Cardiovascular consequences of sleep apnea: I -Epidemiology

Uyku apnesinin kardiyovasküler sonuçları: I- Epidemiyoloji

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ABSTRACT

Obstructive sleep apnea (OSA) is common in general population. There is an accumulating research evidence for an independent relationship between OSA and cardiovascular morbidity and mortality. This relationship is stronger in clinical cohorts compared with the general population, which suggests that concomitant OSA in subjects with traditionally recognized risk factors such as obesity, hypertension, smoking, and hyperlipidemia may provide an additive risk factor for the cardiovascular consequences. In the current article, the clinic-and population-based epidemiologic data will be reviewed in this context. *(Anadolu Kardiyol Derg 2010; 10: 75-80)*

Key words: Obstructive sleep apnea, epidemiology

ÖZET

Obstrüktif uyku apnesi (OSA) genel populasyonda oldukça sık görülen bir hastalıktır. Obstrüktif uyku apne ile kardiyovasküler morbidite ve mortalite arasında bağımsız bir ilişki olduğunu gösteren çalışmalar artmaktadır. Bu ilişki, genel populasyona göre klinik populasyonlarda çok daha kuvvetlidir. Bir başka deyişle, kardiyovasküler risk faktörleri olarak bilinen obesite, hipertansiyon, sigara ve hiperlipidemi vakalarıyla bir arada bulunduğu durumlarda OSA kardiyovasküler hasar riskini daha da artırmaktadır. Bu makalede, literatürde mevcut klinik ve populasyon bazında epidemiyolojik çalışmalar bu bağlamda irdelenecektir. *(Anadolu Kardiyol Derg 2010; 10: 75-80)*

Anahtar kelimeler: Obstrüktif uyku apnesi, epidemiyoloji

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder characterized by repetitive episodes of airflow cessation (apnea) or reduction (hypopnea) despite persistent thoracic and abdominal respiratory effort during sleep. These episodes result in hypoventilation as well as hypoxemia, and provoke awakenings (recurrent arousals) that restore pharyngeal dilator muscle tone and airflow. OSA is generally defined as five or more apneas and/or hypopneas per hour of sleep (apnea-hypopnea index [AHI]>5) assessed by a cardio-respiratory or full polysomnography (PSG) recording.

According to the Sleep Heart Health Study (SHHS), which is, to date, the largest epidemiological study in this field, 24% of men and 9% of women in the middle aged population are affected by OSA (1). It should be emphasized that OSA refers to a laboratory diagnosis. Obstructive sleep apnea syndrome (OSAS), on the other hand, is defined as an AHI ≥5 accompanied by either excessive daytime sleepiness (EDS) or two or more of the following symptoms such as witnessed apneas, recurrent awakenings, waking unrefreshed, morning-headache, daytime fatigue or impaired concentration or memory. The syndrome is reported in 4% of men and 2% of women (1). When symptomatic, the disease may have adverse effects on the social life, employment, productivity and quality of life, and may constitute a high risk for traffic accidents.

OSA has even significant deleterious effects on patients' health, as there is considerable evidence suggesting an increased risk for cardiovascular diseases (CVD) (2). For instance, the cross-sectional studies suggest a significantly high prevalence of OSA in the cardiac clinic populations (3). The adverse impact of a concomitant OSA on the prognosis and outcomes of patients with an already existing CVD has also been demonstrated. Both population-based (4, 5) and sleep

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clinic cohort studies (6, 7) as well as reports from cardiac populations (8) have suggested that OSA contributes to increased mortality independent of the traditionally recognized cardiovascular risk factors. Longitudinal studies indicated an increased incidence of all types of CVD in otherwise healthy OSA patients over a 7-year follow-up (Figure 1) (2). Clinical and epidemiological data suggest an independent association between OSA and mainly systemic hypertension (HT) but also with pulmonary hypertension (PH) and other CVD, such as coronary artery disease (CAD), cardiac arrhythmias, heart failure (HF) and sudden cardiac death (SCD) (3). Hence, OSA has been implicated in the initiation, progression, and resistance to conventional therapeutic strategies of various CVD. However, as the majority of OSA patients (almost 80%) are asymptomatic or minimally symptomatic according to the above-mentioned criteria and may therefore never be considered for the diagnostic investigation and treatment. The remaining question is whether or not all cardiac patients should be investigated for OSA and subsequently be treated regardless of daytime sleepiness in order to improve the cardiovascular outcomes. The current review highlights the clinical and population-based evidence in the literature in this context.

