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REVIEW

The pathogenesis of OSA-related hypertension: what are the determining factors?

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ABSTRACT

Sleep-disordered breathing has a relatively high prevalence, which varies from 3-7% in males and from 2-5% in females in the adult population. Studies published in the literature have shown that sleep apnea is closely related to an increased risk of developing various pathologies, among which arterial hypertension stands out. The prevalence of hypertension in patients suffering from obstructive sleep apnea (OSA) ranges from 35-80% and appears to be related to OSA severity. Approximately 40-50% of patients affected by hypertension are also affected by OSA and this association seems to be stronger in young and middle-aged adults (<50 years of age). The primary objective of this narrative review is to provide an update on what are the main contributing comorbidities to the development of a hypertensive state in patients suffering from OSA, an independent risk factor for diurnal hypertension, implicated as a risk factor for the first stroke, recurrent stroke, and post-stroke mortality. There are a lot of factors that contribute to developing a hypertensive state in OSA patients, some more decisive, others less. More evidence from longitudinal studies is needed on the impact of OSA on cardiovascular risk in females, on the causal link between OSA and arterial hypertension or metabolic diseases, like diabetes and glucose intolerance, and the effect of different kinds of OSA treatment.

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KEY WORDS: Obstructive sleep apnea; Hypertension; Arterial hypertension; Sleep; Sleep apnea syndromes; Phenotype.

Sleep-disordered breathing, especially obstructive sleep apnea (OSA), has a relatively high prevalence; in the adult population, the prevalence varies from 3-7% in males and from 2-5% in females,[1] although methodological differences in the conduct of clinical trials lead to some variability in estimation. Moreover, only 40% of patients suffering from sleep apnea are diagnosed, a critical issue that determines an underestimation of the real prevalence of the disease.[2]

Many studies published in the literature have shown that sleep apnea is closely related to an increased risk of developing various pathologies, such as endocrine and metabolic diseases[3] some types of neoplasms,[4] and cerebral and cardiovascular pathologies,[5] among which arterial hypertension stands out.

Arterial hypertension's prevalence has increased over the past decade and it is predicted to increase by about 60% in 2025.[6]

The prevalence of hypertension in OSA patients ranges from 35-80% and appears to be related to OSA severity. Approximately 40-50% of patients affected by hypertension are also affected by OSA[7] and this association seems to be

stronger in young and middle-aged adults (<50 years of age).[7]

The strong association between OSA and arterial hypertension has been investigated through different studies, such as cross-sectional or longitudinal trials in the general population, cross-sectional studies in OSA patients, case-control studies, and questionnaire-based surveys.

Obstructive sleep apnoea (OSA) has been increasingly linked with excess cardiovascular morbidity and mortality however the mechanisms are still not well understood. Robustly designed studies have shown that treatment of OSA with nasal continuous positive airway pressure improves important intermediate risk factors for CVD including hypertension and endothelial function.

More recently, there has been an increased exploration of arterial stiffness in both cross-sectional and interventional studies in OSA patients. OSA is an independent risk factor for diurnal hypertension and has been implicated as a risk factor for the first stroke, recurrent stroke and post-stroke mortality.[8, 9]

Although OSA and hypertension often coexist, there is a shortage of sufficiently powered studies testing the real interplay between the course of sleep apnea and CVD. It is important to discover the mechanisms that might be responsible for it, also aimed at deciding the better treatment in OSA patients affected also by hypertension.

The purpose of this study, considering the existing literature data, is:

• to discover the determining factors that underline the pathogenesis of OSA-related hypertension, because these two diseases must be considered nowadays as a social health problem, with a very high burden for its management;

• to analyze the risk factors in the general population, for phenotyping subtypes of OSA, considering the heterogeneity of individuals affected by OSA, reflected by varying risk factors, pathophysiological causes, clinical manifestations, and consequences.

Literature search

The primary objective of this narrative review is to provide, according to the most recent literature, an update on what are the main contributing comorbidities to the development of a hypertensive state in patients suffering from obstructive sleep apnea (OSA).

The research was conducted on the PubMed database using a basic string: (((((OSA[Title/Abstract]) or (Obstructive Sleep Apnea [Title/Abstract])) and ((Arterial Hypertension [Title/Abstract]) or (Hypertensive patient [Title/Abstract]) or (Hypertensive state [Title/Abstract])) and ((Pathogenesis [Title/Abstract]) or (Physiopathology [Title/Abstract])))).

