Cardiovascular consequences of sleep apnea: III-Impact of continuous positive airway pressure treatment

Uyku apnesinin kardiyovasküler sonuçları: III- Sürekli pozitif havayolu basınç tedavisinin etkisi

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Abstract

Obstructive sleep apnea (OSA) is a common condition in patients with cardiovascular diseases (CVD). The first line treatment of OSA is continuous positive airway pressure (CPAP), which reduces daytime sleepiness and improves quality of life in sleep-clinic based populations. However, in the cardiac populations, the majority of OSA subjects do not report daytime sleepiness. To date, there is not enough evidence to draw the conclusion that all CVD patients should be investigated for OSA and subsequently be treated with CPAP. The current article focuses on the available research evidence addressing the impact of CPAP on the cardiovascular consequences of OSA in both clinic- and population-based cohorts. *(Anadolu Kardiyol Derg 2010; 10: 274-80)*

Key words: Obstructive sleep apnea, cardiovascular, CPAP

Özet

Obstrüktif uyku apnesi (OSA) kardiyovasküler hastalığı olan kişilerde sık görülmektedir. OSA'nın ilk seçenek tedavi yönetimi olan sürekli pozitif havayolu basıncı (CPAP), uyku kliniği popülasyonlarında gündüz aşırı uyku halini azaltmakta ve yaşam kalitesini artırmaktadır. Kardiyak popülasyonlarda ise OSA vakalarının çoğunda gündüz aşırı uyku hali bulunmamaktadır. Bugüne kadar yapılan çalışmalarda, bütün kardiyak hastaların OSA yönünden araştırılması ve CPAP ile tedavisinin gerekliliğine dair yeterince kanıt bulunmamaktadır. Bu makalede klinik- ve popülasyon-tabanlı kohortlarda CPAP tedavisinin OSA'nın kardiyovasküler komplikasyonları üzerine etkisi tartışılmaktadır.
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Anahtar kelimeler: Obstrüktif uyku apnesi, kardiyovasküler, CPAP

Introduction

The first line treatment of obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP), which has been shown to reduce daytime sleepiness and improve quality of life. However, the majority of patients with CVD and concomitant OSA do not experience daytime sleepiness, i.e. they are asymptomatic, and it has still been hardly debated whether or not all CVD patients with OSA should be treated with regard to cardiovascular aspects. In the current review, we aim to analyze available literature in this context.

Treatment of OSA syndrome

Treatment modalities currently available for clinical OSA management include active weight loss, avoidance of alcohol and sedatives, application of nasal CPAP, oral appliance therapy (enlarging the pharyngeal airway by moving tongue or mandible forwards) and surgical approaches such as tracheostomy, uvulopalatopharyngoplasty and maxillofacial surgery (1). Weight loss in OSA patients may result in a reduction of AHI and improved sleep efficiency. Moreover, avoidance of the supine sleeping position may alleviate breathing disturbances in patients with mild, position-dependent apnea. To date, there is no widely accepted pharmacological therapy for the clinical treatment of OSA. CPAP, applied via a nasal mask is the most commonly used therapy for patients with OSA. However, based on objective measurements of CPAP usage with a covert timer, it has been estimated that less than half of all patients that have been prescribed CPAP use it for more than 4 hours on at least 70% of nights. Thus, in spite of the

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limited compliance, CPAP has been shown to be the most effective treatment modality in OSA (1).

Overall impact of CPAP on OSA

CPAP decreases the AHI reliably to the levels below five in patients with moderate to severe OSA (1). There is also accumulating number of randomized controlled trials (RCT) demonstrating a dramatic improvement in subjective and objective sleepiness in symptomatic OSA patients. It should also be emphasized that untreated OSA was associated with 2.5 fold increased risk of motor vehicle accidents (2). Mazza et al. (3) demonstrated a significant improvement in driving performance in OSAS patients after CPAP treatment. Decline in traffic accidents in OSA patients who were adherent to CPAP was also reported (4). Despite these positive effects in the symptomatic OSA patients recruited from sleep-clinic cohorts, it should be noted that the majority of patients with CVD with concomitant OSA do not experience daytime sleepiness (5), i.e. they are asymptomatic, and therefore, are not recognized and considered for OSA treatment with CPAP.

