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CLINICAL REVIEW

Obstructive sleep apnea and coronary artery disease

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Summary In the recent years intensive research has revealed numerous negative consequences of obstructive sleep apnea (OSA) for the cardiovascular system. The pathophysiological interaction between OSA and coronary artery disease is complex and comprises neural, humoral, mechanical and haemodynamic components. One of the most important effects of OSA is an increase of sympathetic nerve traffic, which persists during the day and is thought to play a key role in the association of OSA and elevated systemic blood pressure. Nowadays, OSA is accepted as an independent risk factor for arterial hypertension. Several investigations support an association of OSA with ischemic ST-segment changes, ventricular arrhythmias, and sudden cardiac death. In line with this, a growing body of evidence strongly supports OSA having prognostic implications for cardiovascular morbidity and mortality. Continuous positive airway pressure (CPAP) has been shown to have several beneficial effects on the cardiovascular system. Uncontrolled studies indicate that it reduces cardiovascular risk in patients with severe OSA and increased risk or manifest coronary artery disease. However, ongoing studies still have to confirm this.

Introduction

Coronary artery disease (CAD) is a chronic, life-threatening disease. Progressive arteriosclerosis in the coronary arteries may lead to intimal thickening and eventual stenosis of the coronary arteries, with flow limitation and a subsequent imbalance of myocardial oxygen supply and demand, causing stable angina pectoris or its equivalents. Atherosclerotic plaque rupture with associated platelet adhesion and thrombus formation form the basis of acute coronary syndromes ranging from unstable angina to non-Q-wave and Q-wave myocardial infarction.[1]

Although mortality due to CAD has slightly decreased in the past decade, CAD remains the most common cause of death, with an incidence of 380 myocardial infarctions per 100 000 persons aged between 36 and 64 years per year.[2] In the

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Physicians' Health Study, the incidence was even higher, with 440 myocardial infarctions per 100 000 physicians per year.[3] Risk factors, lifestyle and socio-economic circumstances probably account for the large regional variation.[2]

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway, thereby inducing apnea and hypopnea episodes despite persistent thoracic and abdominal respiratory effort. The disease has a high prevalence in the general population. It is estimated that in the middle-aged population about 4% of men and 2% of women suffer from manifest OSA.[4] Numerous deleterious effects result from obstructive apnea and hypopnea with large negative intrathoracic pressure changes and blood gas deterioration. It has long been known that OSA causes substantial sleep fragmentation with excessive daytime sleepiness.[5] Moreover, intensive research in recent years has also revealed negative consequences for the cardiovascular system, such as pulmonary hypertension, congestive heart failure, stroke, atrial fibrillation, and left ventricular diastolic dysfunction.[6–10] This review focuses on the association of OSA and coronary artery disease (CAD), including ischemia, ventricular arrhythmias and arterial hypertension, and its prognostic implications.

Pathophysiology

The pathophysiological interaction between OSA and coronary artery disease is complex and comprises neural, humoral, mechanical and hemodynamic components (Figure 1).

Acute effects

Mechanical and hemodynamic effects arise from the recurrent negative intrathoracic pressure changes occurring during airway obstruction. Excessive negative intrathoracic pressure up to -80 cm H_2O lead to an increase of venous return to the right ventricle.[11,12] This volume overload of the right ventricle causes the interventricular septum to shift to the left impeding left ventricular filling.[7,13] This is further impaired by reduced left ventricular relaxation.[14] The transmural pressure of the left ventricle is increased by negative intrathoracic pressure.[15] Thus, airway obstruction acutely increases both left ventricular preload and afterload, which is further increased by surges in blood pressure as detailed below. These mechanisms reduce stroke volume and cardiac output.[16–18]

Sympathetic activation as neural component is thought to be a key mechanism linking OSA to