Which have been associated with time-to-time specific risk factors more frequently reported and that often are indicated as clinical comorbidities, *i.e.*, intermittent hypoxia, arousal threshold and obesity. Subsequently, as shown in Figure 1, the most recent systematic reviews were selected, the bibliography of which was further developed so that more could be learned about the specific comorbidity examined.

Filters such as time ranges and language restrictions have not been set, thus revising as open as possible and free from possible conducting bias.

The drafting of the revision was carried out through the contribution of two authors, who independently dealt with the compilation of the main paragraphs. The remaining two authors then checked the work's quality and methodological goodness by making any changes after having discussed it with the other authors.

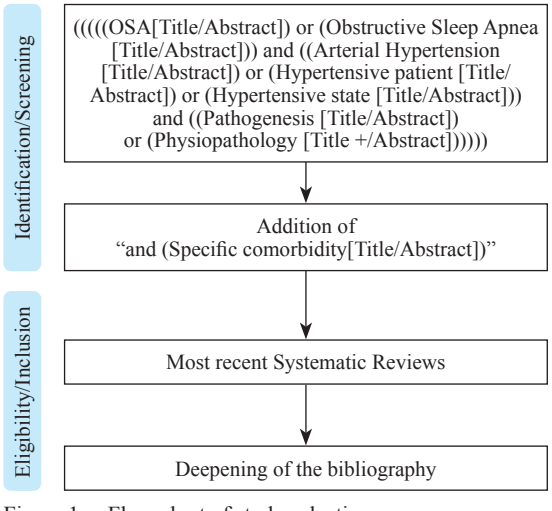

Figure 1.—Flow chart of study selection.

Reviewing the literature, we have identified a lot of risk factors for developing hypertension in patients affected by OSA; among the possible mechanisms, the following should be considered in clinical practice.

Intermittent hypoxia

A lot of data confirms that intermittent hypoxia (IH) secondary to repetitive obstructive apnea events contributes to the state of low-grade systemic inflammation.[10] IH plays an important role in determining inflammation. In fact, in Arnaud's study, it is described how the inflammatory state is characterized by several factors: activation of the major pro-inflammatory transcription factor or factor K, increased expression of pro-inflammatory cytokines and chemokines, and recruitment of macrophages in a pro-inflammatory direction in different tissues. Indeed, it has been established that IH-induced inflammation contributes to the development of atherosclerosis through metabolic dysfunction and remodeling of the vascular system. The primary response to hypoxemia is bradycardia, as seen in the diving reflex.[11] Varying degrees of bradycardia and bradyarrhythmia are often seen in patients with OSA, and in some patients may manifest as Mobitz II, complete heart block, and sinus arrest. Treatment in these cases should usually consist of treatment of apnea, rather than pacemaker placement. Hypoxemia and reperfusion also have important effects on vascular function; these are mediated by several mechanisms, including systemic inflammation, endothelin release, and attenuated production of nitric oxide (NO). Patients with OSA have increased levels of C-reactive protein (PCR)[12] and evidence of leukocyte activation.[13] Hypoxemia is an important trigger for endothelial cell endothelin production.[14] Endothelin is a highly potent vasoconstrictor and acute untreated OSA results in elevations of both endothelin and blood pressure, with attenuation of both after CPAP treatment. Conversely, patients with OSA have reduced levels of circulating NO, which increase after CPAP therapy.[15] These hypoxemia-driven effects on systemic inflammation, endothelin, and NO likely contribute to the endothelial dysfunction evident in patients with OSA.[16]

Studies in animals by Brooks and coworkers[17] showed that while sleep fragmentation acutely increased nighttime blood pressure value, the daytime value was relatively unchanged. In contrast, nighttime blood pressure increased during obstructive apneas, with the persistence of elevated values into the daytime, suggesting that nocturnal hypoxemia, and not arousals, are a key driver for elevated daytime blood pressure, with clear implications for OSA-related hypertension. Hypoxemia may also be an important trigger for OSA-induced atrial fibrillation (AF).