Impact of CPAP on the negative intrathoracic pressure

CPAP leads to a fall in cardiac output (CO) when applied to individuals with normal cardiac function. Conversely, reports indicate that CPAP improves CO in OSA patients (6). As CPAP unloads inspiratory muscles and removes apnea episodes, the treatment reduces the exaggerated negative intrathoracic pressure, and thus, even reverses the increased venous return to the right ventricle (RV), shift of interventricular septum to left as well as the reduced left ventricular (LV) filling. Moreover, effective decline in surges of blood pressure (BP) has also beneficial impact on diastolic function, stroke volume and CO. Overall, CPAP therapy results in decreased LV preload and afterload, reversal of systolic and diastolic dysfunction and normalization of the CO (6).

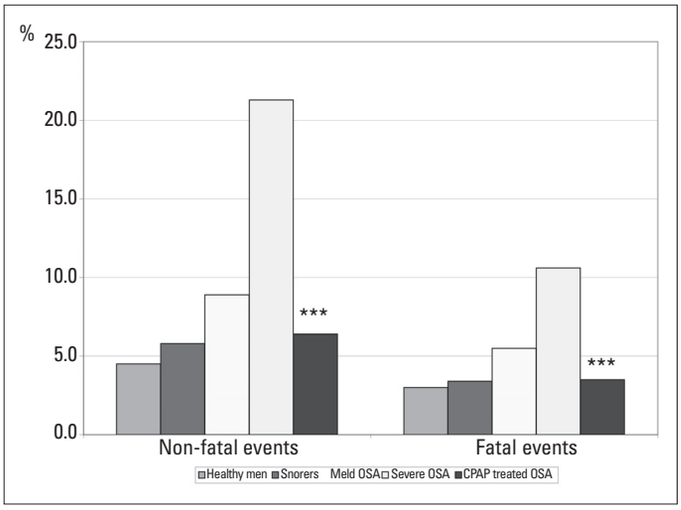

Figure 1. Incidence of non-fatal and fatal cardiovascular events during a 10-year follow-up in men. Depicted is data from healthy men, snorers without OSA, mild OSA, severe OSA and CPAP-treated OSA subjects. (Modified from ref. 58)

CPAP -continuous positive airway pressure, OSA - obstructive sleep apnea

Impact of CPAP on the sympathetic overstimulation

Sympathetic over-activity can be diminished and impaired autonomic dysfunction can be reversed by effective CPAP therapy (7). Besides, CPAP withdrawal even for one week was found to be associated with marked increase in sympathetic activity (8). On the other hand, CPAP leads to significant reductions in plasma norepinephrine levels both by increases in norepinephrine clearance and decreases in diurnal and nocturnal excretion compared with placebo or oxygen therapy (9). CPAP was also shown to be effective in lowering of daytime muscle sympathetic nerve activity. Application of CPAP increases the reduced sensitivity of the arterial baroreflex both during wakefulness and sleep (10, 11). The increase in baroreflex control of heart rate during sleep may be of clinical relevance as it is accompanied by reduced cardiovascular variability which is acknowledged as an independent cardiovascular risk factor.

Impact of CPAP on oxidative stress

Effective CPAP therapy was shown to be associated with a decline in oxidative stress, evaluated either by lipid peroxidation, superoxide release or radical oxygen species (ROS). Even a single night of CPAP treatment significantly reduced the level of oxidative stress in patients with severe OSAS and this reduction was maintained afterwards (12). Thiorexin is a novel oxidative stress marker and was shown to be associated with cardiovascular mortality. Elevated level of thiorexin was found to be significantly decreased after CPAP (13). On the other hand, studies demonstrated the effectiveness of CPAP in normalizing the nitrite oxide (NO) levels which is the most potent natural vasodilator (11). Hence, the accumulated data clearly supports the presence of oxidative stress in OSA and disappearance by effective CPAP treatment.

