Obstructive sleep apnea and arterial hypertension

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ABSTRACT

In recent years there is a growing interest regarding the relationship between obstructive sleep apnea (OSA) and cardiovascular diseases. Consequently, there is a large increase in medical literature of papers on the connections between OSA and hypertension, heart failure, arrhythmias and other cardiovascular diseases. In this work, authors review medical knowledge between OSA, arterial hypertension and cardiovascular diseases.

Introduction: definitions and nosographic hints

The expression *Pickwick syndrome*, which refers to the obese valet of the Charles Dickens novel *The Pickwick Papers*, written in 1837, has been used for a very long time. The boy fell asleep wherever he was and in every situation. The figure of Joe, *the fat boy* of Dickens' pages, is in fact an accurate clinical description of obstructive sleep apnea syndrome (OSAS) in adults. In 1976, Guilleminault created the expression OSAS. In 1988, hypopneas were discovered and there was the introduction of the expression *obstructive sleep apnea-hypopnea syndrome*.

Normally, the pharynx is the only portion of the upper airway without structures preventing collapse. During waking state, muscle tone prevents airway collapse in inspiration. During sleep, there is only a slight reduction of the flow.

In obstructive sleep apnea (OSA), the tongue and the soft palate are sucked against the back wall of the oropharynx, leading to a partial or complete reduction of the air passage (hypopnea and apnea, respectively) (Table 1;[1] Figure 1). Several conditions are OSA associated. If present, the clinician must investigate the presence of OSA (Table 2).

This review is based on the material searched for and obtained via MEDLINE and PubMed up to January 2016. The search terms we used were: *arterial hypertension, obstructive sleep apnea* in combination with *comorbidities, pathophysiology, cardiovascular risk*.

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Diagnosis of obstructive sleep apnea and epidemiological features

There are several questionnaires that allow clinicians to suspect the presence of OSA, based on symptoms and clinical signs (*Epworth sleepiness scale, Berlin questionnaire, sleep apnea clinical score, stop bang questionnaire*). However, the polysomnography is the gold standard for the diagnosis of and the classification of OSA.[1] Polysomnography evaluates several parameters such as the reduction of the air flow in the respiratory tract (the most important factor), its duration, the respiratory efforts of rib cage and abdomen, oxygen saturation, heart rate, electroencephalogram (particularly for the diagnosis of arousals).

However, the clinician has the leading role in the suspect and the diagnosis of OSA, which is still underestimate: 85% of subjects with OSA do not have the diagnosis of this condition.[2] For this reason, the clinician must search for associated conditions (Table 2), symptoms and clinical signs, in particular daytime signs (Table 3). The prevalence of OSA is high, but several studies showed different data. However, important studies performed on a large number of subjects showed a prevalence of 9% in men and of 4% in women,[3,4] with a progressive increased with aging.[5] Further, recent epidemiological data showed a prevalence in subjects aged

30-70 years of 26-34% in men and 17-28% in women.[6,7] The prevalence is higher in hypertensive subjects.

Pills on pathophysiological links between obstructive sleep apnea and cardiovascular disease

Several data are reported in medical literature. From a practical point-of-view, during non-REM sleep there is a reduced metabolic and sympathetic activity, a reduced blood pressure and heart rate, an increased vagal activity. OSA blocks this cardiovascular *relaxation* and causes a series of acute hemodynamic, autonomic, chemical, inflammatory, metabolic effects, which promote or exacerbate cardiovascular diseases (Figure 2). Population-based observational studies of OSA patients showed a prevalence of 60% in subjects with stroke,[8,9] 30% in subjects with coronary artery disease,[10,11] 25% in heart failure.[12,13] The cardiovascular system is particularly involved in OSA. Atherosclerotic disease, cardiac arrhythmias,

Table 1. Definitions and acronyms.