In a cohort study of 3.542 adults, all of whom were free of any history of AF, Gami *et al.*[18] reported that in subjects younger than 65 years of age, OSA was associated with an increased risk of incident AF. The magnitude of the decrease in nocturnal oxygen saturation, but not apnea-hypopnea index (AHI), was an independent predictor of the risk of developing new-onset AF. In patients undergoing cardioversion for AF, observational data also suggest a role for nocturnal hypoxemia as a predictor of the recurrence of atrial fibrillation.[18] Patients with OSA who remain untreated after cardioversion have a markedly increased likelihood of AF recurrence as compared with those whose OSA is treated.[19] In the OSA untreated group, those most likely to recur were those with the most marked nocturnal oxygen desaturation.[19]

Hypoxemia may also be a trigger for nocturnal cardiac ischemia[20] and perhaps myocardial infarction.[21] Increasing levels of nocturnal oxygen desaturation are associated with a heightened likelihood of ST segment depression, an ECG marker of cardiac ischemia.[22] The role of hypoxemia in arrhythmogenesis, including bradycardia, as well as hypoxemia potentiating cardiac ischemia, may be important in understanding mechanisms underlying sudden cardiac death related to OSA. The effect of acute and intermittent hypoxia has also been studied in healthy volunteers. Glucose tolerance was significantly decreased in the acute hypoxic group (75% oxygen saturation for 30 min) as compared with the control group;[23] glucose metabolism was also impaired as evidenced by decreased insulin sensitivity, glucose effectiveness, and insulin secretion in volunteers exposed to acute intermittent hypoxia sustained

over 5 hours.[24] Nocturnal intermittent hypoxia was also associated with an increased risk for developing type 2 diabetes, as shown in a large community-based middle-aged Japanese group.[25] A significative correlation was also noted between the severity of hypoxemia and HbA1C levels in nondiabetic subjects with OSA; treatment with CPAP over 3 to 5 months decreased HbA_{1c} only in patients with severe sleep apnea.[26] Long-term hypoxia can enhance the production of angiotensin II, and upregulate NADPH oxidase activity, which promotes oxidative tissue injury in the hippocampal catecholamine neurons. This selective loss of the catecholaminergic wake-active neurons may contribute to impaired wakefulness.[27] Neuroimaging studies of the brain in patients with OSA have demonstrated structural, morphologic, and functional changes in the brain suggesting a plausible mechanism for cognitive impairment.[28] Morphologic changes manifesting reduction in grey matter volume have also been correlated with neurocognitive changes and the degree of hypoxemia that may improve with CPAP treatment.[29] In the end, *in vitro* studies have demonstrated the pro-oncogenic properties of hypoxia;[30] this is mediated mainly by the enhanced post-translational effect of hypoxia-inducible factor (HIF), which in turn results in increased expression of vascular endothelial growth factor (VEGF), formation of new capillaries, tumor growth, and metastasis. Laboratory studies have also demonstrated that low-frequency intermittent hypoxia has similar proangiogenic and tumor growth-promoting effects.[31, 32]

Inflammation and oxidative stress

There is a very close link between chronic systemic inflammation and OSA. OSA induces a systemic inflammatory response activating the signal transduction pathway leading to the upregulation of inflammatory cytokines and downregulation of anti-inflammatory cytokines.[33] An increase in proinflammatory cytokines, like C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and interleukin 10 (IL-10) in adult patients affected by OSA supports this hypothesis, with a possible association between the apnea-hypopnea index (AHI) and inflammatory cytokine levels. The inflammatory responses may be reversed after OSA treatment.[34] The proinflammatory cytokines, interleukin 17 (IL-17) and interleukin 23 (IL-23) have been recently emphasized. IL-17 is a proinflammatory cytokine secreted predominantly by T helper 17 cells (TH17) and various cells including innate immune cells and nonimmune cells.[35]

IL-23 is a cytokine with immunomodulatory effects and stimulates the production of interferon-gamma. Studies showed that TH17 cells can be regulated by IL-23.[36] There is growing evidence that cell and molecular mechanisms involving inflammatory mediators are up-regulated in patients with OSA; a lot of evidence suggests that the transcription factor nuclear factor kappa B (NF-κB) plays a critical role in this process[37, 38] and controls the expression of many genes including those encoding inflammatory cytokines, such as TNF-a, IL-6, IL-8 and a lot of adhesion molecules, like ICAM-1 and cell receptors.[39] A lot of data in the international literature show an increase in levels of these markers in patients affected by OSA and a clear decrease during therapy with positive pressure ventilation.[40] Oxidative stress is one of the most relevant pathogenetic mechanisms that sustain the cardiovascular consequences of OSA. Chronic intermittent hypoxia exposure induces tissue deoxygenation, followed rapidly by tissue reoxygenation leading to reactive oxygen species (ROS) formation.[41]

TNF-a enhances the production of reactive oxygen species, including inducible nitric oxide (NO) and it is been demonstrated that decreases myocardial contractility in a dose-dependent fashion.[42] ROS may play a pro-inflammatory role by inducing NF-κB and subsequently the expression of proinflammatory cytokines such as interleukin-6, TNF-α, and C-reactive protein.[43] In addition, they may exert proatherogenic effects by increasing lipid peroxidation as shown in a mouse model of OSA.[44]