Hypertension (HT)

The prevalence of HT in sleep clinics is estimated to range between 30-50% (3). Similarly, the prevalence of OSA has been shown to be around 50% in a general HT clinic population (9), where the occurrence of OSA is even higher (80%) in the subgroup of subjects with therapy-resistant HT (10). Baguet JP et al. (11) emphasized the high rate of hypertensive patients in newly diagnosed OSA subjects (67%), not known to be "hypertensive" before undergoing the diagnostic investigation for OSA.

It should also be added that ''dipping phenomena'', which is an almost 10% physiological reduction of blood pressure (BP) during sleep in healthy subjects, is blunted in OSA patients (12). Thus, the blunted fall in nocturnal BP, "non-dipping phenomena", reflecting a high level of cardiovascular risk in HT, is a dominant characteristic of OSA subjects with HT. In other words, in the clinical practice, hypertensive patients resistant to drug treatment as well as the ones with predominantly non-dipping phenomena should be considered for OSA (10, 12).

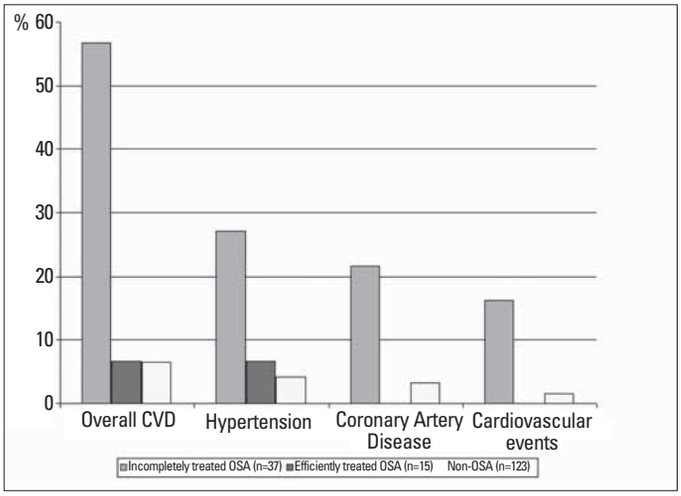

Figure 1. Incidence of cardiovascular diseases during a 7-year follow-up in middle-aged men otherwise healthy at baseline. Proportion of individuals with incidence of cardiovascular disease, hypertension, CAD and cardiovascular event (stroke, MI or cardiovascular death). Depicted is data from patients without OSA as well as from those incompletely or efficiently treated for OSA (Modified from reference 2)

Longitudinal population and sleep clinic studies consistently suggest an increased risk for incident HT at follow-up in the subjects with OSA (13, 14). Age, body mass index (BMI), family history of HT and male gender has been defined as phenotypic risk factors in the development of HT among OSA patients (15). Notably, current HT management guidelines have acknowledged OSA as an identifiable and independent cause of HT and therefore recommended BP screening amongst OSA patients (16).

Pulmonary hypertension (PH)

The prevalence of PH has been found between 17-52% in OSA patients with pulmonary or cardiac diseases (17). However, sleep clinic studies reported only 20% of prevalence in patients with no clinical history of chronic obstructive pulmonary disorder or lung diseases. Nevertheless, the clinical classification of PH identifies sleep apnea in the category of respiratory disorders associated with PH (18).

The prevalence of PH was reported to be around 20% in OSA patients without a concomitant chronic obstructive pulmonary disease (COPD). In the OSA group with concomitant COPD the prevalence was up to 52% (17). However, the pulmonary artery pressure was found to be modestly elevated (25-30 mm Hg), and it is also suggested that oxygen desaturations predicts the risk of PH much better than AHI in these patients.