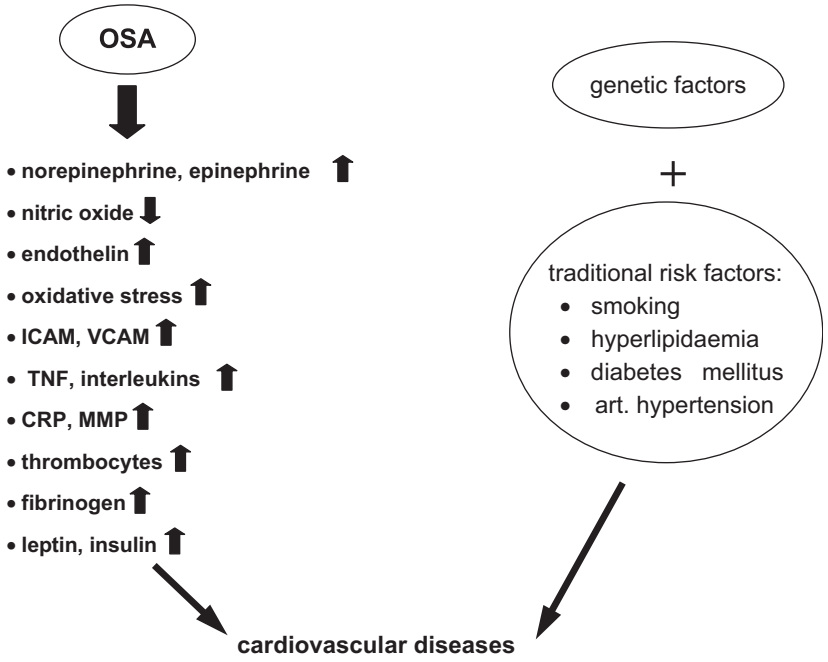

Figure 1 Pathophysiology of cardiovascular diseases. On the left, pathophysiological consequences of OSA are displayed, on the right OSA-independent factors predisposing to cardiovascular diseases are shown. ICAM = intercellular adhesion molecule-1; VCAM = vascular cell adhesion molecule-1, TNF = tumour necrosis factor-a, CRP = C-reactive protein; MMP = matrix metalloproteinases. Adapted from Schulz et al.[103] with permission.

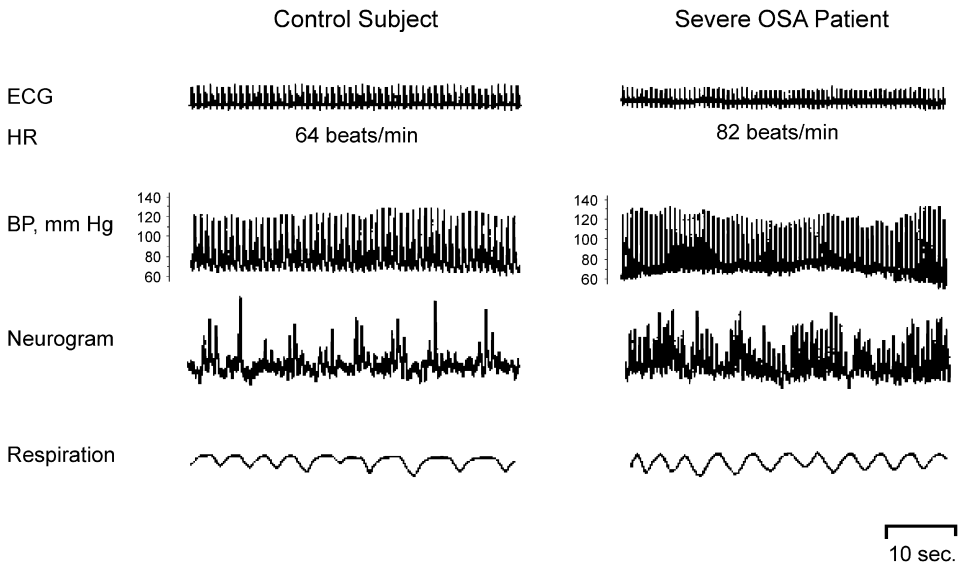

Figure 2 Consequences of OSA (right) as compared to control (left) on ECG, blood pressure, sympathetic activation, and respiration. The OSA patient has a faster heart rate, increased blood pressure variability, and markedly elevated muscle sympathetic nerve activity. HR = heart rate; BP = blood pressure ECG = electrocardiogram; OSA = obstructive sleep apnea. Reproduced with permission from Narkiewicz et al.[26]

