Thoracic Society (J. P. Bakker).

References

1. Aihara K, Oga T, Chihara Y, Harada Y, Tanizawa K, Handa T, Hitomi T, Uno K, Mishima M, Chin K. Analysis of systemic and airway inflammation in obstructive sleep apnea. *Sleep Breath* 17: 597-604, 2013.
2. Aihara K, Oga T, Harada Y, Chihara Y, Handa T, Tanizawa K, Watanabe K, Hitomi T, Tsuboi T, Mishima M, Chin K. Analysis of anatomical and functional determinants of obstructive sleep apnea. *Sleep Breath* 16: 473-481, 2012.
3. Arnaud C, Dematteis M, Pepin JL, Baguet JP, Levy P. Obstructive sleep apnea, immuno-inflammation, and atherosclerosis. *Semin Immunopathol* 31: 113-125, 2009.
4. Atkeson A, Jelic S. Mechanisms of endothelial dysfunction in obstructive sleep apnea. *Vasc Health Risk Manag* 4: 1327-1335, 2008.
5. Badran M, Ayas N, Laher I. Cardiovascular complications of sleep apnea: Role of oxidative stress. *Oxid Med Cell Longev* 2014: 985258, 2014.
6. Baessler A, Nadeem R, Harvey M, Madbouly E, Younus A, Sajid H, Naseem J, Asif A, Bawaadam H. Treatment for sleep apnea by continuous positive airway pressure improves levels of inflammatory markers - a meta-analysis. *J Inflamm (Lond)* 10: 13, 2013.
7. Bakker JP, Campana LM, Montesi SB, Balachandran J, Deyoung PN, Smales E, Patel SR, Malhotra A. A pilot study investigating the effects of continuous positive airway pressure treatment and weight-loss surgery on autonomic activity in obese obstructive sleep apnea patients. *Journal of Electrocardiology* 47: 364-373, 2014.
8. Bakker JP, Edwards BA, Gautam SP, Montesi SB, Duran-Cantolla J, Aizpuru F, Barbe F, Sanchez-de-la-Torre M, Malhotra A. Blood pressure improvement with continuous positive airway pressure is independent of obstructive sleep apnea severity. *J Clin Sleep Med* 10: 365-369, 2014.
9. Baltzis D, Bakker JP, Auster M, Tellechea A, Eleftheriadou I, Ostrovsky Y, Malhotra A, Patel SR, Veves A. Type 2 diabetes and obstructive sleep apnea synergistically affect endothelial function. *Diabetes* 63(1): A116, 2014.
10. Betteridge DJ. What is oxidative stress? *Metabolism* 49: 3-8, 2000.
11. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 23: 168-175, 2003.
12. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 373: 82-93, 2009.
13. Buchner NJ, Quack I, Woznowski M, Stahle C, Wenzel U, Rump LC. Microvascular endothelial dysfunction in obstructive sleep apnea is caused by oxidative stress and improved by continuous positive airway pressure therapy. *Respiration* 82: 409-417, 2011.
14. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. *J Clin Sleep Med* 3: 409-415, 2007.
15. Camacho M, Teixeira J, Abdullatif J, Acevedo JL, Certal V, Capasso R, Powell NB. Maxillomandibular advancement and tracheostomy for morbidly obese obstructive sleep apnea: A systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 152: 619-630, 2015.
16. Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nunez N, Caballero-Martinez I, Catalan-Serra P, Almeida-Gonzalez CV. Role of sleep apnea and continuous positive airway pressure therapy in the incidence of stroke or coronary heart disease in women. *Am J Respir Crit Care Med* 189: 1544-1550, 2014.
17. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *Eur Heart J* 32: 1484-1492, 2011.
18. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* 103: 1763-1768, 1993.
19. Casey KR. Heart failure, central sleep apnea, CPAP, and arousals: Another piece of the puzzle. *Sleep* 32: 13-14, 2009.
20. Celen YT, Peker Y. Cardiovascular consequences of sleep apnea: I-epidemiology. *Anadolu Kardiyol Derg* 10: 75-80, 2010.
21. Chiner E, Andreu AL, Sancho-Chust JN, Sanchez-de-la-Torre A, Barbe F. The use of ambulatory strategies for the diagnosis and treatment of obstructive sleep apnea in adults. *Expert Rev Respir Med* 7: 259-273, 2013.