Snoring

As early as 1980 Lugaresi *et al.*[45] in their study in San Marino had shown a correlation between snoring, hypertension, and obesity. After that,

several studies examined the association between snoring and hypertension, demonstrating that habitual snoring was significantly higher than among those who did not snore, suggesting that snoring may be an independent risk factor for hypertension.[46] In the same way, a clinical study by Khazaie *et al.*[47] indicated that snoring is a risk factor for hypertension independently of BMI, AHI, age, waist, neck circumference and apnea. The early identification and management of snoring may reduce cardiovascular risk and truly the burden of hypertension associated with sleep apnea and snoring in the population.

Sleep fragmentation, sleep loss, and insomnia

Several lines of evidence in the literature demonstrated that sleep loss[48] and insomnia[49] are associated with an increased incidence of hypertension. The mechanisms underlying these associations might be related to inappropriate physiological arousal due to an alteration in stress system functions,[50] related to the activation of the sympathetic nervous system and pro-inflammatory pathways.[51] Sleep alterations might impair adaptation to stress through allostasis and contribute to allostatic load, thus compromising stress resiliency and increasing blood pressure.[52] Sleep loss due to partial and total experimental sleep deprivation might induce sustained increases in blood pressure in either normotensive, pre-hypertensive or hypertensive subjects, in both elderly and young adults, male and female subjects. A study by Faraut *et al.*[51] provides further evidence in this field by addressing the association between hypertension and sleep duration in patients referring to primary care physicians in the frame of a cross-sectional survey, which included about 1000 participants. The principal finding of this study is that sleeping 5 hours or less was independently associated with a higher prevalence of hypertension. This finding largely confirms the results obtained in previous studies. Other key factors influencing the relationship between sleep duration and hypertension are gender and obesity.[53] Sleeping less than 5 hours per night was associated with a higher prevalence of hypertension compared with sleeping 7 hours among women but not among men;[54] in particular, the association seems to be stronger in pre-menopausal than in post-menopausal women.[55] There is a relationship between slow wave sleep (SWS) per cent and increased blood pressure. After adjustment for age, race, and body mass index, the only sleep index to remain significantly associated with incident hypertension was SWS percentage, which was inversely associated with incident hypertension, independent of sleep duration and fragmentation and sleep-disordered breathing. Selective deprivation of SWS may contribute to adverse blood pressure in older men.[56] The evidence that hypertension is more prevalent in patients with insomnia than in good sleepers has been demonstrated in several studies over the past 20 years.[53] Possible mechanisms underlying the relationship between sleep deprivation, short sleep duration, insomnia, and hypertension are suppressive effects of good sleep on the stress system[50] and the pro-inflammatory system[57] (Figure 2). Sleep loss due to both prolonged sleep reduction and insomnia might act as a chronic stressor, activating the sympathetic nervous system and systemic inflammation.[53]

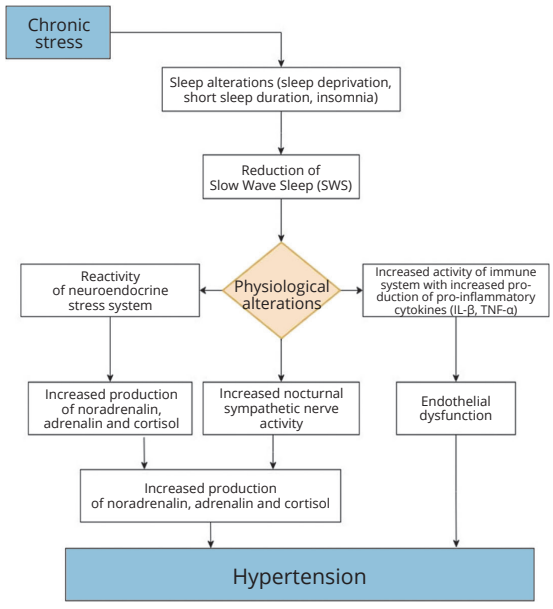

Figure 2.—Relationship between chronic stress and hypertension.
NAD: noradrenaline; AD: adrenaline; BP: blood pressure; TNF: tumor necrosis factor; IL: interleukin (modified from Palagini *et al.*).[53]