cardiovascular diseases.[19] During apnea the inhibitory effect of pulmonary stretch receptors on central sympathetic discharge is reduced.[7] In addition, hypoxia and hypercapnia stimulate central and peripheral chemoreceptors, further enhancing sympathetic activity.[20,21] Furthermore, an increase of the chemoreflex drive in OSA patients compared to normal controls may contribute to increased sympathetic nerve traffic.[22,23] Arousals terminating the apnea further contribute to sympathetic activation.[24,25] As a result heart rate is increased, furthermore the boost in vascular resistance leads to profound surges in blood pressure[26,27] (Figure 2). Recurrent arousals may also propagate the cycling of obstructive, mixed or even central apneas.

During sleep, numerous occlusions occur in patients with OSA, repeatedly straining the heart and circulation throughout the night.

Chronic effects

Sympathetic activation is not limited to the night but persists during daytime, as evidenced by norepinephrine concentration in plasma and urine as well as muscle sympathetic nerve activity.[19,27–31] In line with this, OSA patients have higher heart rates, a more blunted heart rate variability, and higher blood pressure variability than healthy controls.[26,32] Autonomic imbalance has been identified as a potent risk factor for cardiovascular events.[33,34] Increased daytime blood pressure in OSA patients is also believed to be substantially caused by the higher sympathetic nerve traffic.[30] In patients with chronic heart failure, sympathetic activation is associated with impaired endothelial function resulting in decreased exercise-induced vasodilatation in skeletal muscle. Sympathetic activation has also been linked to a decreased amount of type 1 skeletal muscle fibers, to cardiomyocyte injury and apoptosis and to catabolic/anabolic imbalance with muscle wasting and lipolysis.[35–38] Some data indicate a connection between sympathetic activation, impaired glucose tolerance and leptin resistance.[39–41] OSA patients have higher fasting blood glucose levels and are at increased risk of developing diabetes mellitus.[42,43] Furthermore, leptin levels in OSA patients are higher than in matched similarly obese persons without OSA, and this may predispose to platelet aggregation.[40,44] Leptin resistance may increase the tendency to weight gain in OSA patients. OSA is independently associated with an increased incidence of the metabolic syndrome.[45] Given the current high incidence of obesity, the prevalence of OSA and the metabolic syndrome will continue to rise in the coming years.[46] Obesity itself has numerous adverse effects on CAD risk factors and is clearly associated with cardiovascular disease. It predisposes to arterial hypertension and left ventricular hypertrophy, compromises diastolic and systolic ventricular function, adversely affects plasma lipids and contributes to insulin resistance.[47] These negative consequences can be reversed by weight reduction.[46–49] Other factors

also contribute to a disturbance of the vascular micromilieu linking OSA with arterial hypertension, atherosclerosis and thus coronary artery disease. Impairment of endothelial function is present in OSA patients, increased levels of endothelin as well as decreased release of NO have been described.[12,32,41,50–56] Endothelial dysfunction is an established precursor of arterial hypertension and has been linked to increased risk of cardiovascular events.[54,57–59] Oxidative stress and decreased antioxidant capacity, as seen in OSA, may be another trigger leading to atherosclerosis in these patients.[60–64] Inflammation may also contribute to the development of atherosclerosis.[41,65,66] Several studies showed increased levels of cytokines,[67] matrix metalloproteinases,[68] acute phase proteins,[69,70] as well as endothelial adhesion molecules.[71] First data indicate that CD8+ T-lymphocytes may also play a role in this inflammatory process.[72] Recently, an association of OSA and elevated levels of creatine phosphokinase from skeletal muscle has been shown.[73] Direct evidence for advanced atherosclerosis in OSA patients as compared to matched controls derives from studies investigating the carotid arteries. These studies revealed an increase in pulse wave velocity, diameter and intima-media-thickness of the carotid arteries in OSA patients.[74–76] The thickness was directly related to the extent of nightly desaturations and was positively correlated with serum concentrations of inflammatory mediators.[77,78]

Finally, hypercoagulability may, by predisposing to clot formation, contribute to atherosclerosis.[12] Increases of hematocrit, plasma fibrinogen and blood viscosity have been shown in OSA.[79–82]

In summary, numerous acute and chronic effects contribute to the development of cardiac ischemia, arterial hypertension as well as coronary artery disease. In the following, we will elucidate clinical consequences deriving from the above-outlined pathophysiologic changes.