Impact of CPAP on vascular inflammation

The results of the studies regarding the impact of CPAP treatment on levels of inflammatory markers are conflicting. Levels of circulating soluble adhesion molecules, which mediate adhesion of leucocytes to the vascular endothelium, such as ICAM-1, E-selectin and IL-8 were shown to be reduced with CPAP (14, 15). Inversely, no change has been reported in soluble VCAM-1 levels (15). Studies indicated that CPAP may lower the elevated levels of TNF-α, total lymphocytes, IL-6 as well as C-reactive protein (CRP) levels especially in patients who were compliant with CPAP (16).

Impact of CPAP on endothelial function

Six months of CPAP treatment was shown to improve endothelial dysfunction in normotensive men (17) and especially in desaturating OSA patients (18). It was also shown that endothelial function was worsened after CPAP withdrawal to the baseline values, supporting the fact that reversal of this dysfunction is dependent on ongoing CPAP use. Increased level of NO and

reduced level of vasoconstrictor substances were also documented in OSA patients treated with CPAP (19).

Impact of CPAP on coagulation factors

There are discordant reports regarding the effect of CPAP therapy on coagulation factors. While decreased platelet activation, aggregability (20), fibrinogen levels (21) were reported, no difference was found in hematocrit, whole blood viscosity and coagulation factors in OSA patients on CPAP treatment (22). However, one recent study demonstrated significantly reduced whole blood viscosity, plasma viscosity, the aggregation index and increased aggregation half-time following CPAP treatment (23).

Impact of CPAP on metabolic system

The positive effects of two months of CPAP therapy resulted in reduction of total cholesterol, LDL, leptin, ApoB (24) and the homeostasis model assessment (HOMA), which has been suggested as a method to assess IR and secretion from the fasting glucose and insulin concentrations. However, in another study, CPAP provided no change in lipids or the proportion of patients with metabolic syndrome compared to sham CPAP group after 6 weeks of trial (25). Good compliance to CPAP was documented to improve insulin resistance (IR), even at long-term if CPAP was regularly used (26). Several studies demonstrated improvement in glucose levels as well as hemoglobinA1c with CPAP in subjects with both type II diabetes and OSA (27). However, in two RCTs, CPAP treatment did not affect insulin sensitivity or glycogenic control neither in diabetics (28) nor in non-diabetics (25). Likewise, in a recent study by Murri et al. (29), no significant change in IR with CPAP was indicated. Interestingly, a paradoxical increase in glucose level during acute CPAP application in non-diabetic obese OSA syndrome patients was also documented (30). These inconsistent results may be due to the low number of patients or insufficient treatment period to modify IR or metabolic profile in these studies. However due to the inconsistent results of CPAP studies, the beneficial impact of CPAP still needs to be proven.

Impact of CPAP on atherosclerosis

The beneficial effect of CPAP therapy in reversing early signs of atherosclerosis has been demonstrated by Drager and colleagues (31). The authors randomized 24 severe OSA patients free of cardiovascular comorbidities either to CPAP or no intervention. Patients treated with CPAP for 4 months showed a significant decline in plasma concentrations of norepinephrine and CRP in addition to reductions in both carotid intima media thickness (IMT) and carotid to femoral artery pulse wave velocity. As no concurrent change in weight, lipid levels or BP was noted while the sympathetic activity and systemic inflammation were reduced, these findings indicate that CPAP treatment of OSA reverses atherosclerosis independent of BP or lipids. Supportively, in a recent study, Kohler and co-workers (32) demonstrated a significant reduction in arterial stiffness in OSA patients who were randomized to CPAP for 4 weeks compared to the sham-CPAP group .

Impact of CPAP on hypertension (HT)

CPAP therapy was suggested to be effective both in normotensive and hypertensive OSA subjects although the significance of reduction was found to be higher in the hypertensives (33). Moreover, the studies demonstrated significant reductions in nocturnal and daytime BP in OSA patients with refractory HT. It should also be added that there is data suggesting that hypertensive OSA patients regarded as "non-dippers" may convert to ''dippers'' after CPAP treatment, thereby, restoring the physiological nocturnal dipping blood pressure pattern (34). In contrary, there are also negative results regarding the impact of CPAP on blood pressure in mild OSA. Barnes et al. (35) observed no change of 24 hour BP in mild to moderate OSA after an 8-week treatment period. However, this study was criticized to have included normotensive subjects as there was no rationale to expect a blood pressure reduction in subjects who were not hypertensive. In another RCT, conducted in hypertensive OSA patients with no sleepiness, CPAP had no significant impact on blood pressure reduction (36). These results have also raised the question whether or not the outcomes were related with the duration of CPAP treatment. Indeed, a 24-month follow-up study demonstrated a dose dependent blood pressure response to CPAP treatment supporting that beneficial effect can be achieved in long-term even in the initially incompletely treated hypertensive OSA subjects (37). Overall, greater response to CPAP therapy was found to be associated with CPAP compliance, severity of OSA, sleepiness and the co-existence of initial HT (33).