Coronary artery disease (CAD)

Numerous studies revealed an increased prevalence of OSA in CAD patients varying between 35% and 57% compared to age-matched controls (19). It has also been proposed that the prevalence of OSA increases by the severity of CAD. On the other hand, the occurrence of symptomatic CAD was estimated to range between 25-40% in OSA patients (19). Moreover, OSA patients have been shown to experience nocturnal myocardial ischemia and electrocardiography changes frequently without clinically significant CAD.

It has also been suggested that increased oxygen demand and reduced oxygen supply following OSA may trigger an attack of angina pectoris in patients with CAD, who already have reduced coronary flow reserve. The increased risk of incident myocardial ischemia during sleep was demonstrated in OSAS patients with CAD (20). However, a recent study, conducted in a stable CAD cohort failed to show such a relationship (21).

Nocturnal OD were found to be correlated with the severity of coronary atherosclerosis and also suggested to be an important predictor for coronary re-stenosis in CAD patients treated with percutaneous coronary intervention (PCI) (22). Moreover, Nakashima and coworkers (23) indicated that OSA might inhibit recovery of left ventricular function in patients who

experienced ST-elevation myocardial infarction (MI). Recently, in CAD patients undergoing elective PCI, coexisting OSA was shown to be associated with re-stenosis and increased lumen loss at 7 month-follow-up (24). Moreover, concomitant OSA constituted an almost 12-fold increase in risk for major adverse cardiac events (sudden death, re-infarction, revascularization), at 6 month follow-up in patients with acute coronary syndrome who were treated by PCI (25). The adverse impact of OSA in CAD patients with regard to complications such as stroke as well as mortality has also been reported (26).

Regarding the incident of CAD in OSA patients, a 7-year prospective study demonstrated that untreated OSA was associated with a 5-fold increase in this context independent of age, sex, BP, diabetes or smoking (27). In spite of the high risk ratios in the clinical populations, the relationship between OSA and CAD seems to be modest in population-based cohorts. For instance, the risk ratio of having CAD was 1.27 in subjects with AHI>11 compared to AHI<3 (28). On the other hand, a family history of premature death due to CAD has been reported to be two-fold in subjects with OSA compared to those without OSA (29).

Cardiac arrhythmias

Bradyarrhythmias

Cardiac arrhythmias are accepted to occur more frequently in subjects with OSA especially during sleep and increase with the severity of disease (30). Bradycardia, first to third degree atrioventricular (AV) conduction block and sinoatrial node block during apneas have been reported in OSA patients. Becker et al. reported AV-block II-III and/or sinus arrest in 7% of an unselected group of OSA patients and the prevalence was even higher (20%) in the subgroup with severe OSA (31). On the other hand, in cardiac populations, there is also data suggesting a high prevalence of OSA in patients treated with pacemaker. For instance, Garrigue and coworkers found OSA among 59% of patients in whom Holter recordings showed isolated bradyarrhythmias (32). It was also argued that a sleep study should be performed before implanting a pacemaker, as treatment of OSA may reduce the need for pacing. In the population-based SHHS, the proportion of subjects with pacemaker-implantation was significantly higher in the OSA group compared to the subjects without OSA (33).

Tachyarrhythmias

In sleep-clinic cohorts, atrial fibrillation (AF), nonsustained ventricular tachycardia and complex ventricular ectopy were found to be more common in subjects with OSA (30). Furthermore, in the population-based SHSS, those subjects with severe OSA (AHI>30/h) had higher risk of nocturnal complex arrhythmias compared with non-OSAS subjects with odds ratios of 3.4 for non-sustained ventricular tachycardia, 4.2 for AF and 1.7 for complex ventricular ectopy, respectively (33). The higher occurrence of life threatening ventricular arrhythmias amongst OSA patients (30, 34) was suggested to contribute to the abnormal circadian pattern of sudden death in OSA patients (35).

In cardiac populations, AF has a significant importance among arrhythmias related with OSA. Gami and co-workers (36) evaluated patients with AF who were in need of cardioversion and found OSA in 50% of this group compared to an estimated prevalence of 30% in a general cardiology clinic population. Moreover, studies in HF patients suggest a more common prevalence of AF in patients with OSA (37). It should also be added that in patients undergoing cardiac surgery, the presence of OSA was shown to predict postoperative AF (38).

