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Obstructive sleep apnea and atherosclerosis—update 2019

Atherosclerosis describes the narrowing of an artery due to formation of plaques. Depending on where these atherosclerotic plaques appear, they result in different manifestations, such as coronary heart disease, peripheral arterial disease, cerebral arterial disease, and their secondary disorders such as myocardial infarction or stroke. Cardiovascular diseases (CVD) are the leading cause of death in developed countries [1]; 31% of all deaths worldwide are due to CVD [2]. There are several risk factors contributing to the genesis of atherosclerosis. The major risk factors are smoking, hypertension, dyslipidemia, and diabetes. Obstructive sleep apnea (OSA) is highly associated with CVD [3, 4] and cardiovascular events like coronary revascularization, myocardial infarction, stroke, or cardiovascular death.

Obstructive sleep apnea is a sleep disorder where breathing becomes shallow or stops completely, caused by obstruction of the upper airway. It is the most common type of sleep apnea. Estimates of its prevalence vary between 2 and 50%, with a higher prevalence among men and of mild OSA [5, 6]. The prevalence is approximately three to four times higher in populations with CDV than in those without [7]. There is an especially high prevalence among people with resistant hypertension (70–83%), heart failure (>50%), and stroke [7–9]. Therefore, screening for OSA is particularly recommended in these individuals.

An apnea is defined as a cessation of breathing for more than 10 s; a hypopnea is a reduction of airflow with an oxygen desaturation of the blood by more than 4% [10]. The number of apnea and hypopnea episodes per hour define the apnea–hypopnea index (AHI). OSA is defined as AHI ≥ 5/h plus daytime sleepiness, or AHI ≥ 15/h. The degree of its severity is defined as follows: AHI 5–14.9/h defines mild, 15–29.9/h moderate, and ≥30/h severe OSA [10, 11]. Due to the cessation of airflow, oxygen desaturations occur until the apnea is ended by a so-called arousal, a short interruption of sleep [12, 13]. The frequent alternations of hypoxemia and arousals lead to sleep fragmentation. These are accompanied by activation of the sympathetic nerve system, oxidative stress, systemic inflammation, and intrathoracic pressure swings, which lead to progression of atherosclerotic lesions. Arousals do not compulsorily lead to complete awakening but make sleep less restorative and cause the blood pressure to rise [13]. The combination of OSA with its typical accompanying symptom, daytime sleepiness, is called obstructive sleep apnea syndrome (OSAS). Daytime sleepiness is often assessed by questionnaires, such as the Epworth Sleepiness Scale (ESS) [3]. A test result of ≥11 points indicates significant daytime sleepiness.

Further symptoms include snoring, headache, and memory deficits, up to symptoms of dementia. As one can imagine, by causing severe daytime sleepiness, falling asleep several times a day, and possibly even the imposition of a driving ban, OSAS can have a serious effect on people's lives. All in all, patients with OSAS suffer from poor sleep and life quality [5].

Pathomechanisms linking OSA and atherosclerosis

Obstructive sleep apnea, particularly when severe, is strongly associated with CVD such as coronary heart disease, atrial fibrillation, congestive heart failure, stroke, and peripheral arterial disease [3, 7, 12–15]. All these diseases share common risk factors, such as arterial hypertension or metabolic syndrome.

As OSA is often attended by the abovementioned comorbidities, which are also risk factors for atherosclerosis, it is difficult to evaluate the exclusive impact of OSA on atherosclerosis. Nevertheless, there are several pathophysiological changes in OSA supposed to have a direct influence on atherosclerosis [6], as demonstrated in numerous animal and human studies. The apneic events in OSA lead to intermittent hypoxemia, sleep fragmentation, and intrathoracic pressure swings, which are considered as main links between OSA and atherosclerosis [4, 14].

Intermittent hypoxemia and sleep deprivation seem to contribute to dyslipidemia, systemic inflammation, neuronal nerve activity, and oxidative stress [7, 15–18]. Furthermore, the reactive oxygen species formed induce systemic inflammation and endothelial dysfunction, further promoting atherosclerosis [17, 19]. The idea of hypoxemia contributing to formation of atherosclerotic lesions is additionally supported by findings showing that the nightly amount of hypoxemia is associated with CVD [20]. Beyond that, it induces new and contributes to existing atherosclerotic lesions in mouse models [15].