Cardiovascular consequences

Myocardial ischemia

As mentioned above, myocardial ischemia occurs as a result of reduced oxygen supply or increased oxygen demand. OSA may reduce myocardial blood flow and/or increase demand by acute changes in heart rate on the one hand and increase in afterload on the other hand. This occurs in the setting of reduced oxygen supply caused by apnea-associated hypoxemia. These factors may predispose to myocardial ischemia. Indeed, asymptomatic ST-segment depressions during sleep were evident in patients with OSA but without clinical evidence of CAD.[83] Further evidence was added by Alonso-Fernandez et al.,[84] who reported a higher incidence of asymptomatic arrhythmias and ST-segment depression in patients with OSA as compared to controls. However, the coronary status was not evaluated. Andreas et al.[85] could not confirm these results, concluding that OSA does not lead to ischemic ST-segment changes in the absence of CAD. ST-segment depressions seem highly frequent in patients complaining of nocturnal angina, and are associated with episodes of oxygen desaturation. OSA was present among 9 of 10 ischemic patients who suffered from nocturnal angina pectoris.[86] Another study revealed that 5 out of 14 patients with OSA and CAD suffered from nocturnal myocardial ischemia. Apnea and oxygen desaturation were present in 85% of the ischemic episodes.[87] Mooe et al.[88] found nocturnal ST-segment depression in 31% of 226 patients with angina pectoris undergoing coronary angiography. However, a temporal association between ST-segment depression and apnea–hypopnea or desaturation was found only in 19% of nocturnal ST-segment depressions. In summary, there is evidence for nocturnal myocardial ischemic events triggered by OSA in patients with CAD. However, in patients without concomitant CAD, the data is inconclusive. From a pathophysiological point of view, OSA-induced nocturnal myocardial ischemia in the latter patient population seems unlikely.

Several studies have supported a possible association between the time pattern of myocardial infarction and sleep apnea. The rise in sympathetic activity during increasing REM sleep in the early morning hours might contribute to this relation.[27] The prevalence of sleep apnea was significantly higher in those patients experiencing myocardial infarction during sleep or in the morning hours.[89–91] Of note, a recent study indicates that OSA might inhibit recovery of left ventricular function in patients with ST-elevation myocardial infarction.[92]

Ventricular arrhythmia and sudden cardiac death

Early investigations indicated that non-sustained ventricular arrhythmias are common in OSA patients.[93,94] Flemons et al.,[95] however, detected no significant difference in the occurrence of cardiac arrhythmias in patients with and without OSA. Subsequent studies in patients with and without chronic heart failure again implicate an association

between OSA and ventricular arrhythmias.[96,97] Recent data from the Sleep Heart Health Study, investigating 228 patients with severe sleep apnea (Apnea–hypopnea index (AHI) > 30/h) and 338 subjects without (AHI < 5/h), also support the relation of OSA and ventricular arrhythmia (nonsustained ventricular tachycardia, bigemminy, trigemminy or quadrigemminy).[98] A significant relation was detected between sleep apnea and the occurrence of ventricular premature beats. After adjusting for several confounding factors including CAD, patients with severe sleep apnea were three times as likely to have nonsustained ventricular tachycardia, and almost twice as likely to have complex ventricular ectopy. Alteration of QT rate dependence seen in patients with OSA might contribute to increased ventricular irritability.[99] Recently, Gami and coworkers[100] showed a peak in sudden death from cardiac causes during sleeping hours in patients with OSA in contrast to those without. More than half of patients investigated had concomitant arterial hypertension, heart failure and CAD. However, the study was not prospectively designed, the patient population investigated was relatively small ($n = 112$), and some of the OSA patients were treated with CPAP.