22. Christou K, Moulas AN, Pastaka C, Gourgoulianis KI. Antioxidant capacity in obstructive sleep apnea patients. *Sleep Med* 4: 225-228, 2003.
23. Ciccone MM, Scicchitano P, Zito A, Cortese F, Boninfante B, Falcone VA, Quaranta VN, Ventura VA, Zucano A, Di Serio F, Damiani MF, Resta O. Correlation between inflammatory markers of atherosclerosis and carotid intima-media thickness in Obstructive Sleep Apnea. *Molecules* 19: 1651-1662, 2014.
24. Conte MS, Belkin M, Upchurch GR, Mannick JA, Whittemore AD, Donaldson MC. Impact of increasing comorbidity on infrainguinal reconstruction: A 20-year perspective. *Ann Surg* 233: 445-452, 2001.
25. de la Pena M, Barcelo A, Barbe F, Pierola J, Pons J, Rimbau E, Ayllon O, Agusti AG. Endothelial function and circulating endothelial progenitor cells in patients with sleep apnea syndrome. *Respiration* 76: 28-32, 2008.
26. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 90: 47-112, 2010.
27. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: Implications for comorbidities. *Chest* 147: 266-274, 2015.
28. Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: Meta-analysis of prospective cohort studies. *Atherosclerosis* 229: 489-495, 2013.
29. Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest* 131: 1379-1386, 2007.
30. Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. *Nat Clin Pract Endocrinol Metab* 4: 444-452, 2008.
31. Dziewas R, Ritter M, Usta N, Boentert M, Hor H, Dittrich R, Schabitz WR, Ringelstein EB, Young P. Atherosclerosis and obstructive sleep apnea in patients with ischemic stroke. *Cerebrovasc Dis* 24: 122-126, 2007.
32. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 5: 144-153, 2008.
33. Edwards KM, Tomfohr LM, Mills PJ, Bosch JA, Ancoli-Israel S, Loredo JS, Dimsdale J. Macrophage migratory inhibitory factor (MIF) may be a key factor in inflammation in obstructive sleep apnea. *Sleep* 34: 161-163, 2011.
34. Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD, Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep M. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 5: 263-276, 2009.
35. Feng J, Zhang D, Chen B. Endothelial mechanisms of endothelial dysfunction in patients with obstructive sleep apnea. *Sleep Breath* 16: 283-294, 2012.
36. Fletcher EC. Effect of episodic hypoxia on sympathetic activity and blood pressure. *Respir Physiol* 119: 189-197, 2000.
37. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* 22: 72A-84A, 1993.
38. Foster GE, Poulin MJ, Hanly PJ. Intermittent hypoxia and vascular function: Implications for obstructive sleep apnoea. *Exp Physiol* 92: 51-65, 2007.
39. Franklin SS. Arterial stiffness and hypertension: A two-way street? *Hypertension* 45: 349-351, 2005.

40. Gilat H, Vinker S, Buda I, Soudry E, Shani M, Bachar G. Obstructive sleep apnea and cardiovascular comorbidities: A large epidemiologic study. *Medicine (Baltimore)* 93: e45, 2014.
41. Gonchar O, Mankovska I. Moderate hypoxia/hyperoxia attenuates acute hypoxia-induced oxidative damage and improves antioxidant defense in lung mitochondria. *Acta Physiol Hung* 99: 436-446, 2012.
42. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. *Circulation* 122: 352-360, 2010.
43. Greenberg HE, Sica A, Batson D, Scharf SM. Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. *J Appl Physiol* 86: 298-305, 1999.
44. Guilleminault C, Quo SD. Sleep-disordered breathing. A view at the beginning of the new Millennium. *Dent Clin North Am* 45: 643-656, 2001.
45. Guo Y, Pan L, Ren D, Xie X. Impact of continuous positive airway pressure on C-reactive protein in patients with obstructive sleep apnea: A meta-analysis. *Sleep Breath* 17: 495-503, 2013.
46. Guven SF, Turkkani MH, Ciftci B, Ciftci TU, Erdogan Y. The relationship between high-sensitivity C-reactive protein levels and the severity of obstructive sleep apnea. *Sleep Breath* 16: 217-221, 2012.
47. Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerdt S, Poppe K, Dupont A, Velkeniers B. The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: Evidence from a meta-analysis of placebo-controlled randomized trials. *Arch Intern Med* 167: 757-764, 2007.
48. Hoyos CM, Melehan KL, Liu PY, Grunstein RR, Phillips CL. Does obstructive sleep apnea cause endothelial dysfunction? A critical review of the literature. *Sleep Med Rev* 20: 15-26, 2014.
49. Huang Z, Liu Z, Luo Q, Zhao Q, Zhao Z, Ma X, Liu W, Yang D. Long-term effects of continuous positive airway pressure on blood pressure and prognosis in hypertensive patients with coronary heart disease and obstructive sleep apnea: A randomized controlled trial. *Am J Hypertens* 28: 300-306, 2015.
50. Hussain SF, Irfan M, Waheed Z, Alam N, Mansoor S, Islam M. Compliance with continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea among privately paying patients- a cross sectional study. *BMC Pulm Med* 14: 188, 2014.
51. Imadojemu VA, Mawji Z, Kunselman A, Gray KS, Hogeman CS, Leuenberger UA. Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy. *Chest* 131: 1406-1413, 2007.
52. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 2015 [Epub ahead of print].
53. Iturriaga R, Andrade DC, Del Rio R. Enhanced carotid body chemosensory activity and the cardiovascular alterations induced by intermittent hypoxia. *Front Physiol* 5: 468, 2014.
54. Jelic S, Le Jemtel TH. Inflammation, oxidative stress, and the vascular endothelium in obstructive sleep apnea. *Trends Cardiovasc Med* 18: 253-260, 2008.
55. Jurado-Gamez B, Bujalance Cabrera C, Caballero Ballesteros L, Marin Hinojosa C, Munoz Cabrera L, Perez-Jimenez F, Lopez-Miranda J. Association of cellular adhesion molecules and oxidative stress with endothelial function in obstructive sleep apnea. *Intern Med* 51: 363-368, 2012.
56. Jurado-Gamez B, Fernandez-Marin MC, Gomez-Chaparro JL, Munoz-Cabrera L, Lopez-Barea J, Perez-Jimenez F, Lopez-Miranda J. Relationship of oxidative stress and endothelial dysfunction in sleep apnoea. *Eur Respir J* 37: 873-879, 2011.
57. Kasai T, Inoue K, Kumagai T, Kato M, Kawana F, Sagara M, Ishiwata S, Ohno M, Yamaguchi T, Momomura S, Narui K. Plasma pentraxin3 and arterial stiffness in men with obstructive sleep apnea. *Am J Hypertens* 24: 401-407, 2011.
58. Katsoulis K, Kontakiotis T, Spanogiannis D, Vlachogiannis E, Kougioulis M, Gerou S, Daskalopoulou E. Total antioxidant status in patients with obstructive sleep apnea without comorbidities: The role of the severity of the disease. *Sleep & Breathing = Schlaf & Atmung* 15: 861-866, 2011.
59. Kohler M, Craig S, Nicoll D, Leeson P, Davies RJ, Stradling JR. Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea. *Am J Respir Crit Care Med* 178: 984-988, 2008.
60. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 7: 677-685, 2010.
61. Kohli P, Balachandran JS, Malhotra A. Obstructive sleep apnea and the risk for cardiovascular disease. *Curr Atheroscler Rep* 13: 138-146, 2011.
62. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, Boehlecke B, Brown TM, Coleman J, Jr., Friedman L, Kapen S, Kapur VK, Kramer M, Lee-Chiong T, Owens J, Pancer JP, Swick TJ, Wise MS, American Academy of Sleep M. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 29: 375-380, 2006.
63. Kwon Y, Duprez DA, Jacobs DR, Nagayoshi M, McClelland RL, Shahar E, Budoff M, Redline S, Shea S, Carr JJ, Lutsey PL. Obstructive sleep apnea and progression of coronary artery calcium: The multi-ethnic study of atherosclerosis study. *J Am Heart Assoc* 3: e001241, 2014.
64. Kylintireas I, Craig S, Nethononda R, Kohler M, Francis J, Choudhury R, Stradling J, Neubauer S. Atherosclerosis and arterial stiffness in obstructive sleep apnea—a cardiovascular magnetic resonance study. *Atherosclerosis* 222: 483-489, 2012.
65. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 42: 1547-1554, 2003.
