La Medicina del Lavoro

Med Lav 2017; 108, 4: 276-282
DOI: 10.23749/mdl.v108i4.6427

Obstructive Sleep Apnea Syndrome (OSAS) and Cardiovascular System

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Key words: Obstructive Sleep Apnea Syndrome (OSAS); cardiovascular diseases; arterial hypertension

Parole chiave: Sindrome delle apnee ostruttive del sonno (OSAS); patologie cardiovascolari; ipertensione arteriosa

Summary

There is increasing evidence of a relationship between Obstructive Sleep Apnea (OSA) and cardiovascular diseases. The strong association between OSA and arterial hypertension, in particular in patients with resistant hypertension and/or a non-dipping profile, has been extensively reported. The relationship between OSA and high blood pressure (BP) has been found independent from a number of confounders, but several factors may affect this relationship, including age and sex. It is thus important to better assess pathophysiologic and clinical interactions between OSA and arterial hypertension, also aimed at optimizing treatment approaches in OSA and hypertensive patients with co-morbidities. Among possible mechanisms, cardiovascular autonomic control alterations, altered mechanics of ventilation, inflammation, endothelial dysfunction, and renin–angiotensin–aldosterone system should be considered with particular attention. Additionally, available studies also support the occurrence of a bidirectional association between OSA and cardiovascular alterations, in particular heart failure, stroke and cardiac arrhythmias, emphasizing that greater attention is needed to both identify and treat sleep apneas in patients with cardiovascular diseases. However, a number of aspects of such a relationship are still to be clarified, in particular with regard to gender differences, effect of sleep-related breathing disorders in childhood, and influence of OSA treatment on cardiovascular risk, and they may represent important targets for future studies.

Riassunto

«La sindrome delle apnee ostruttive del sonno (OSAS) e l'apparato cardiovascolare». *Esistono ormai numerose evidenze di letteratura che sottolineano come esista uno stretto legame tra le apnee ostruttive nel sonno (OSA, da Obstructive Sleep Apnea) e le patologie cardiovascolari. L'associazione tra OSA e ipertensione arteriosa, in particolar modo nei pazienti con ipertensione resistente al trattamento o profilo non dipping, è quella più estesamente trattata in letteratura. La relazione tra OSA ed ipertensione, pur risultando indipendente da altri fattori di rischio potenzialmente confondenti, può essere modulata da diverse componenti come il sesso e l'età. Analizzare a fondo i meccanismi*

Pervenuto il 4.5.2017 - Accettato il 3.7.2017

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patogenetici che soggiacciono alla relazione tra apnee ostruttive nel sonno ed ipertensione arteriosa (ed in generale le patologie cardiovascolari) costituisce una tappa fondamentale per cercare di ottimizzare i possibili approcci terapeutici sia sul versante del trattamento delle apnee che su quello cardiovascolare nel paziente con comorbidità. I meccanismi potenzialmente coinvolti sono molteplici, ma sicuramente un ruolo primario viene svolto da: alterazioni del controllo autonomico cardiovascolare, alterazioni della meccanica ventilatoria nel sonno, infiammazione, disfunzione endoteliale e sistema renina angiotensina. La valutazione dei disturbi del respiro nel sonno e la loro eventuale terapia, anche nel paziente con patologie cardiovascolari, svolge quindi un importante ruolo in termini eziopatogenetici. Da non dimenticare sono anche gli aspetti prognostici, potenzialmente bidirezionali, di questa associazione, in particolare nel contesto, oltre che dell'ipertensione arteriosa, anche dello scompenso cardiaco, dell'ictus, e delle aritmie cardiache. Rimangono tuttavia alcuni aspetti da chiarire e che dovrebbero essere oggetto di studi futuri, soprattutto per quello che riguarda le differenze di genere, l'età infantile e l'impatto del trattamento dell'OSA sul rischio cardiovascolare.

There is increasing evidence of a relationship between Obstructive Sleep Apnea (OSA) and cardiovascular diseases.

The strong association between OSA and arterial hypertension is probably the first and most extensively described one, and it has been investigated through different types of studies, such as cross-sectional and longitudinal investigations in the general population, cross-sectional studies in OSA patients, case-control studies and questionnaire-based surveys.