Apnea: reduction of airflow >90% at least of 10 s in adult
Hypopnea: reduction of airflow (≥50%) + reduction of oxygen saturation ≥3% or arousal; or: reduction of airflow (≥30%) + reduction of oxygen saturation ≥4%
Apnea/hypopnea (AHI index): number of apnea and hypopnea per hour of sleep (significant if >5/h); this index is used to classify the gravity of OSA Classification of the American Academy Sleep Medicine:[1] - AHI 5-14/h mild - AHI 15-30/h moderate - AHI >30/h severe
Obstructive sleep apnea (OSA): upper airways obstruction occurring during sleep (AHI >5/h), with interruption or reduction of breath >10 s, diagnosed with polysomnography (instrumental diagnosis) Obstructive sleep apnea syndrome (OSAS): OSA with related symptoms (OSA+A and/or B criteria). **Criteria A:** excessive daytime sleepiness that is not better explained by other factors **Criteria B:** two or more of the following symptoms that are not better explained by other factors: - Choking or gasping during sleep - Recurrent awakenings from sleep - Unrefreshing sleep - Daytime fatigue - Impaired concentration
Arousal: obstructive apnea ends with a very short awakening that restores the flow through the airways. Generally, it does not reach the state of consciousness, but is a sort of *lightening* of the state of sleep. Arousal is a defense mechanism that activates the dilator muscles of the neck and prevents asphyxiation in OSA. It is accompanied by sudden increases in pressure and heart rate. Arousal duration is about 5-7 s. Awakening is mainly induced by stimulation of the chemoreceptors (hypoxia, hypercapnia) and of pharyngeal mechanical reflexes
Respiratory effort-related AROUSAL (RERA): events characterized by increased respiratory effort during sleep caused by flow limitation in the upper airways that is terminated by an arousal from sleep

Table 2. Conditions associated with obstructive sleep apnea.

Obesity
Age >50 years
Male sex
Habitual snoring
Craniofacial and oropharyngeal abnormalities (anatomical situations that reduce the caliber of the upper airways, such as enlargement of the tonsils and adenoids, macroglossia, *etc.*)
Large neck
Smoke
Alcohol consumption
Pregnancy
Hypothyroidism
History of cardiovascular disease
Daytime sleepiness

especially during night time (sinus-atrial atrioventricular blocks, supraventricular and ventricular tachycardia, paroxysms of atrial fibrillation),[14,15] diabetes mellitus, metabolic syndrome.[16] In arterial hypertension, refractory hypertension and non-dipping status are the most common, in particular if left ventricular hypertrophy coexists.

Correlations between obstructive sleep apnea and hypertension

The prevalence of OSA is particularly high in hypertensive patients (30-50%) and even more in those who snore.[17,18] OSA is now considered as an independent causal factor of arterial hypertension,[19,20] in particular in hypertensive subjects aged <60.[21,22]

Several epidemiological studies demonstrated an increased prevalence of arterial hypertension in subjects with OSA, with an increased association with the severity of this disease. Lavie and coworkers demonstrated a linear increase in hypertension with the severity of OSA, measured with the apnea/hypopnea index (AHI).[23] The Wisconsin trial demonstrated that the risk of developing hypertension linearly increased with the severity of OSA with an odds ratio of 2.89 when AHI is ≥15 (P=0.002).[24] Recently, another study showed that hypertension is more common in subjects with OSA, when compared to controls and that the incidence increased with the gravity of the disease.[25] Furthermore, OSA is more common in hypertensive subjects with non-dipping status, when compared with dipping snoring subjects.[26]

In 2012, the European Society of Hypertension, the European Respiratory Society and the European COST (COoperation in Scientific and Technological research) published a *Position paper on the management of patients with obstructive sleep apnea and hypertension*, with an accurate review of the correlations between OSA, hypertension and cardiovascular diseases.[16]

The pathophysiological links of these correlations are not still clear. However, the most important mechanisms seem to be: i) sympathetic activation; ii) renin-angiotensin system activation (RAS); iii) increased

Table 3. Clinical symptoms, characteristics and objective findings suggesting a high probability for obstructive sleep apnea syndrome.

Nighttime symptoms and clinical signs
Witnessed apneas
Loud, frequent and intermittent snoring
Dry mouth
Thirsty during the night
Nocturnal diuresis
Choking, dyspnea
Disturbed sleep
Sweating
Daytime symptoms and clinical signs
Increased daytime sleepiness
Daytime fatigue
Attention deficit disorders
Headache, preferably in the morning hours