Arousal threshold

There is clear evidence of the relationship between blood pressure values and sleep quality. It has been hypothesized by several authors that the peak rise in blood pressure values during obstructive apnea was due to hypoxia-induced sympathetic response,[58] to post-apnea vagal-mediated inflation,[59] and to the release of the very negative intrathoracic pressure, which occurs during the obstructive segment.[60]

A clinical study performed by Guilleminault *et al.*[61] demonstrated that none of these effects is necessary to explain the rise and fall in blood pressure values, that occur at the end of apnea during the resumption of respiration. Arousal may explain the increase in blood pressure independently of hypoxia or the increase in respiratory efforts against a partial or complete obstruction of the airway. Compared to blood pressure values in uninterrupted sleep, there were significantly different increases in systolic and diastolic blood pressure depending on the type of arousal. There was always a change in diastolic and systolic blood pressure with auditory stimulation, even when no visual signs of EEG changes were noted.[61] The changes were more marked in diastolic than systolic values, however, with EEG arousals. Arousals leading to an awakening produced significantly higher systolic and diastolic increases than any other type of arousal. Alpha EEG arousals also lead to significantly different increases in systolic and diastolic blood pressure than do k complexes. Arousals from sleep indicated by EEG recording were reflected more in blood pressure values increases than in HR changes.[61] Moreover, Amatoury *et al.*[62] demonstrated that average arousal intensity is independent of the preceding respiratory stimulus. This is consistent with arousal intensity being a distinct trait. Respiratory and pharyngeal muscle responses increase with arousal intensity. Thus, patients with higher arousal intensities may be more prone to respiratory control instability and, finally, to a higher variation of blood pressure values and day-to-night dipping. The correction of abnormal increases in respiratory efforts and elimination of sleep fragmentation with nasal CPAP has a significant effect on blood pressure. This indicates that arousals and mechanical changes involving respiratory efforts can impact blood pressure on a chronic basis.[62]

Artery stiffness and endothelial dysfunction

Many studies have reported that patients with OSA show vaso-reactive dysfunction, vascular remodeling,[63] and accelerated progression of atherosclerosis.[64] Considering arterial stiffness as a new marker of cardiovascular risk,[65] it has been recently reported[66] as being increased in patients with OSA. A lot of factors can potentially have a negative impact on the vascular system in patients affected by OSA. Nocturnal apneas initiate several pathophysiological mechanisms related to adrenergic activation and are accompanied by chemoreflex-mediated increases in sympathetic activity in the peripheral blood vessels. Toward the end of an apneic episode, blood pressure can reach very high levels[67] and the pattern of blood pressure at night has specific features.[68] Recurrent hypoxemic stress increases the release of vasoactive and trophic substances, including renin, noradrenaline, thromboxane A2, and endothelin, along with decreased production of vascular nitric oxide and high vasoconstriction reactivity.[68]

Expression of NO synthase (eNOS) and activated eNOS, markers of endothelial NO production and activity, was significantly lower whereas expression of nitrotyrosine, a marker of oxidative stress, was significantly greater in OSA patients than in OSA-free subjects.[69] Moreover, it has been described that endothelial progenitor cells are reduced in OSA patients as compared to healthy subjects[69, 70] and that many mediators involved in oxidative stress, such as TNF, IL-1, IL-6, IL-8, e HIF-1, can also play a determinant role in endothelial dysfunction.[71] These abnormalities affect the stiffness of the arterial wall. Another major mechanism leading to changes in the walls of the central arteries is protein glycation;[72] under chronic conditions, this leads to active vascular inflammation and then to proliferation, consolidation of the intima and changes in the media, resulting in stiffer arteries. Several studies have also suggested hypercoagulability in patients with OSA, but these investigations

were generally limited by small numbers and or inadequate control for potential confounding variables such as obesity and smoking.[7, 73] Robustly designed studies have shown that treatment of OSA with nasal continuous positive airway pressure improves important intermediate risk factors for CVD including hypertension and endothelial function.[72]

Renin-angiotensin-aldosterone system (RAAS)

In the literature, there are very little data about the correlation between obstructive sleep apnea and RAAS, even if this correlation is the object of study in the last two decades. A study by Pratt-Ubunama *et al.*[74] on seventy-one consecutive subjects referred to the University of Alabama for resistant hypertension has demonstrated that the association between obstructive apnea and primary aldosteronism is common in subjects affected by resistant hypertension but not in control subjects. While cause and effect cannot be inferred, the data suggest that aldosterone excess may contribute to OSA severity. Hypertension occurring in subjects with OSA is more likely to be severe, resistant to antihypertensive treatment, and associated with alterations in day-to-night blood pressure changes.[17] Moreover, a study by Clark *et al.*[75] demonstrated that antagonists of mineralocorticoid receptors drugs (*i.e.* spironolactone) reduce Apnea-Hypopnea Index (AHI) and both central and obstructive events.