Prevalence of hypertension in OSAS patients ranges from 35 to 80% and appears to be influenced by OSA severity. On the other hand, approximately 40 to 50% of hypertensive patients are affected by OSA (29,30).

The relationship between OSA and high blood pressure (BP) has been found independent from a number of confounders but several factors may affect this relationship, including age and sex. According to population-based cross-sectional and longitudinal studies, OSA is associated with hypertension more strongly in young to middle aged adults (<50 years of age). A significant effect of OSA on BP regulation in children has also been suggested, although the body of evidence is still limited compared with data in adults.

Indeed, OSA has been acknowledged as a novel, frequent and modifiable cause of systemic resistant hypertension by the European Society of Hypertension/ European Society of Cardiology guidelines (published in 2007 and updated in 2013) for the management of arterial hypertension (21, 22).

A deeper assessment of pathophysiologic and clinical interactions between OSA and arterial hypertension has been reported in a position paper published by a panel of experts participating by the European Union COST (COoperation in Scientific and Technological research) ACTION B26 on OSA, with the endorsement of the European Respiratory Society (ERS) and the European Society of Hypertension (ESH) (29, 30).

Particularly, there is increasing evidence that diagnosis of an association between OSA and hypertension, as well as the need of their combined treatment, should be considered in patients with refractory hypertension and a non-dipping blood pressure profile (6, 21, 22, 31) as also confirmed by the recent European Society of Hypertension Practice Guidelines for ambulatory blood pressure monitoring (32).

Mechanisms involved in the association between arterial hypertension and OSA

Given the link between OSA and hypertension (and in general between OSA and cardiovascular diseases), it is important to define the mechanisms that might be responsible for it, also aimed at optimizing treatment approaches in OSA and hypertensive patients with co-morbidities. Among the possible mechanisms, the following should be considered.

Cardiovascular autonomic control alterations

Autonomic nervous system regulates heartbeats, myocardial contractility and arterial blood pressure (ABP) through a constant interaction between its

two branches, namely sympathetic and vagal fibers. Cardiovascular autonomic control is dynamically modified in different physiological conditions, such as wakefulness and sleep.

In healthy subjects, sympathetic activity progressively decreases from wakefulness to non-REM sleep, with consequent reduction of heart rate, myocardial contractility and ABP. Vice versa, REM sleep is associated with a marked increase of sympathetic activity at levels similar or even higher than wakefulness (41).

It is worth noting that patients with OSA have an important alteration of cardiovascular autonomic control during wake and sleep. In fact, apneic events that occur during night time cause a significant fragmentation of sleep structure, thus altering the physiological interactions between sleep and cardiovascular system mediated by central and reflex neural mechanisms.

During each apneic event, a marked increase of sympathetic activity is observed. This increase is mediated by chemoreflex activation induced by hypoxia and hypercapnia, with consequent vasoconstriction and heart rate changes. Forced inspiration after a forced expiration with obstructed airways (Müller maneuver) induces an enhancement of negative intrathoracic pressure (up to -80 cmH_2O), resulting in increase of left ventricular afterload and left ventricular filling. Negative intrathoracic pressure induces a stretching of aortic wall, which activates baroreceptors and is responsible for intermittent inhibition of sympathetic activity (39).

When an arousal occurs, respiration causes a rapid increase of venous return and a subsequent increase of cardiac output. Because peripheral circulation is still under conditions of marked vasoconstriction, the final effect is a drastic increase of ABP that induces, together with the recovery of respiration, a subsequent inhibition of sympathetic activity (39).

Together with the autonomic modulation directly induced by apneic events during sleep, sympathetic overactivity that characterizes OSA seems to be linked to an increased reflex activity of peripheral chemoreceptors, which become more sensitive to hypoxic stimulation, with consequent enhancement of autonomic, hemodynamic and ventilatory responses (26, 42).

This persistent state of sympathetic overactivity during either wake and sleep plays a key role in the development of arterial hypertension and a number of cardiovascular complications such as arrhythmias, decompensation of congestive heart failure, coronary artery diseases and sudden cardiac death (44).

Altered mechanics of ventilation

In patients with obstructive sleep apnea, the interruption of airflow, despite persistent vigorous respiratory efforts against an occluded airway, leads to progressive decreases in intrathoracic pressure, which may have important effects on cardiac function (28).