In summary, there is some evidence for an association between sleep-disordered breathing, ventricular arrhythmia and sudden cardiac death. This data is further supported by the fact that emotional stress, mediated presumably by elevated sympathetic tone, has been shown to be a trigger for sudden cardiac death.[101,102] From the data detailed above, it is thus reasonable to postulate that OSA is a risk factor for sudden cardiac death, especially if concomitant structural heart disease is present.

Arterial hypertension

About half of OSA patients suffer from arterial hypertension, while in about a quarter of patients with hypertension a concomitant OSA is present.[54,103] In patients with drug-resistant hypertension an even higher OSA prevalence of 83% has been described.[104] A direct link for a causal relationship between OSA and arterial hypertension was provided from animal studies in rats and dogs.[105–107] Four dogs were chronically instrumented to generate artificial nocturnal OSA. Acute effects were a transient increase of blood pressure during the night. Importantly, after 3 months the animals also suffered from an increase in blood pressure during the day. Evidence for an association between OSA and arterial hypertension in humans has been shown in many studies.[59,108–111] The Sleep Heart Health Study, a cross-sectional analysis of > 6000 participants, showed an independent association between OSA and hypertension.[110] However, a subgroup analysis revealed that in persons older than 65 years this association did not persist.[112] The most compelling evidence for the contributory effect of OSA to arterial hypertension comes from the Wisconsin Sleep Cohort Study.[111] It showed that OSA is an independent risk factor for the development of arterial hypertension during a four-year follow-up period. Furthermore, the odds ratio for developing arterial hypertension increased with the severity of OSA. The results of a recent study indicate a possible sex-dependent difference in susceptibility to hypertension development in OSA as an association between OSA and hypertension was not evident in post-menopausal females.[113]

Nowadays, the association of OSA and arterial hypertension is widely accepted and has resulted in a recommendation of the Joint National Committee of the NIH to evaluate patients with arterial hypertension for the presence of OSA.[114] Of note, an association between OSA and thoracic aortic dissection has been evaluated.[115] This association seems reasonable as arterial hypertension is the main risk factor for thoracic aorta dissection.

As arterial hypertension is a major risk factor for the development of coronary artery disease, and as OSA is now a recognised cause of hypertension, sleep-disordered breathing should be considered an important factor in the development of CAD.

Coronary artery disease

Prevalence

As mentioned above, the prevalence of OSA in the normal middle-aged population is about 2–4%. Different studies have shown a higher prevalence of OSA in patients with coronary artery disease. The largest study included 142 men with CAD verified by angiography. Polysomnographic evaluation revealed a significantly higher apnea hypopnea index (AHI) in this patient population compared to age-matched controls. An AHI > 10/h has been shown in 37% of the patients with CAD.[116] Several studies on slightly overweight patients with CAD yielded similar results with an incidence of OSA between 31% and 50%.[88,117–122]

Hung and coworkers[123] investigated male patients after myocardial infarction and found a mean AHI of 13/h, whereas the AHI was only 4/h in male controls without evidence of ischaemic heart disease. In another study the prevalence of CAD was 25% in patients with OSA proven by

polysomnography.[124] However, this high prevalence might be caused by a referral bias since the investigating institution has a local reputation for CAD.

As OSA and coronary artery disease share some common risk factors such as obesity, male sex, smoking, and advanced age,[4,125,126] the question of a causal relationship between OSA and CAD remains.