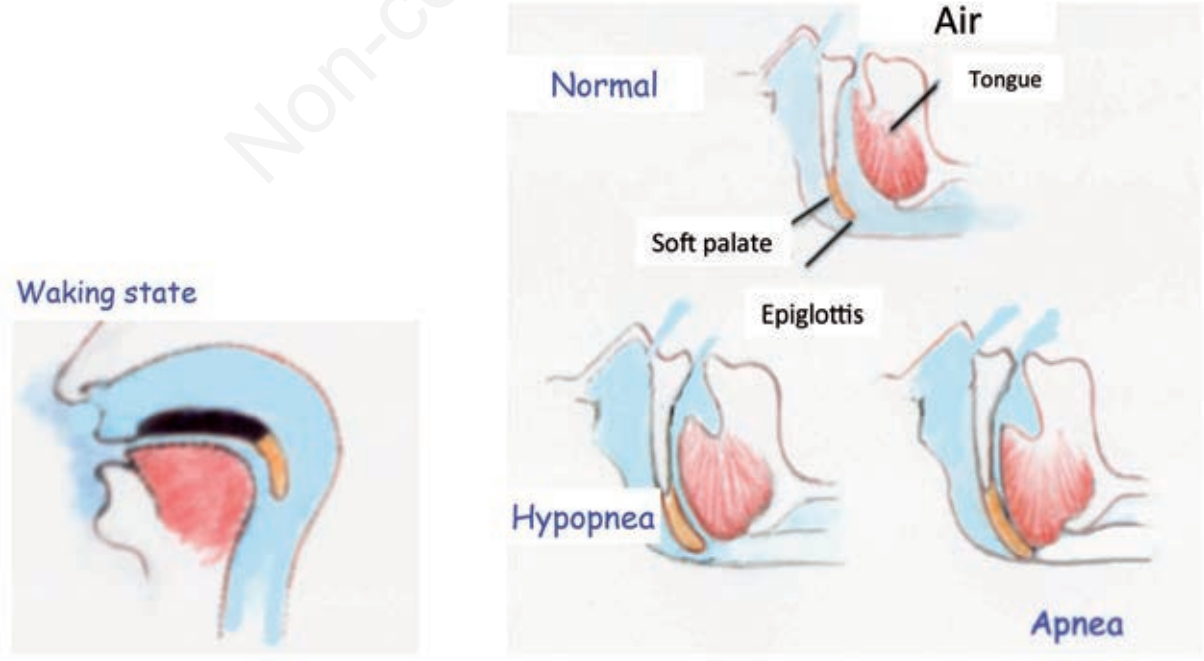

Figure 1. Possible mechanisms of total or partial obstruction of the upper airways during sleep in obstructive sleep apnea.

levels of vasoconstrictors such as norepinephrine and endothelin; iv) endothelial dysfunction; v) arterial stiffness due to repeated arousals; vi) metabolic factors.

The first two might be the most involved. Several studies showed an overactivation of the sympathetic system in subjects with OSA, in particular during night time but also during daytime.[27] The sympathetic overactivation is not only due to obesity: Grassi *et al*.[28] clearly demonstrated that is also present in subjects with OSA but without obesity: obesity had addictive effects in OSA subjects on sympathetic activation, but both OSA and obesity presented an independent role.

The relationship between plasma aldosterone levels and OSA is complex and not clear yet. Different studies showed in resistant hypertension a linear correlation between plasma aldosterone levels and severity of OSA.[29] This could mean that RAS is involved in OSA-dependent hypertension. However, another possibility is that the RAS-induced sodium retention could cause accumulation of fluid in the tissues of the neck supporting the airway collapse during sleep.[17,30,31] A large meta-analysis demonstrated that ACE gene I/D polymorphism predicted the risk for OSA complicated with hypertension, and more importantly, genetically-reduced serum ACE activity might be a causal risk factor for OSA. The clinical value of this finding is still unknown.