Inflammation

There are several inflammatory mechanisms responsible for an increase of cardiovascular risk which are involved also in OSA, as documented by an increase in C- Reactive Protein, IL-6 and TNF-α plasma levels (13). Moreover, cyclic hypoxia and re-oxygenation in OSA generate reactive oxygen species and oxidative stress, with the associated increase in circulating levels of inflammatory markers, thus promoting inflammation in the frame of a vicious cycle (5, 14).

Endothelial dysfunction

Endothelial dysfunction is a systemic pathological condition characterized by imbalance between vasoconstriction and vasodilation due to the release of endothelium-derived vasoactive mediators. Endothelial dysfunction has been considered as an early marker of vascular damage and a predicting factor for cardiovascular events also in OSA patients. Some studies have suggested that OSA patients show endothelial dysfunction as quantified by assessment of forearm vascular flow, intima-media thickness, carotid–femoral pulse-wave velocity, changes in number of circulating endothelial progenitor cells and vascular endothelial growth factor (20). The most important endothelium-derived vasodilator molecule is nitric oxide that is reduced in OSA patients (4). Moreover, it has been described that endothe-

lial progenitor cells are reduced in OSA patients as compared to healthy subjects (15). Finally, it is important to consider that a large number of mediators involved in oxidative stress, such as TNF, IL-1, IL-6, IL-8 e HIF-1, can also play a role in determining endothelial dysfunction (2).

Renin-angiotensin-aldosterone system

There are very limited data trying to correlate OSA with various markers of renin-angiotensin-aldosterone system (RAAS) activity, but available data suggest the occurrence of a positive correlation between plasma aldosterone concentrations and OSA severity, in particular in patients with resistant hypertension (35). Moreover, a recent study has shown that spironolactone, an antagonist of mineralocorticoid receptors, reduces apnea-hypopnea index (AHI) affecting the number of both central and obstructive events (8). All the above observations clearly support a contribution of OSA to the pathogenesis of cardiovascular diseases but evidence is also available on the occurrence of a bidirectional association between OSA and cardiovascular alterations.

Obstructive sleep apnea as a cause of cardiovascular diseases

A large amount of studies showed that severe untreated OSA (AHI>30) is related to fatal and non-fatal cardiovascular events, and all-cause mortality (27, 37, 45, 46).

Ischaemic heart disease

Prospective and cross-sectional studies report an association between OSA and coronary artery disease and untreated OSA seems to adversely influence prognosis in patients with coronary artery disease. In the Sleep Heart Health study OSA was a significant predictor of incident coronary heart disease (as quantified by myocardial infarction, revascularization procedures, or coronary heart disease death). This was shown in males up to 70 yrs of age (adjusted HR 1.10, 95% CI 1.00-1.21; per 10-unit increase in AHI) but not in older males or in females of any age (11, 37).

Stroke

OSA is associated with a very high cerebrovascular risk. Prevalence of sleep-related breathing disorders, in particular of OSA, in patients with stroke or transient ischemic attacks, is significantly higher as compared to the general population (50-70%) (3). In a Swedish cohort of 182 middle-aged men, over 10 years of follow-up, 14% of patients with OSA experienced a stroke (34). Prospective data in a larger population (5,422 participants followed for a median of 8.7 years) confirmed that incident cardiovascular diseases, including stroke, were significantly associated with sleep-disordered breathing in men (36). The Sleep Heart Study (6,424 patients) showed a relative stroke risk of 1.58 for patients with an AHI involving more than 10 events per hour compared with patients without OSA. Moreover, in another prospective cohort study, patients with an AHI>10 over a 3-year follow-up showed an increased relative risk of combined stroke and death of 1.97, rising to 3.3 when AHI >36 (38). Finally, there are suggestions that stroke is more prevalent in patients with OSA and patent foramen ovale (PFO) (7).

Congestive heart failure

Untreated OSA may promote functional and morphological cardiac alterations, inducing

left ventricular dysfunction, disease progression and increased mortality in heart failure patients (25, 33). In the Sleep Heart Health Study, the presence of OSA was associated to a 2.38 relative risk of having heart failure, independent of other known risk factors (11).