Heart failure (HF)

The relationship between sleep disordered breathing and heart failure (HF) is yet not fully understood. Observational studies indicate an increased prevalence of both obstructive and central apneas in HF patients and many patients may exhibit both OSA and central sleep apnea (CSA).

Central Sleep Apnea and Cheyne-Stokes Respiration in HF

A certain form of breathing pattern that is seen in HF is called Cheyne-Stokes respiration (CSR), which is crescendo–decrescendo breathing, separated by periods of central apneas (CSA). This pattern is suggested to be a consequence of HF and may occur in 30-40% of the HF patients (37). The patients with CSA/CSR generally described as older and non-obese subjects with at least moderate to severe left ventricular (LV) dysfunction (LVEF<30) and with predominantly concomitant CAD. CSR is suggested to be a predictor of mortality in these patients (39).

OSA in HF

As OSA may contribute to the pathogenesis of HF and can develop as a consequence of HF, there is a paradox relationship between these two conditions. OSA was detected in range of 11-64% patients with HF, most of who were free of EDS (37). Male gender and advanced age especially in women are accepted to be risk factors for the development of OSA in HF patients. On the other hand, it has also been suggested that OSA may contribute to acute HF as the time of acute dyspnea episodes were found to be more common during sleeping hours in HF patients with concomitant OSA (40). Moreover, Roebuck and colleagues (41) have suggested increased short-term mortality in patients with severe HF and OSA while no change was detected regarding at long-term (over 4 years).

HF in OSA

An increased prevalence (25-50%) of LV hypertrophy was demonstrated in sleep clinic patients without a known CVD (11,42). Dursunoglu et al. (42) assessed left ventricular mass and myocardial performance index in 67 OSAS patients without any cardiac or pulmonary disease and found that thickness of interventricular septum and LV posterior wall, LV mass and LV mass index as well as left ventricular global dysfunction were higher in severe OSAS patients compared to those in mild to moderate OSAS. Not only systolic but also diastolic dysfunction of the LV was shown to be common (36%) in OSA patients without a known CVD and there is a positive relationship between severity of OSA and the severity of the LV diastolic dysfunction (43). Association between right heart function and OSA has also been addressed in several studies. Attenuated RV contractility as well as RV hypertrophy and impaired RVEF was demonstrated in 18% of otherwise healthy OSA subjects

(44). Moreover, there was also a dose-response relationship between RVEF and AHI in the absence of lung disease in the sleep-clinic cohorts (44).

In addition, data from the population based SHHS demonstrated a significant association between OSA and HF, with an adjusted OR of 2.4 for HF for the subjects with the highest quartile of AHI (>11/h) compared to those with the lowest quartile (AHI<1.3/h) (28).

Cardiovascular mortality

The prevalence of sudden cardiac death (SCD) is higher in OSA patients and OSA may be involved in the pathogenesis of nocturnal sudden death (35). Gami and coworkers (35) showed a peak in sudden death from cardiac causes during sleeping hours, namely, 10 pm to 6 am in patients with OSA in contrast to the traditional window of cardiovascular vulnerability which is 6 and 11 am.

The potential risk factors for cardiovascular death are regarded as systemic HT, CAD, cardiac arrhythmias and HF, which all are common in OSA (3). Moreover, OSA was shown to accelerate the mortality rates within group of patients with CVD (8, 45). For instance, AHI was found to be an independent predictor of cardiovascular mortality at a 5-year follow-up in patients with CAD (8).

OSA has been increasingly recognized as an important contributing factor to mortality. Regardless of the co-existence of CVD, OSA was found to be associated with increased all-cause mortality (4, 5, 46). A report from Australia identified OSA as a risk factor for overall mortality at 13.4 yr-follow-up, independent of age, gender, BMI, BP, total cholesterol, HDLC, diabetes and angina (4). Likewise, in another population-based 18-year follow-up study, both overall and cardiovascular mortality risks were significantly increased with the OSA severity (5). Moreover, in the SHHS cohort, fully adjusted hazard ratio for all cause mortality in severe OSA was reported as 1.5 compared to those without OSA (46).