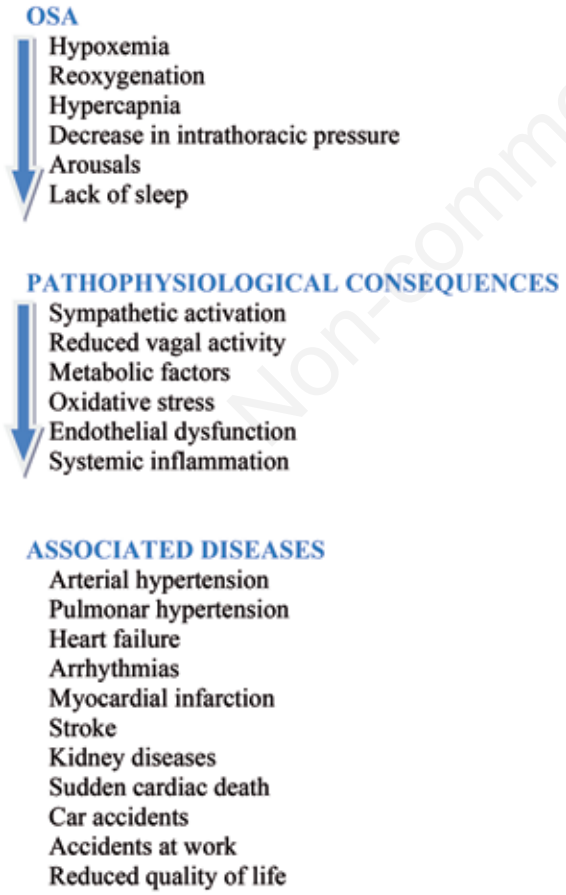

Figure 2. Pathophysiological links between obstructive sleep apnea (OSA) and associated cardiovascular diseases.

In hypertensive subjects, the ambulatory blood pressure monitoring (ABPM) can be very helpful in confirming the clinical suspicion of OSA. Recently, Torres and coworkers proposed a score to identify the subjects with AHI ≥15. The score is based on sex, ABPM, anthropometric, demographic, biological data.

The total score is the sum of: i) male sex (25); ii) diurnal blood pressure (BP) <109 mmHg (20); iii) obesity (19); iv) lowest value of diastolic BP during night ≥15; v) heart rate (beat/min).

A total score >113 identifies subjects with AHI ≥15 (sensibility 84%, specificity 64%).[32]

As showed above, a non-dipping status is associated with OSA. Furthermore, OSA subjects with a non-dipping status predict a worse cardiovascular prognosis when compared to those dipper, as showed in a Japanese trial.[33]

Which drugs should be used?

Up to date, few studies evaluated the effects of antihypertensive drug treatment on OSA severity. Moreover, these studies have included a small number of subjects and no comparable populations and presented several methodological differences. Therefore, it is not possible to establish definitive recommendations.[16] However, according to the available pathophysiological knowledge of the relationship between OSA and hypertension, antihypertensive drugs that modulate sympathetic activity and the RAS might be the best treatment options for hypertension in OSA patients. The most promising is spironolactone: by reducing para-pharyngeal edema and secondary upper airway obstruction, this drug appears to improve OSA severity and to reduce BP.[34]

Has obstructive sleep apnea treatment beneficial effects on hypertension?

An important question is: has a patient with OSA and hypertension a beneficial effect on hypertension with the treatment of this syndrome? OSA manage-

Table 4. Management of obstructive sleep apnea.

Weight loss
Avoid alcohol, hypnotics, sedatives
Change the night-time position
Oral device
Upper airways surgery
Nasal continuous positive airway pressure

Table 5. Published meta-analyses of the effect of continuous positive airway pressure on blood pressure in obstructive sleep apnea patients.

Meta-analysis (year)	Study number Patients included	Blood pressure measurements	Follow-up (weeks)	Blood pressure drop (mmHg)
Bazzano *et al.*[39] (2007)	16 studies 818 patients	Office BP ABPM	2	SBP –2.46 DBP –1.83
Alajmi *et al.*[40] (2007)	10 studies 587 patients	Office BP ABPM	4	SBP –1.38 (NS) DBP –1.52 (NS)
Mo y He *et al.*[41] (2007)	7 studies 471 patients	ABPM	4	24-h SBP –0.95 (NS) 24-h DBP –1.78
Haentjens *et al.*[42] (2007)	12 studies 572 patients	ABPM	1	24-h SBP –1.64 24-h DBP –1.48
Montesi *et al.*[43] (2012)	28 studies 1948 patients	Office BP ABPM	1-24	Daytime SBP –2.58 Daytime DBP –2.01 Nighttime SBP –4.09 Nighttime DBP –1.85
Fava *et al.*[44] (2014)	31 studies 1820 patients	Office BP ABPM	4-208	SBP –2.6 DBP –2.0 Daytime SBP –2.2 Daytime DBP –1.9 Nighttime SBP –3.8 Nighttime DBP –1.8
Bakker *et al.*[45] (2014)	8 studies 968 patients	Office BP ABPM	6-52	SBP –2.27 DBP –1.78 Patients with uncontrolled hypertension: SBP –7.1 DBP –4.3

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Modified from Torres* et al., *2015.*[32]