Table 1 Review of important randomized controlled trials assessing the effects of CPAP therapy on cardiovascular events in OSA patients [27, 36, 44, 45]

Author, year of publication	Number of patients vs. control	Characteristics	Intervention	AHI	ESS	Results
Barbé et al., 2012 [27]	357 vs. 366	Nonsleepy patients with CAD	CPAP vs. usual care	>20	≤10	No significant reduction of AHT or CV events
McEvoy et al., 2016 [36] SAVE	1346 vs. 1341	Established CAD or cerebrovascular disease	CPAP + usual care vs. usual care alone	ODI ≥ 12	≤15	No significant reduction of CV events Improved health-related quality of life and mood
Peker et al., 2016 [44] RICCADSA	122 vs. 122	Nonsleepy patients with CAD	CPAP vs. usual care	≥15	<10	No significant reduction of CV events Significant reduction of CV events in patients with CPAP use ≥4 h/night
Yu et al., 2017 [45]	5683 OSA patients	Meta-analysis of 10 RCTs, including SAVE and RICCADSA	PAP vs. standard care or sham	–	–	No significant reduction of CV events or death

ACS acute coronary syndrome, *AHI* apnea/hypopnea–index (events/hour), *AHT* arterial hypertension, *CAD* coronary artery disease, *CV* cardiovascular, *ESS* Epworth sleepiness scale, *OSA* obstructive sleep apnea, *PAP* positive airway pressure, *CPAP* continuous positive airway pressure, *RCT* randomized controlled trial

Furthermore, there are hemodynamic and mechanistic changes in the thorax during an apnea. The unsuccessful attempts to breath against the closed upper airway lead to activation of the sympathetic nerve system, negative intrathoracic pressure, and thus an increased left ventricular transmural gradient and an increased left ventricular afterload, together causing diastolic dysfunction, a rise in arterial blood pressure, and shear stress of the arterial wall [4, 21]. The hemodynamic changes lead to a rise in blood pressure and renal hypoperfusion, as shown in a pig model study. Here, an obstructive apnea was imitated in pigs and a negative intrathoracic pressure was thus built up. Heart rate, blood pressure, renal blood flow, and the neurohumoral response (plasma renin activity, plasma aldosterone concentration, urinary protein/creatinine ratio) were quantified. The measurements were repeated after renal denervation. The repeated tracheal occlusions caused a rise in blood pressure, reduced renal perfusion, and induced neurohumoral changes. These changes could be attenuated by renal denervation, while hypoxia and hypercapnia did not change. Therefore, the authors concluded that the effects on blood pressure and the neurohumoral response were mainly mediated by the sympathetic drive, rather than by the blood gases alone [22].

Additionally, snoring itself has been identified as possibly influencing endothelial functions in a ventilated rabbit model [23]. The vibration is assumed to be transmitted through the thorax up to the arterial wall, thus decreasing vasodilatation [24].

The activation of the sympathetic nerve system in OSA has been verified in further animal and human models. For example, a direct measurement of neuronal activity via neurogram in rats and microneurography in humans has been performed. The sympathetic activation leads to vasoconstriction and a higher blood pressure and heart rate even during daytime [18, 25].

In addition to the vascular, inflammatory, hemodynamic, mechanical, and neural pathological pathways, there is also a metabolic one. There is a known correlation between OSA and metabolic syndrome [28]. Metabolic syndrome is a combination of obesity, hypertension, impaired glucose tolerance, and dyslipidemia, resulting in a predisposition for atherosclerosis. Several pathophysiological reactions caused by OSA—e. g., the increase in sympathetic hormones and elevation of inflammatory markers like tumor necrosis factor (TNF)-alpha, C-reactive protein (CRP), or interleukin (IL)-6—lead to both increased insulin resistance and atherosclerosis. These pathologies not only seem to coexist, but may also have synergistic effects [28] that possibly further increase the risk of atherosclerosis.

The current German S3 guidelines for "Sleeping Disorders—Sleep-Related Abnormal Breathing" state that an association of OSA with atherosclerosis is probable but not proven [3]. The abovementioned processes that connect OSA with atherosclerosis are explanations for a direct influence on the one hand, and common pathologic pathways on the other. Both are closely related and hard to separate. All in all, it is ultimately unclear whether OSA itself causes atherosclerosis, although the results of present research clearly imply that it does.