OSA as risk factor for CAD

From the above-mentioned pathophysiological considerations, the fact that OSA is associated with increased risk for arterial hypertension, and the high prevalence of OSA in patients with CAD, the hypothesis of OSA being a risk factor for CAD seems plausible. However, this causal relationship is presently not as clear-cut as it is for arterial hypertension. Although several studies revealed an association of OSA with CAD, their value was mostly limited because of selection bias, small number of patients, or the absence of a control group. Peker and coworkers[120] demonstrated an independent correlation between OSA and CAD in 62 patients requiring intensive care for angina pectoris or myocardial infarction. After a 5-year follow-up of this CAD group, the AHI was the only independent predictor of cardiovascular mortality.[127] This association was further supported by another study following 308 subjects without hypertension or any coronary vascular disease from a sleep clinic during a period of 7 years.[128,129] Those patients with OSA at baseline had a 4.9-fold increased risk for coronary vascular disease independent of age, sex, blood pressure, diabetes or smoking. The above-mentioned Sleep Heart Health Study revealed a modest, but significantly increased risk of 1.2 (95%, CI 0.99–1.62) of self-reported CAD in those patients with an AHI >30/h compared to those with an AHI <1.5/h.[110] Of note, this analysis was based on a small number of patients in the highest AHI quartile, which might have attenuated the effect described above. However, sleep-disordered breathing was associated more strongly with self-reported heart failure and stroke than with CAD. In another study 408 patients with coronary artery disease underwent polysomnographic evaluation and were followed for a median of 5.1 years. An oxygen desaturation index of $\geqslant 5$/h was associated with a 70% relative increase in the primary composite endpoint of death, cerebrovascular events, and myocardial infarction.[130] Recently, another important observational study by Marin et al.[131] has been published. The authors investigated simple snorers, patients with untreated obstructive sleep apnoea–hypopnoea, patients treated with CPAP, and healthy men recruited from the general population over a follow-up period of 10 years ($n = 1651$). Endpoints were defined as non-fatal (non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) and fatal (death from myocardial infarction or stroke) cardiovascular events. Multivariate analysis showed that the risk of fatal (odds ratio 2.87, 95% CI 1.17–7.51) and non-fatal (3.17, 1.12–7.51) cardiovascular events was significantly increased in severe untreated OSA patients as compared to healthy controls (Figure 3). Patients with mild-to-moderate untreated OSA had an intermediate risk for cardiovascular events. This indicates a dose-effect

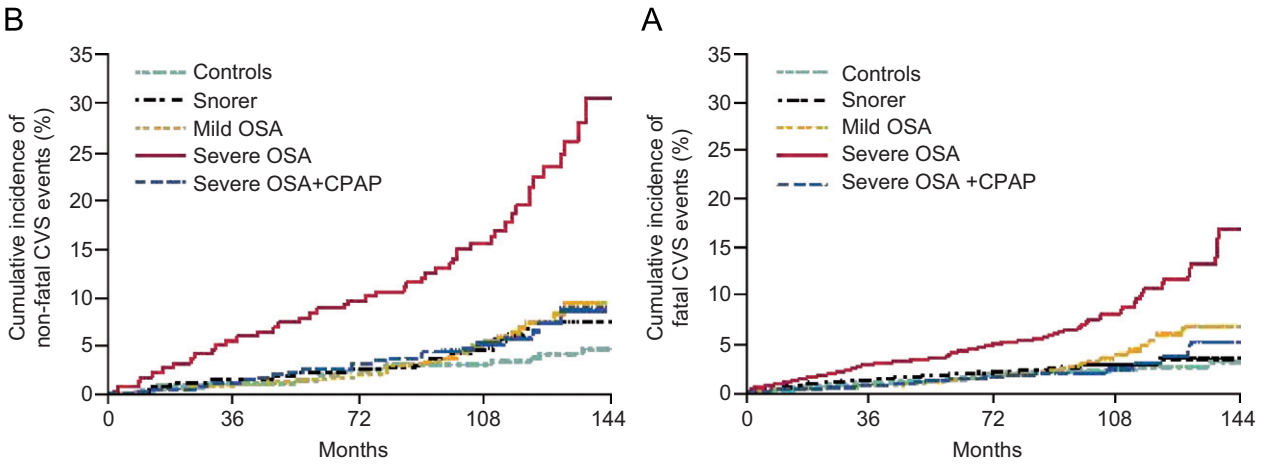

Figure 3 Cardiovascular consequences of OSA. On the left the cumulative percentage of non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography) and on the right of fatal events (death from myocardial infarction or stroke) are shown for the different subgroups as detailed in the figure. Reproduced with permission from Marin et al.[131]

relation. Schäfer et al.[123] also demonstrated an independent association between moderate OSA and myocardial infarction.

Although the association of OSA and CAD is not definitely established at present, the data strongly supports OSA being a risk factor for CAD. One causative link comprises arterial hypertension. Furthermore, much evidence seems to indicate another connection via endothelial dysfunction as detailed above.