Regarding the all-cause mortality studies in the sleep-clinic cohorts, to date, few data exist. Lavie et al. (47) found BMI as well as Respiratory Disturbance Index to be associated with overall mortality in men during a mean follow-up period of 4.6 years. In another study, Yaggi and coworkers (7) demonstrated that OSA was related with stroke or death with an almost doubled hazard ratio in a sleep-clinic cohort.

Available data regarding OSA and cardiovascular mortality is based on observational long term studies. The latest population-based SHHS suggested an increased CAD related mortality in men aged 40-70 years with severe OSA (46). In a previous 10-year follow-up study, Marin and coworkers (48) identified age, concomitant CVD and untreated severe OSA as independent predictors for cardiovascular mortality. Overall, these observational data support the increased cardiovascular mortality in OSA patients both in population and sleep clinic cohorts.

OSA and traditionally recognized risk factors for CVD

OSA, smoking and CVD

Cigarette smoking, which is common in clinic populations, has been suggested to be an independent risk factor for OSA by some authors whereas some others do not support this. Interestingly, some beneficial effects of nicotine, including protection against OSA, were discussed in the early 1990s (49), however, overnight transdermal nicotine administration was shown adversely to affect sleep and respiratory parameters in non-smokers (50) and a recent study has revealed that smoking interacts with OSA to increase cardiovascular risk (51).

OSA, obesity and CVD

At the 26-yr follow-up of subjects in the Framingham study, obesity was found to be a significant predictor of CVD, independent of other risk factors (52). Obesity is common in OSA (53) and inversely, approximately 50% of morbidly obese subjects have OSA (54). In a study of a sleep clinic cohort (53), waist circumference (an index of central obesity) and respiratory disturbance index were independent predictors of both morning systolic and diastolic blood pressures in multivariate analysis. Cardiorespiratory consequences of OSA in patients with massive obesity was addressed (55) by comparing the results of a comprehensive evaluation in apneic and non-apneic patients with BMI>40 kg/m^2 and without COPD. They diagnosed severe OSA (AHI>40) in 25 out of 60 patients (42%). The OSA patients did not differ significantly from the non-OSA subjects with regard to age (47 vs 43 yr), BMI (>50 kg/m^2 in both), waist/hip ratio, pulmonary function test parameters, prevalence of smoking history as well as diabetes mellitus. A moderate daytime hypoxemia, mild PHT and moderate hypertrophy of the interventricular septum were more frequently observed in the OSA group than in the non-OSA subjects.

OSA, Metabolic Syndrome (MetS) and CVD

The prevalence of MetS is higher in OSA patients than in general population or in obese non-OSA subjects (56). Available data suggests a significant association between insulin resistance (IR) and OSA as well as with atherosclerosis, advocating for that metabolic disturbances may well be a significant link between OSA and CVD (57). Large population based studies such as SHHS and the Wisconsin Cohort Study both identified OSAS as an independent risk factor for IR, after adjustment for potential confounding variables (58). Moreover, reports from sleep clinics demonstrated the association between the degree of IR and severity of OSA (57). Indeed, severe OSA was accompanied by five-fold increase in the risk of diabetes mellitus (59). Hence, the International Diabetes Federation Taskforce on Epidemiology and Prevention has recently recommended that health professionals working in both DM and OSA should ensure that a patient presenting with one condition is considered for the other (60).

Conclusion

OSA is common in general population and associated with increased cardiovascular morbidity and mortality in both population-and clinic-based epidemiological studies. However, mechanisms of actions and the relative magnitude of the impact of OSA on cardiovascular structure and function remain to be

resolved. The impact of OSA on CVD is confounded by traditionally recognized cardiovascular risk factors, and the absolute long-term consequences of untreated OSA remain to be better understood. Considering that OSA is highly prevalent in the general population, and in particular, in patients with multiple cardiovascular risk factors, there is a need to clarify these associations. A significant independent or synergistic influence of OSA on CVD will also advocate that treatment of the breathing disorder should be considered also in asymptomatic (non-sleepy) OSA patients with or without concomitant cardiovascular risk factors. The mechanisms regarding this relationship as well as impact of alleviation of sleep apneas will be addressed in the coming review articles.

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