The effect of CPAP therapy on atherosclerosis

Continuous positive airway pressure (CPAP) is the standard therapy for OSA and a class I recommendation [11] for moderate to severe OSA (AHI ≥ 15/h) and mild OSA (AHI ≥ 5/h) with daytime sleepiness or cardiovascular comorbidities [3, 4]. Several cross-sectional and longitudinal studies have shown that OSA is associated with elevated blood pressure, one of the main risk factors for atherosclerosis [29, 30]. Furthermore, OSA is associated with CVD as a consequence of atherosclerosis [12–16, 21, 26, 31]. OSA is seen as a modifiable atherosclerotic risk factor, and its treatment may help to reduce cardiovascular

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Obstructive sleep apnea and atherosclerosis—update 2019

Abstract

Obstructive sleep apnea (OSA) is a common disorder that has been associated with an increased risk of atherosclerosis and its clinical manifestations. While treatment with continuous positive airway pressure (CPAP) has been shown to exert several beneficial effects on cardiovascular disease and prognosis in observational studies, CPAP was not effective in three recent randomized controlled trials unless it was used for more than 4 hours of sleep.

Keywords

Continuous positive airway pressure · Cardiovascular diseases · Hypertension · Coronary artery disease · Risk factors

Obstruktive Schlafapnoe und Arteriosklerose – Update 2019

Zusammenfassung

Die obstruktive Schlafapnoe (OSA) stellt eine häufige Erkrankung dar, die mit einem erhöhten Risiko für Arteriosklerose und deren klinischen Manifestationen in Zusammenhang gebracht wird. In Beobachtungsstudien wurden zwar für die Behandlung mit kontinuierlichem positivem Atemwegsdruck („continuous positive airway pressure", CPAP) verschiedene günstige Auswirkungen auf Herz-Kreislauf-Erkrankungen und deren Prognose nachgewiesen, in drei aktuellen randomisierten kontrollierten Studien stellte sich die CPAP-Therapie jedoch nicht als wirksam heraus, wenn sie nicht mindestens vier Stunden lang während des Schlafs eingesetzt wurde.

Schlüsselwörter

Kontinuierlicher positiver Atemwegsdruck · Kardiovaskuläre Erkrankungen · Hypertonie · Koronare Herzkrankheit · Risikofaktoren

complications [14]. CPAP therapy creates, as its name implies, a continuous positive airway pressure, and thereby functions as a splint for the upper airway. It prevents airway collapse and, accordingly, the intrathoracic pressure swings and cycles of hypoxemia and arousals. This affects the pathophysiology in several beneficial ways.

For many of the abovementioned mediators promoting the atherosclerotic process in OSA, a positive effect of CPAP therapy has been investigated in smaller studies and has been reviewed repeatedly [4, 5, 14].

Patients with heart failure profit from the improved hemodynamic situation under CPAP therapy. This effect is explained, for instance, by an increased cardiac output due to the reduction of afterload and an improvement of diastolic function. Both right and left ventricular function can improve [30]. The effects on, e. g., blood pressure, were shown to occur immediately, which promotes the idea of the direct effect on the hemodynamic situation under the given therapy [31].

Furthermore, positive airway pressure (PAP) therapy has been shown to attenuate sympathetic nerve activity [25, 30]. Some studies reveal that CPAP even reduces atherosclerosis itself, as measured by carotid artery intima–media thickness (IMT), which is a well-accepted predictor for cardiovascular risk and a surrogate marker for early stages of atherosclerosis [32]. These effects could not be reproduced in randomized controlled trials [33]. However, a recent meta-analysis showed that the effects on IMT are significant in subgroups with more severe OSA and longer-term CPAP use [33].

As to its effect on the reduction of arterial hypertension, findings are inconsistent. Some studies do not support the notion of CPAP therapy lowering the blood pressure significantly, particularly in nonsleepy patients [27, 34, 35]. A meta-analysis of randomized controlled trials showed a significant reduction in arterial hypertension in sleepy OSA patients, with increasing effects with longer nightly CPAP use and a higher baseline AHI [28]. Two meta-analyses of five respectively six randomized controlled trials showed a significant reduction of blood pressure in resistant hypertension, with a larger effect than that reported in OSA patients without resistant hypertension [36, 37]. OSA is typically linked to resistant, nocturnal, and nondipper hypertension [38]. Nondippers seem to have an even higher incidence of cardiovascular events, and CPAP therapy is presumably more effective in treating resistant hypertension [39].