Sympathetic activation

It is well known that OSA is associated with a selective potentiation of autonomic, hemodynamic, and ventilatory responses to peripheral chemoreceptor activation by hypoxia. Bilateral carotid body denervation was achieved by sectioning of the carotid sinus nerve and chemical sympathectomy prevented hypertension[76] suggesting that it depended on chemoreceptor activation and was mediated by the sympathetic nervous system. Cardiovascular autonomic control is dynamically modified in different physiological conditions, such as wakefulness and sleep.[70] OSA patients are characterized by a derangement in autonomic cardiovascular regulation, both during the night and during the day. Both hypoxia and hypercapnia result in sympatho-excitation.[77] When combined, these stimuli synergistically increase sympathetic activity. Sleep apnea results in yet greater levels of sympathetic activation in normal humans. Hypertensive subjects, who are at high risk for sleep apnea, have an exaggerated sympathetic nerve response to hypoxia, and sympathetic activation during sleep apnea results in adverse cardiovascular effects and sudden death and contributes to daytime essential hypertension.[78] During apneic episodes there is an increase in efferent sympathetic neural activity, due to chemoreflex stimulation, triggered by the reduction in arterial oxygen pressure and by hypercapnia occurring during the episodes and represents one of the major factors responsible for the increases in blood pressure values and hearth rate, characteristic after apneic episodes.[7] Patients with obstructive sleep apnea have high sympathetic activity, even during normoxic wakefulness. The chemoreflex is an important mechanism for the regulation of both breathing and autonomic cardiovascular function. Abnormalities in chemoreflex mechanisms may therefore be implicated in increased cardiovascular stress in patients with OSA.[79]

Narkiewicz *et al.*[80] showed that the peripheral chemoreflex response to hypoxia is potentiated in patients with OSA and the chemoreflex appears to be a potent mechanism for sympathetic activation, overriding the combined restraining influences of increased blood pressure and increased ventilation. This finding suggests that not only the ventilatory but also the chemoreflex-mediated sympathetic autonomic response to hypoxia is augmented in OSA. They also shown that the blood pressure increase during hypoxia is markedly exaggerated in OSA patients.[80] These findings are important in understanding the absence of any nocturnal blood pressure decline in untreated sleep apneics, in whom repetitive apneic episodes elicit surges in blood pressure throughout the night.[67] Furthermore, pressor responses and consequent baroreflex resetting to a higher set point may be implicated in the development of sustained hypertension in these patients.[81] The exaggerated pressure response to hypoxia

in OSA is explained in part by the greater increase in heart rate. However, other factors, such as impaired hypoxic vasodilator effects, cannot be excluded.[80] The reduction of baroreflex sensitivity has been shown to improve after chronic treatment with CPAP.[7] Finally, the degree of autonomic impairment occurring at night in OSA patients may have an impact on daytime symptoms and it is truly a marker of excessive daytime sleepiness.[7, 82] We also know that sympathetic activation is involved in both heart failure and atrial fibrillation associated with OSA.[83, 84]

Hypercapnia

There are very little data in the literature about the association between hypercapnia (pCO_2 >45 mmHg) and OSA. Hypercapnia seems to be related to obesity (obesity hypoventilation syndrome-OHS) and COPD (also known as overlap syndrome), in the absence of other known causes of hypercapnia. The mechanism by which obesity leads to chronic daytime hypercapnia is complex and not fully understood. Higher body surface area in obese patients is associated with an increase in carbon dioxide production.[85] Therefore, obesity is not the only determinant of hypoventilation, because chronic daytime hypercapnia develops in less than one-third of severely obese individuals.[86] The Apnea-Hypopnea Index (AHI) has been reported by some studies to be an independent risk factor for the development of hypercapnia.[87] A meta-analysis by Kaw *et al.*,[88] performed with the aim to identify the determinants of chronic daytime hypercapnia in obese patients with OSA (OHS), has suggested that chronic daytime hypercapnia is associated with the following three factors: the severity of OSA, BMI and the degree of restrictive chest wall mechanics associated to the mean nocturnal oxyhemoglobin saturation, as also testified by the results of the study by Resta *et al.*[89] There is also a relationship among diurnal $PaCO_2$ and TST SpO_2<90% (total sleep time with oxyhemoglobin saturation <90%), which is only partially obvious.[14] It is well known that the severity of the oxyhemoglobin desaturations during sleep depends not only on the level of diurnal baseline SpO2 and PaO2 but also on the nocturnal hypoventilation, which may be present in these patients and may be independent of the diurnal level of $PaCO_2$. Therefore TST SpO_2<90% could be considered an expression of the severity of sleep-related respiratory disturbances, that is to say, apneic-hypopnea events and hypoventilation.[90] In patients with OSA and COPD, hypercapnia was related to the degree of airways obstruction; in contrast, in obese patients with OSA but no evidence of obstructive airways disease, hypercapnia was related to the degree of the restrictive ventilatory defect and the severity of OSA as measured by the degree of nocturnal oxyhemoglobin desaturation.[90, 91] A large study of Japanese patients[87] with OSA showed only AHI to be a predictor of hypercapnia, although this index was not independent of BMI.