66. Lavie L. Oxidative stress—a unifying paradigm in obstructive sleep apnea and comorbidities. *Prog Cardiovasc Dis* 51: 303-312, 2009.
67. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia—revisited—the bad ugly and good: Implications to the heart and brain. *Sleep Med Rev* 20C: 27-45, 2015.
68. Lavie L. Oxidative stress inflammation and endothelial dysfunction in obstructive sleep apnea. *Front Biosci (Elite Ed)* 4: 1391-1403, 2012.
69. Lin QC, Chen LD, Yu YH, Liu KX, Gao SY. Obstructive sleep apnea syndrome is associated with metabolic syndrome and inflammation. *Eur Arch Otorhinolaryngol* 271: 825-831, 2014.
70. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: A systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 5: 720-728, 2012.
71. Lui MM, Lam DC, Ip MS. Significance of endothelial dysfunction in sleep-related breathing disorder. *Respirology* 18: 39-46, 2013.
72. Lurie A. Endothelial dysfunction in adults with obstructive sleep apnea. *Adv Cardiol* 46: 139-170, 2011.
73. Makarenko VV, Usatyuk PV, Yuan G, Lee MM, Nanduri J, Natarajan V, Kumar GK, Prabhakar NR. Intermittent hypoxia-induced endothelial barrier dysfunction requires ROS-dependent MAP kinase activation. *Am J Physiol Cell Physiol* 306: C745-752, 2014.
74. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, Barbe F, Vicente E, Wei Y, Nieto FJ, Jelic S. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* 307: 2169-2176, 2012.
75. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* 365: 1046-1053, 2005.
76. Martin K, Stanchina M, Kouttab N, Harrington EO, Rounds S. Circulating endothelial cells and endothelial progenitor cells in obstructive sleep apnea. *Lung* 186: 145-150, 2008.
77. Martinez-Garcia MA, Campos-Rodriguez F, Catalan-Serra P, Soler-Cataluna JJ, Almeida-Gonzalez C, De la Cruz Moron I, Duran-Cantolla J, Montserrat JM. Cardiovascular mortality in obstructive sleep apnea in the elderly: Role of long-term continuous positive airway pressure treatment: A prospective observational study. *Am J Respir Crit Care Med* 186: 909-916, 2012.
78. Martinez-Garcia MA, Campos-Rodriguez F, Soler-Cataluna JJ, Catalan-Serra P, Roman-Sanchez P, Montserrat JM. Increased incidence of nonfatal cardiovascular events in stroke patients with sleep apnoea: Effect of CPAP treatment. *Eur Respir J* 39: 906-912, 2012.
79. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, Lloberes P, Diaz de Atauri MJ, Somoza M, Masa JF, Gonzalez M, Sacristan L, Barbe F, Duran-Cantolla J, Aizpuru F, Manas E, Barreiro B, Mosteiro M, Cebrian JJ, de la Pena M, Garcia-Rio F, Maimo A, Zapater J, Hernandez C, Grau SanMarti N, Montserrat JM, Spanish Sleep N. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: The HIPARCO randomized clinical trial. *Jama* 310: 2407-2415, 2013.
80. Martinez-Garcia MA, Soler-Cataluna JJ, Ejarque-Martinez L, Soriano Y, Roman-Sanchez P, Illa FB, Canal JM, Duran-Cantolla J. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: A 5-year follow-up study. *Am J Respir Crit Care Med* 180: 36-41, 2009.
81. McEvoy RD, Anderson CS, Antic NA, Chen B, He Q, Heeley E, Huang S, Huang Y, Wang J, Zhong N. The sleep apnea cardiovascular endpoints (SAVE) trial: Rationale and start-up phase. *J Thorac Dis* 2: 138-143, 2010.
82. McNicholas WT. Arousal in the sleep apnoea syndrome: A mixed blessing? *Eur Respir J* 12: 1239-1241, 1998.

83. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: Long-term prognosis. *Am J Respir Crit Care Med* 164: 1910-1913, 2001.
84. Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke* 37: 2317-2321, 2006.
85. Netzer N, Werner P, Jochums I, Lehmann M, Strohl KP. Blood flow of the middle cerebral artery with sleep-disordered breathing: Correlation with obstructive hypopneas. *Stroke* 29: 87-93, 1998.
86. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farre R. Sleep-disordered breathing and cancer mortality: Results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 186: 190-194, 2012.
87. Paton JF, Ratcliffe L, Hering D, Wolf J, Sobotka PA, Narkiewicz K. Revelations about carotid body function through its pathological role in resistant hypertension. *Curr Hypertens Rep* 15: 273-280, 2013.
88. Paton JF, Sobotka PA, Fudim M, Engelman ZJ, Hart EC, McBryde FD, Abdala AP, Marina N, Gourine AV, Lobo M, Patel N, Burchell A, Ratcliffe L, Nightingale A. The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. *Hypertension* 61: 5-13, 2013.
89. Patt BT, Jarjoura D, Haddad DN, Sen CK, Roy S, Flavahan NA, Khayat RN. Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 182: 1540-1545, 2010.
90. Peker Y, Glantz H, Thunstrom E, Kallryd A, Herlitz J, Ejdeback J. Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea–RICCADSA trial. *Scand Cardiovasc J* 43: 24-31, 2009.
91. Peppard PE, Ward NR, Morrell MJ. The impact of obesity on oxygen desaturation during sleep-disordered breathing. *Am J Respir Crit Care Med* 180: 788-793, 2009.
92. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 177: 1006-1014, 2013.
93. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *Jama* 284: 3015-3021, 2000.
94. Pettersen KH, Bugenhagen SM, Nauman J, Beard DA, Omholt SW. Arterial stiffening provides sufficient explanation for primary hypertension. *PLoS Comput Biol* 10: e1003634, 2014.
95. Phillips CL, Butlin M, Wong KK, Avolio AP. Is obstructive sleep apnoea causally related to arterial stiffness? A critical review of the experimental evidence. *Sleep Med Rev* 17: 7-18, 2013.
96. Pialoux V, Hanly PJ, Foster GE, Brugniaux JV, Beaudin AE, Hartmann SE, Pun M, Duggan CT, Poulin MJ. Effects of exposure to intermittent hypoxia on oxidative stress and acute hypoxic ventilatory response in humans. *Am J Respir Crit Care Med* 180: 1002-1009, 2009.
97. Pickering TG. Arterial stiffness as a cause of resistant hypertension? *J Clin Hypertens (Greenwich)* 9: 390-395, 2007.
98. Priou P, Gagnadoux F, Tesse A, Mastronardi ML, Agouni A, Meslier N, Racineux JL, Martinez MC, Trzepizur W, Andriantsitohaina R. Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. *Am J Pathol* 177: 974-983, 2010.
99. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. *Am J Epidemiol* 160: 521-530, 2004.
100. Querido JS, Sheel AW, Cheema R, Van Eeden S, Mulgrew AT, Ayas NT. Effects of 10 days of modest intermittent hypoxia on circulating measures of inflammation in healthy humans. *Sleep Breath* 16: 657-662, 2012.
101. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *Am J Respir Crit Care Med* 182: 269-277, 2010.
102. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *Am J Respir Crit Care Med* 182: 269-277, 2010.
103. Scorza FA, Cavalheiro EA, Scorza CA, Galduroz JC, Tufik S, Andersen ML. Sleep apnea and inflammation—getting a good night's sleep with Omega-3 supplementation. *Front Neurol* 4: 193, 2013.
104. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep & breathing = Schlaf & Atmung* 14: 131-136, 2010.
105. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 163: 19-25, 2001.
106. Somers VK, Mark AL, Zavala DC, Abboud FM. Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans. *J Appl Physiol (1985)* 67: 2095-2100, 1989.
107. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T, American Heart Association Council for High Blood Pressure Research Professional Education Committee CoCC, American Heart Association Stroke C, American Heart Association Council on Cardiovascular N, and American College of Cardiology F. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 118: 1080-1111, 2008.
108. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. *Ther Adv Chronic Dis* 6: 273-285, 2015.
109. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 137: 95-101, 2010.
110. Stiefel P, Sanchez-Armengol MA, Villar J, Vallejo-Vaz A, Moreno-Luna R, Capote F. Obstructive sleep apnea syndrome, vascular pathology, endothelial function and endothelial cells and circulating microparticles. *Arch Med Res* 44: 409-414, 2013.