Effect of CPAP treatment

General therapeutic options for OSA comprise first of all reduction of body weight, which may reduce the severity of OSA,[132] but also abstinence from alcohol and sedatives, positional therapy or treatment of nasal obstruction. More specific therapeutic options for OSA involve oral appliances or in selected patients surgical approaches.[133,134] Recently, atrial overdrive pacing has been suggested as new alternative therapy for OSA, however subsequent studies could not confirm the beneficial results.[135–138] The most effective treatment for OSA is continuous positive airway pressure (CPAP) treatment.[139] Positive airway pressure prevents upper airway collapse by acting as a pneumatic splint. This method maintains airway patency and oxyhemoglobin saturation, resulting in improvement of sleep quality, reduction of daytime sleepiness, and augmentation of neurocognitive function.[140] Additionally, multiple positive effects of CPAP on the cardiovascular system have been described and shall be reviewed in the following section.

Pathophysiology

CPAP therapy markedly reduces nocturnal sympathetic activation, thereby reducing heart rate and blunting blood pressure surges.[27,141–143] In patients with OSA and chronic heart failure it has been shown that CPAP reduces left ventricular preload and afterload.[144,145] Importantly, several investigations showed that nocturnal, and daytime sympathetic activation is reduced by CPAP therapy.[146–149] Furthermore, CPAP therapy has a positive effect on oxidative stress and endothelial dysfunction.[36,50,53,60,150] Data on glucose intolerance and CPAP treatment at present are conflicting, while there is evidence that CPAP reduces leptin levels.[151–155] Finally, CPAP therapy positively influences platelet aggregability and fibrinogen levels.[79,156,157]

Ischemia and ventricular arrhythmia

Several studies indicate a protective role of CPAP treatment on ischemia and ventricular arrhythmias. CPAP therapy ameliorates nocturnal ST-segment depression and angina.[86,158] Furthermore ventricular repolarization changes, which may contribute to higher ventricular irritability, are reversed by CPAP therapy.[159] Finally, a reduction of ventricular irritability in patients with chronic heart failure and central or OSA by CPAP was observed.[160] This data was confirmed by Ryan et al.,[161] who investigated patients with chronic heart failure and OSA. The authors found a significant reduction of ventricular premature beat frequency in those patients treated with CPAP as compared to those without CPAP therapy.

Arterial hypertension

Several placebo-controlled investigations revealed a positive effect of CPAP treatment on 24-h blood pressure.[162–165] This effect seems independent of increased nocturnal oxyhemoglobin by CPAP.[166] However, the positive effect seems dependent on the severity of sleep apnea and hypertension. In the study by Faccenda et al.[162] only normotensive patients with a median AHI of 35/h were investigated, the reduction in blood pressure in the overall population was minimal. Pepperell et al.[163] demonstrated a reduction of 3.3 mmHg in 24 h mean arterial blood pressure, this effect was distinct especially in those patients with severe OSA. Becker et al.[164] investigated mostly patients with severe OSA and a high proportion of patients with arterial hypertension. The investigators could show a reduction in mean arterial blood pressure of 9.9 mmHg after 9 weeks of CPAP treatment (Figure 4). In mild to moderate sleep apnea, however, no change of 24 h blood pressure was observed after an 8-week treatment period.[167] Recently, Campos-Rodriguez et al.[168] documented no additional blood pressure reduction by CPAP in patients with OSA and known hypertension already receiving antihypertensive medical treatment.[168] Two studies indicate that presence of symptoms is another important predictor for an improvement of blood pressure by CPAP.[169,170] These studies investigated patients with OSA but without daytime sleepiness and were unable to demonstrate a favourable effect of CPAP on arterial blood pressure. Altogether patients with severe OSA, daytime sleepiness and arterial hypertension seem to benefit most from CPAP treatment.