Severe OSA (AHI ≥ 30/h) is independently associated with cardiovascular events and cardiovascular death in both men and women [29, 40]. Observational studies support the hypothesis that CPAP therapy reduces cardiovascular events [29, 40–43], but due to the lack of large randomized controlled trials, it is not finally clear whether patients really profit from CPAP therapy in terms of cardiovascular morbidity and mortality. To date, three larger randomized controlled trials have been performed to approach this question. These are summarized in **Table 1**.

The multicenter randomized SAVE study included more than 1300 patients with a diagnosis of coronary artery disease or cerebrovascular disease. Therapy with CPAP did not prevent cardiovascular events in patients with moderate to severe OSA and established CVD [36]. It should be noted that in this patient population, the average duration of CPAP therapy was only 3.3 h per night, but there was also no significant difference in the subgroup analysis of adherent patients compared to the control group [36]. There was indeed, however, a significant reduction in daytime sleepiness (quantified by ESS), accidents with injury, and improvement in quality of life.

The RICCADSA trial, also published in 2016, examined whether asymptomatic patients with mild to moderate OSA benefit from CPAP treatment. In this monocentric randomized controlled trial, 244 CAD patients (shortly after coronary revascularization) with OSA (AHI > 15/h) without daytime sleepiness were included. Patients were randomized into two groups with either autoCPAP or no ventilation therapy. The combined primary endpoint comprised a further coronary revascularization, myocardial infarction, stroke, and cardiovascular death. The primary endpoint did not differ significantly between the two groups [44]. Thus, the treatment of asymp-

tomatic OSA with CPAP therapy did not seem to improve the cardiovascular outcome of the intention-to-treat group. However, patients seemed to profit from application for more than 4 h per night and a good compliance [44]. It is debatable whether this is solely achieved by the CPAP treatment or generally better compliance and health consciousness. Similar results were shown by Barbé et al.: CPAP therapy did not lead to a significant reduction in arterial hypertension or cardiovascular events [27].

A recent meta-analysis comparing ten randomized controlled trials, including the SAVE study and RICCADSA trial, failed to show a reduction in cardiovascular events or cardiovascular death. As possible reasons, low adherence among the patients and a relatively small number of clinical endpoints occurring were discussed [14]. The effect of CPAP therapy on nonsleepy OSA patients with acute coronary syndrome (ACS) will be evaluated in the ISAAC trial, which has not yet been finally published [46]. The actual data concentrate on secondary cardiovascular prevention. The patients enrolled in the abovementioned studies already suffered from CAD; the knowledge of CPAP therapy as a primary prevention is limited. This may be interesting to investigate, as atherosclerosis is a chronic disease developing over the course of time and patients may profit from an earlier intervention.

Conclusion

OSA is associated with atherosclerosis and consequently with CVD. It is not entirely clear to which extent OSA causes atherosclerosis itself, and how much is simply due to common pathologic pathways. Nevertheless, there are many vascular, inflammatory, neuronal, and mechanical changes occurring in OSA which promote the formation of atherosclerotic plaques. CPAP has been shown to attenuate several of these pathological changes.

Considering the insights offered by recent research, CPAP treatment is recommended for patients with symptomatic OSA, as it improves quality of life, daytime sleepiness, cognition, and wellbeing. CPAP treatment for OSA in nonsleepy patients for cardiovascular risk reduction cannot be recommended for all patients at present. However, patients with better compliance seem to profit from CPAP therapy, and one may speculate that more hours of CPAP application result in improved sleep quality, quality of life, blood pressure, and thus even in fewer cardiovascular events. Therefore, further randomized controlled trials with bigger sample sizes are required to definitively identify subgroups or special phenotypes which may profit from CPAP therapy and to evaluate its long-term effects on atherosclerosis. We should be aware that cardiovascular comorbidities are frequent in OSA patients, and an optimal treatment of cardiovascular risk factors should be aimed for in all OSA patients.

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Compliance with ethical guidelines

Conflict of interest. L. Biener, C. Pizarro, G. Nickenig, and D. Skowasch declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

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