Target organ damage

Target organ damage is highly related to cardiovascular risk in hypertensive patients and data are also available on the possibility that OSA might affect the development of hypertension-related organ damage.

Blood vessels

OSA and hypertension are independently associated with increased stiffness of large arteries that

may contribute to left ventricular (LV) remodeling. Subjects with OSA were shown to display higher values of aortic stiffness, and lower large artery distensibility than controls (9).

Cardiac structure and function

As already mentioned, OSA can affect cardiac structure and function (18). Left atrial diameter, interventricular septal thickness, left ventricular posterior wall thickness, left ventricular mass index and prevalence of left ventricular hypertrophy were increased in normotensive individuals with OSA as well as in patients with hypertension without OSA, as compared with normotensive individuals without OSA (10). Both right ventricular and left ventricular systolic and diastolic functions are impaired in patients affected by OSA with or without hypertension (43). Thus, OSA may induce cardiac structural and functional changes that together with intermittent hypoxia and autonomic alterations could predispose to cardiac arrhythmias, in particular to incidence and recurrence of atrial fibrillation and sudden cardiac death (12).

Kidney

In patients with chronic kidney diseases OSA is more prevalent than in the general population, and an association between OSA and proteinuria as well as an improvement of proteinuria after OSA treatment, have been described. However, whether such a link is independent of BMI and BP values is still controversial (1, 23, 40).

Retina

OSA and arterial hypertension can impair optic nerve function by means of alterations in retinal vascular function. Eye disorders more frequently observed in association with OSA include nonarteritic anterior ischemic optic neuropathy, papilledema secondary to raised intracranial pressure and an optic neuropathy with an associated visual field defect that may mimic glaucoma. With regard to ocular alterations, it needs to be emphasized that conflicting evidence is available about an association between OSA and glaucoma (24).

Obstructive sleep apnea as a consequence of cardiovascular diseases

Congestive heart failure

Central sleep apnea, characterized by synchronous arrest of nasal flow and respiratory movements, is the most frequently described sleep-related breathing disorder linked to heart failure. However, also the prevalence of OSA in congestive heart failure patients is increased, ranging between 10% and 25%. One of the possible mechanisms linking heart failure and OSA is the "fluid shift theory" based on the hypothesis that upper airways obstruction during sleep could be related to the fluid migration from the legs to the upper part of the body when heart failure patients affected by lower limbs edema during daytime shift to the supine position during sleep (33). However, while evidence is available that sleep-related breathing disorders are associated with a worse prognosis in heart failure patients (16), whether and how these respiratory problems need to be treated is still a debated issue. Data exists supporting a positive effect of ventilation support devices (CPAP /BIPAP) in patients with OSA and heart failure, although a recently published study has shown that adaptive servo-ventilation (ASV) treatment during sleep in patients with a left ventricular ejection fraction of 45% or less and CSA resulted in an increased rather than in a reduced cardiovascular mortality (19).

Stroke

Prevalence of central sleep apneas and periodic breathing during sleep in patients with acute stroke is high (30-40%), probably reflecting an increased rate of new-onset stroke associated with sleep disordered breathing. The latter hypothesis seems to be also confirmed by the improvement of central sleep apnea in the transition from the acute to the subacute phase of stroke. However more than 50% of patients still exhibit an AHI of at least 10 events per hour 3 months after the acute event [86-89], mostly because obstructive events tend to persist over time (3). Little is known about the clinical relevance of OSA in the acute phase (first few days)

of ischemic stroke, but available data seem to suggest a relationship between OSA severity and stroke severity [85,90]. Considering the clinical evolution in patients with stroke, sleep apneas were associated with duration of hospitalization, increased mortality and poor functional outcome (17).

Conclusions

In conclusion, convincing evidence is supporting an influence of OSA on cardiovascular diseases, especially for arterial hypertension, heart failure, stroke and cardiac arrhythmias.

However, a number of aspects of such a relationship are still to be clarified, in particular with regard to gender differences, effect of sleep-related breathing disorders in childhood and influence of OSA treatment on cardiovascular risk.

Undoubtedly, however, in spite of these yet persisting uncertainties, available studies emphasize that greater attention is needed to both identify and manage sleep apneas in patients with cardiovascular diseases.

No potential conflict of interest relevant to this article was reported by the authors

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