Impact of CPAP on coronary artery disease (CAD)

In a longitudinal study of the incident CAD in a sleep-clinic cohort, efficient treatment of OSA had a protective effect (38). In a non-randomized observational study, Cassar and coworkers (39) found significantly lower incidence of cardiac deaths in OSA patients treated with CPAP following percutaneous coronary intervention (PCI) compared with the untreated OSA patients. In another observational study, Milleron et al. (40) demonstrated a significant reduction in the composite cardiovascular end-point (incidence of new coronary events, acute coronary syndrome, hospitalization for cardiac failure and coronary revascularization requirement as well as cardiovascular mortality) in CAD patients with treated OSA compared to OSA patients who refused CPAP. To date, there is a lack of RCTs to draw the conclusion that all CAD patients should be investigated for OSA and subsequently be treated with CPAP. An ongoing randomized intervention with CPAP in CAD and OSA (RICCADSA) trial (41), addressing if CPAP treatment reduces the combined rate of new revascularization, MI, stroke and cardiovascular mortality over a 3-year period in CAD patients with OSA will hopefully contribute to better defining the prognostic value of CPAP in this context.

Impact of CPAP on cardiac arrhythmias

In a recent study, OSAS was prevalent in 68% of patients with nocturnal bradyarrhythmias and CPAP treatment was shown to efficiently eliminate nocturnal asystoles, which in turn eliminated the need for pacemaker implantation (42). Moreover, in the group of atrial fibrillation (AF) patients undergoing successful electrical cardioversion, the rate of recurrence of AF within one year was significantly higher in inadequately treated OSAS patients compared to the efficiently treated subjects (43). The incidence and the severity of ventricular arrhythmias were also shown to be reduced by CPAP treatment (44). In patients with OSA and systolic dysfunction, a RCT suggested a 58% reduction in the frequency of ventricular premature complexes during sleep, and a parallel reduction in nocturnal urinary norepinephrine concentrations were observed after one month of CPAP therapy (45). Furthermore, ventricular repolarization changes, which may contribute to higher ventricular irritability, were reversed by CPAP treatment (46).

Impact of CPAP on pulmonary arterial hypertension (PH)

Alchanatis and coworkers (47) have demonstrated that 6 months of CPAP treatment ameliorates PH in patients with OSA. In a recent RCT with CPAP vs sham-CPAP in 23 patients with OSA and concomitant PH, effective CPAP therapy for a 12-week period was associated with significant improvements in echocardiographic measurements of pulmonary arterial pressure (PAP) (48). Moreover, increased pulmonary vascular reactivity to hypoxia was also reported to be reversed by CPAP treatment in PH patients with concomitant OSA (49).

Impact of CPAP on heart failure (HF) with OSA

Altered cardiac functions and structural changes in HF patients and concomitant OSA seem to be reversible with effective CPAP treatment (6). Efficient treatment of OSA was shown to be associated with improved RV function, improved diastolic function as well as improvement in LV functions, dimensions and contractility. Cardiovascular mechanisms, such as increased blood pressure, heart rate and daytime muscle sympathetic nerve activity, which all are involved in the poor prognosis of HF patients were found to be reduced with CPAP. In this context, using cardiac C-11 acetate positron emission tomography in HF patients with OSA, obstructive apneas were shown to depress cardiac function acutely while CPAP treatment was associated with improved cardiac function (50). However, despite the beneficial effects of CPAP on structural and functional parameters as well as clinical findings in HF patients, it has yet not proven whether these effects also imply an improvement in long-term prognosis of patients with HF and concomitant OSA. Indeed, Kasai et al. (51) showed that the risk for death and hospitalization was significantly higher among untreated and less CPAP-complaint OSA patients compared to that among efficiently treated OSA subjects. It should also be added that, CPAP therapy provided significant improvement in the symptoms and hemodynamics as well as left and right ventricular morphology and function in severe OSAS patients who had no known CVD (6). Bayram et al. (52) indicated a significant improvement in LV systolic and diastolic dysfunction after 6 month of CPAP treatment in 28 newly diagnosed moderate to severe OSAS patients who were free of structural heart disease, pulmonary disease, diabetes mellitus, dyslipidemia, alcoholism, neuromuscular disease, renal failure or malignancy at baseline.