Finally, the role of OSA in the pathogenesis of hypoventilation has been well established by the resolution of hypercapnia in the majority of patients with hypercapnic OSA or OHS with short-term treatment with either positive airway pressure therapy or tracheostomy.[88] This improvement occurs without any significant changes in body weight or respiratory system mechanics.[90] Gender is not associated with hypercapnia;[88] BMI and the AHI are significantly higher in hypercapnic patients, and FEV_1% is significantly lower in patients with hypercapnia, such as %VC (vital capacity) and %TLC (total lung capacity).[88]

Anthropometric variables

A lot of scientific data testifies to the complex interaction between sex, age, menopausal status, and the cross-sectional association between sleep duration and the prevalence of hypertension. Lombardi *et al.*[91] underlined that sleep deprivation might have a stronger effect on blood pressure levels and cardiovascular and metabolic problems in women than in men. Stranges *et al.*[55] have done a clinical study on a large population-based sample, including 3027 white men (43.5%) and women (56.5%) from the Western New York Health Study, performed between 1996 and 2001; on a multi-variate analysis, short sleep duration (<6 hours of night sleep) was associated with a significantly increased risk of hy-

pertension compared with a sleep duration of at least 6 hours per night in women, but not in men. When considering also menopausal status in subgroup analyses, the effect of short sleep duration and hypertension was stronger among premenopausal than among postmenopausal women and it was independent of socioeconomic status, traditional cardiovascular risk factors and psychiatric comorbidities.[55]

Sex differences in sympathetic control of blood pressure in humans after acute intermittent hypoxia exposure have been described. Dain Jacob in 2020[92] has done a study among 49 subjects, young (<45 years of age), healthy, non-obese (BMI<30 Kg/m^2), and non-smokers, with the aim to examine sex-related differences in the effect of intermittent hypoxia on sympathetic control of blood pressure in humans. Major findings of the work include that increases in blood pressure following acute intermittent hypoxia, observed in young men, are not present in young women, despite similar increases in muscle sympathetic nerve activity (MSNA) and that any effect of intermittent hypoxia on persistent increases in MSNA and blood pressure is independent of a change in sympathetic baroreflex sensitivity.[92] These results extend preclinical work showing that female rats exposed to chronic intermittent hypoxia do not develop high blood pressure[93] and are consistent with a lower incidence of hypertension in women with sleep apnea compared with men.[94] Dain *et al.*[92] also observed a significant fall in total peripheral resistance in women, following intermittent hypoxia, that did not occur in men; it's likely that a decrease in adrenergic-mediated vasoconstriction or possibly an increase in b-adrenergic receptor-mediated vasodilation following intermittent hypoxia may contribute. Because anywhere from 10% to 50% of hypoxic vasodilation is attributed to the b-adrenergic receptors,[95] the Authors speculate that attenuated vasoconstriction following intermittent hypoxia-mediated increases in MSNA in women occurs *via* catecholamines preferentially binding to b-adrenergic receptors in the skeletal muscle vasculature.[92] Estrogen is an established regulator of b-adrenergic vascular receptors and increases b-adrenergic receptor expression.[96] This notion strengthens the likelihood that hormone levels (*e.g.*, estradiol) may play a protective effect in these findings.[96] In addition to sex-specific differences in sympathetic neurovascular transduction after acute intermittent hypoxia, divergent blood pressure responses between men and women may be the result of differences in the cardiac response to intermittent hypoxia. There is a tendency for the systolic blood pressure response to intermittent hypoxia to be greater in men compared with women,[92] and *post hoc* analysis uncovered a significant correlation between cardiac output and systolic blood pressure in men but not women; it is likely that a portion of the overall effect of intermittent hypoxia on blood pressure in men may be related to greater cardiac output *via* a greater inotropic response, as already described in the literature.[97] Changes in cardiac control of blood pressure following acute intermittent hypoxia are further supported by a fall in cardiac baroreflex sensitivity in men.[92] In addition to sex, age also seems to affect the cardiovascular changes induced by alterations in sleep patterns. Sleep deprivation (quantified as a sleep duration of £5 hours/night) was reported to be associated with a higher risk of hypertension in middle-aged adults but not in children or elderly individuals.[91, 98, 99]