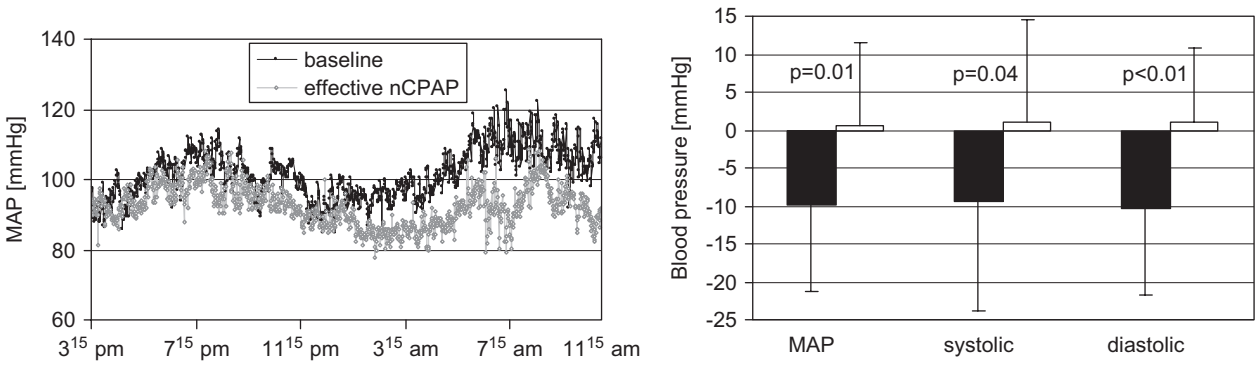

Figure 4 Effect of CPAP treatment on arterial hypertension in OSA. On the left the time course of mean arterial pressure before (black) and during (grey) therapeutic CPAP treatment are shown. On the right the effect of therapeutic CPAP (black) and subtherapeutic CPAP (white) on mean, systolic, and diastolic blood pressure are displayed. MAP = mean arterial pressure; systolic = systolic arterial pressure; diastolic = diastolic arterial pressure. Reproduced with permission from Becker et al.[164]

Coronary artery disease

Milleron et al.[171] were the first to investigate the long-term effect of OSA treatment on cardiovascular event rates. Fifty-five patients with OSA and CAD were investigated, 25 patients were treated with CPAP, whereas 29 patients declined treatment. The patients were followed for a median of 87 months. OSA treatment significantly reduced the risk of occurrence of the composite endpoint of cardiovascular death, acute coronary syndrome, hospitalisation for heart failure, or need for coronary revascularisation. This data was supported by Doherty et al.,[172] who compared the cardiovascular outcomes of 61 patients intolerant to CPAP with 107 patients on CPAP treatment over an average follow-up time of 7.5 years. Deaths from cardiovascular disease were more common in the untreated group than in the CPAP group. The strongest evidence for a protective role came from the above mentioned investigation by Marin et al.[131] While patients with severe untreated OSA had a significantly higher risk for non-fatal and fatal cardiovascular events, treatment with CPAP significantly reduced cardiovascular risk in patients with severe OSA (Figure 3).

In summary, CPAP treatment has prognostic implications in patients with severe OSA and increased cardiovascular risk or present CAD.

Practice points

- OSA has multiple negative neural, humoral, mechanic and hemodynamic consequences, underlying the association of OSA and coronary artery disease.
- OSA is an independent risk factor for arterial hypertension. Thus, patients with first diagnosed arterial hypertension should be screened for OSA.
- CPAP therapy can reduce blood pressure especially in patients with arterial hypertension, severe sleep apnea and daytime sleepiness.
- The presence and severity of OSA has prognostic relevance for the risk of fatal and non-fatal cardiovascular events.
- CPAP treatment can prevent cardiovascular events in patients with severe OSA.

Research agenda

- Basic pathophysiologic mechanisms resulting in disturbance of the vascular micromilieu need further clarification, the impact of CPAP treatment on reversal of the observed changes needs to be evaluated in more controlled settings.
- The association of OSA and ventricular arrhythmias needs to be established in prospective, controlled trials. The association of sudden cardiac death and OSA needs clarification.
- The effects of CPAP treatment on blood pressure in patients without daytime symptoms needs further evaluation.
- CPAP treatment in patients with OSA without symptoms but with concomitant cardiovascular disease should be substantiated by a prospective controlled trial investigating cardiovascular morbidity and mortality benefits.

- Effects of non-CPAP treatments of OSA (such as positional therapy or oral devices) upon cardiovascular outcomes are required.

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