Impact of CPAP on HF with central sleep apnea and Cheyne-Stokes respiration (CSA/CSR)

A randomized controlled trail revealed a significant improvement in LV ejection fraction (LVEF) at 3 months and a relative risk reduction of 81% in the mortality-cardiac transplantation rate over a median of 2.2-year follow-up period in those who used CPAP compared to controls (53). In the subsequent years, a multicenter Canadian study (CANPAP) evaluated 258 patients with HF and CSA (54). Although there were significant improvements in LV function and exercise capacity, survival rates were not better in the CPAP-treated group. However, in the post-hoc analysis of this study, the authors demonstrated a benefit with regard to mortality, when AHI was reduced to the levels below 15 per hour by CPAP (55). At present, CPAP treatment is recommended as a routine procedure in the acute cardiogenic pulmonary edema as it improves intrathoracic fluid dynamics regardless of the existence of sleep apnea. However, available data does not support the routine use of CPAP in stable chronic HF patients who are free of OSA. It should also be added that other forms of noninvasive ventilation such as bilevel positive airway pressure (BIPAP) and non-invasive positive airway pressure (NPAP) have also been offered in HF patients with CSA/CSR. Some RCTs suggested the superiority of BIPAP to CPAP in improvement of LVEF in patients with systolic dysfunction and CSA and in reducing the CSA-CSR index (56). However, as these patients already hyperventilate and are high risk of hypocapnia, which in turn also may trigger central apneas, the use of BIPAP was not supported widely. On the other hand, a novel treatment approach, adaptive pressure supported ventilation (ASV) has shown to stabilize breathing by reducing hypoxemia and hypocapnia, and thus, ameliorate CSR-CSA, improve LV function and cardiopulmonary exercise (57).

Impact of CPAP on cardiovascular mortality

In the observational 10-year follow-up study of males from a sleep clinic cohort, Marin and coworkers (58) identified untreated severe OSA (AHI>30/h) as an independent predictor for cardiovascular mortality while the patients treated with CPAP demonstrated a significantly lower non-fatal and fatal cardiovascular event incidence rates similar to those obtained in the general population (Fig. 1). In another study of the impact of CPAP treatment on non-fatal and fatal cardiovascular events, Doherty and coworkers (59)

demonstrated a protective effect of the treatment in a cohort of 168 OSA patients over 7.5 years. Moreover, in a larger OSA population, Buchner et al. (60) suggested that effective treatment with CPAP was associated with a 64% reduction in cardiovascular events independent of age, gender, cardiovascular risk factors and baseline comorbidities at 6-year follow-up.

Conclusion

Obstructive sleep apnea is common in general population and associated with increased cardiovascular morbidity and mortality in both population- and clinic-based epidemiological studies. Although there is scientific support for a considerable impact of OSA on vascular structure and function, it is likely that development of CVD is determined by multiple genotypic and phenotypic factors. However, OSA may not only induce CVD, but also the obstructive events in themselves may worsen the prognosis of an already existing CVD. The increasing recognition of OSA as an independent, additive, or even synergistic risk factor for CVD, early identification of high-risk persons and a consensus on well-defined treatment strategies in such patients seems to be urging. CPAP treatment reduces daytime sleepiness, improves quality of life and has to some extent beneficial effect on the prognosis of CVD in clinic-based cohorts. However, the majority of CVD patients with concomitant OSA do not report daytime sleepiness. Ongoing and future RCTs will contribute to defining the impact of CPAP as a non-pharmacological intervention for CVD patients with OSA regardless of daytime sleepiness.

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