111. Stradling JR, Craig SE, Kohler M, Nicoll D, Ayers L, Nunn AJ, Bratton DJ. Markers of inflammation: Data from the MOSAIC randomised trial of CPAP for minimally symptomatic OSA. *Thorax* 70: 181-182, 2014.
112. Strollo PJ, Jr., Rogers RM. Obstructive sleep apnea. *N Engl J Med* 334: 99-104, 1996.
113. Strollo PJ, Jr., Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP, Group ST. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 370: 139-149, 2014.
114. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, Cistulli PA. Oral appliance treatment for obstructive sleep apnea: An update. *J Clin Sleep Med* 10: 215-227, 2014.
115. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Altaf QA, Piya MK, Barnett AH, Stevens MJ. Obstructive sleep apnea and diabetic nephropathy: A cohort study. *Diabetes Care* 36: 3718-3725, 2013.
116. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Mughal S, Jose B, Piya MK, Barnett AH, Stevens MJ. Obstructive sleep apnea and diabetic neuropathy: A novel association in patients with type 2 diabetes. *Am J Respir Crit Care Med* 186: 434-441, 2012.
117. Tamisier R, Pepin JL, Remy J, Baguet JP, Taylor JA, Weiss JW, Levy P. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. *Eur Respir J* 37: 119-128, 2011.
118. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A* 105: 1044-1049, 2008.
119. Trzebski A. Arterial chemoreceptor reflex and hypertension. *Hypertension* 19: 562-566, 1992.
120. Utriainen KT, Airaksinen JK, Polo O, Laitio R, Pietila MJ, Scheinin H, Vahlberg T, Leino KA, Kentala ES, Jalonen JR, Hakovirta H, Parkkola R, Virtanen S, Laitio TT. Sleep apnoea is associated with major cardiac events in peripheral arterial disease. *Eur Respir J* 43: 1652-1660, 2014.
121. Utriainen KT, Airaksinen JK, Polo O, Raitakari OT, Pietila MJ, Scheinin H, Helenius HY, Leino KA, Kentala ES, Jalonen JR, Hakovirta H, Salo TM, Laitio TT. Unrecognised obstructive sleep apnoea is common in severe peripheral arterial disease. *Eur Respir J* 41: 616-620, 2013.
122. Vlachantoni IT, Dikaiakou E, Antonopoulos CN, Stefanadis C, Daskalopoulou SS, Petridou ET. Effects of continuous positive airway pressure (CPAP) treatment for obstructive sleep apnea in arterial stiffness: A meta-analysis. *Sleep Med Rev* 17: 19-28, 2013.
123. Wang X, Ouyang Y, Wang Z, Zhao G, Liu L, Bi Y. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: A meta-analysis of prospective cohort studies. *Int J Cardiol* 169: 207-214, 2013.
124. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: The challenge to effective treatment. *Proc Am Thorac Soc* 5: 173-178, 2008.
125. Wozniak DR, Lasserson TJ, Smith I. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev* 1: CD007736, 2014.

126. Xie W, Zheng F, Song X. Obstructive sleep apnea and serious adverse outcomes in patients with cardiovascular or cerebrovascular disease: A PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)* 93: e336, 2014.
127. Xie X, Pan L, Ren D, Du C, Guo Y. Effects of continuous positive airway pressure therapy on systemic inflammation in obstructive sleep apnea: A meta-analysis. *Sleep Med* 14: 1139-1150, 2013.
128. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 353: 2034-2041, 2005.
129. Yim-Yeh S, Rahangdale S, Nguyen AT, Jordan AS, Novack V, Veves A, Malhotra A. Obstructive sleep apnea and aging effects on macrovascular and microcirculatory function. *Sleep* 33: 1177-1183, 2010.
130. Yim-Yeh S, Rahangdale S, Nguyen AT, Stevenson KE, Novack V, Veves A, Malhotra A. Vascular dysfunction in obstructive sleep apnea and type 2 diabetes mellitus. *Obesity (Silver Spring)* 19: 17-22, 2011.
131. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 31: 1071-1078, 2008.
132. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *Jama* 291: 2013-2016, 2004.
133. Zhou S, Wang Y, Tan Y, Cai X, Cai L, Cai J, Zheng Y. Deletion of metallothionein exacerbates intermittent hypoxia-induced oxidative and inflammatory injury in aorta. *Oxid Med Cell Longev* 2014: 141053, 2014.