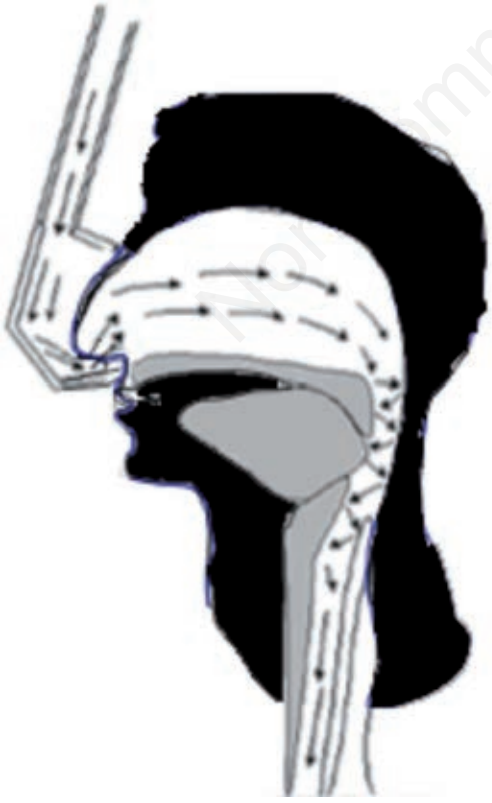

Figure 3. Continuous positive airway pressure effects on upper airways.

ment is multifactorial (Table 4), but a key intervention is the weight loss. Nocturnal continuous positive airway pressure (CPAP) is the best treatment of OSA by keeping the upper airways open with a support tire that prevents the oscillations of the pharyngeal wall in all directions, in particular that transverse (Figure 3). The beneficial role of CPAP on cardiovascular diseases and on hypertension is still debated. In early 2000s, some studies showed beneficial effects, both on hypertension[35] and on fatal and non-fatal cardiovascular events.[36] However, up to date, many studies showed methodological differences with different results.[37] These differences and limitations are due to several factors such as age, sex, body mass index, hypertension degree and adequate antihypertensive treatment, as well as severity, treatment used in the control group (sham-CPAP use or not).[32,38] Despite these limits, several meta-analyses demonstrated a concordant mild effect of CPAP on blood pressure, with a drop of approximately 2-3 mmHg, in particular during night time (Table 5).[32,39-45] These studies showed that the biggest reduction in BP values is present in some subgroups of subjects:[38] i) uncontrolled and resistant hypertension; ii) OSA severe; iii) major symptoms (daytime sleepiness); iv) better compliance to CPAP (at least 5-6 h/night).

Obstructive sleep apnea and resistant hypertension

Recent reported data showed a high prevalence of OSA in patients with resistant hypertension. Logan and coworkers showed in 41 subjects with resistant hypertension a prevalence of OSA (AHI >10) of 83%.[46] Pedrosa and collaborators confirmed these data. Their study demonstrated that OSA was the first cause of resistant hypertension (64%), followed by essential hypertension (34.4%), primary hyperaldosteronism (5.6%), renal artery stenosis (2.2%), nephropathy (1.6%), thyroid disease (0.8%).[47]

The prevalence of resistant hypertension increases with OSA severity, measured with AHI, and is above 85% in subjects with AHI >30.[48] Office blood pressure measurements and ABPM showed that prevalence of OSA increased progressively in these subgroups: controlled hypertension, masked hypertension, white-coat hypertension, true resistant hypertension.[48] In subjects with OSA and resistant hypertension, the CPAP caused a BP drop of 3-5 mmHg. Lozano *et al*.[49] showed that the best and significant results in lowering blood pressure in patients with resistant hypertension treated with CPAP in addition to conventional therapy occurred only in those with good adherence to CPAP (at least 5-6 h of night-time period). These subjects showed an average pressure drop around 7-10 mmHg.[50] Moreover, the number of patients with nocturnal dipping increases in this group, while not varied in the control group.

Conclusions

As discussed above, many problems of the topic of this review are still unsolved. In particular, the link between OSAS, hypertension and cardiovascular risk must be better defined and requires further study. Also CPAP treatment of OSA and the real beneficial effects on blood pressure and cardiovascular risk are still unclear. There is therefore need for extensive studies.

Despite these limits, current evidence is sufficient to recommend more attention to identify and treat hypertension associated with OSA, and particularly to seek the sleep disorders in patients diagnosed with hypertension, especially in uncontrolled and resistant hypertension or in subjects with a non-dipping status. The clinician must not ignore these things in everyday clinical practice, otherwise he limits the effectiveness of his interventions designed to reduce blood pressure and cardiovascular risk.

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