Finally, obesity also plays a significant role in the association between elevated OSA, sleep fragmentation, vascular endothelial inflammation, increased risk for cardiovascular diseases and, at least, glucose levels and lipids metabolism,[69, 100] as already described in "Artery stiffness and endothelial dysfunction" paragraph, to which we refer.

Genetic aspects

There are genetic factors, which may be responsible for the expression of cardiovascular diseases and metabolic syndrome in the context of OSA. OSA is an independent risk factor for diurnal hypertension;[101] however, it is clear from family and epidemiological studies that a complex interplay between heritable factors and environmental risks such as dietary sodium intake, alcohol consumption, and body weight results in the final expression of the disease.[42] The most successful studies have been those identifying Mendelian

forms of hypertension, which comprise the minority of hypertensive patients.[102] Data from a Han Chinese population were examined for the association of polymorphisms in a gene involved in the angiotensin system genes (modulation of hypoxic responses at altitude; effects on hypertension) with OSA.[103] Findings suggested that the angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism was potentially involved in the development of central obesity and thereby may have contributed to the expression of OSA and hypertension.[103] The importance of gene polymorphisms in OSA and hypertension may lie in predicting the reversibility of abnormal vascular responses with treatment.[104] Systemic inflammation plays an important role in all stages of atherosclerosis and there is growing evidence that cell and molecular mechanisms involving inflammatory mediators are up-regulated in patients with OSA.[37] OSA is a complex, polygenic disease with several etiologies interacting to produce a single phenotype. OSA is not just a sporadic, but also a familial condition. The major factor affects ting progress in genetic studies remains a solid definition of OSA phenotype. Further investigations should be undertaken into whether the OSA phenotype remains static throughout life, or whether it changes with time and under different environmental conditions[42] The role of epigenetic phenomena as well as epistasis (gene-gene interactions) is underestimated and highlights influences that are difficult to measure with accuracy.[42]

Phenotypic subtypes

Several studies have attempted to clarify disease heterogeneity and personalize OSA management. The clinical OSA phenotypes can vary in symptoms; sleepy *vs.* insomniac *vs.* asymptomatic patients.[100] Also, the underlying pathophysiological phenotypes of OSA can be anatomical or non-anatomical, like functional impairment of pharyngeal dilator muscles during sleep, low respiratory arousal threshold, and increased propensity for awakenings or respiratory control instability because of the high loop gain mechanism.[100]

A large cross-sectional analysis conducted on 23,000 OSA patients at diagnosis, using the multinational ESADA,[105] applying a latent class analysis (LCA) to identify OSA phenotypes in the European population, representing broad geographical variations, has allowed dividing patients into eight distinct clusters, subdivided into two distinct categories.

In the first category, there are four gender-based phenotypes, corresponding to 54% of the included patients (12,504 patients):[105]

• cluster 2: older obese men (100%), with high AHI (46.2 events/h), daytime sleepiness (ESS 11/24), with the greatest number of comorbidities, like hypertension, cardiac failure, COPD and diabetes;

• cluster 6: overweight younger to middle-aged men, with BMI 28.3 kg/m^2, low AHI (17.5 events/h), ESS score 9/24 and a low frequency of comorbidities compared to other clusters;

• cluster 7: overweight middle-aged women (100%), with BMI 29.6 kg/m^2, with low AHI (12.8 events/h), ESS 10/24 and low comorbidities;

• cluster 8: older obese women (100%), with BMI 36.3 kg/m^2, high AHI (60.8 events/h), daytime sleepiness (ESS 13/24), and a lot of comorbidities.

In the second category there are the remaining clusters (46% of the population involved in the analysis-10635 patients):[105]

• cluster 1: younger sleepy obese (90.6% men), with BMI 36.3 kg/m^2, high AHI (60.8 events/h), daytime sleepiness (ESS 13/24), and fewer comorbidities;

• cluster 3: obese comorbid patients, mainly men (73%), with BMI 31.2 kg/m^2, moderate AHI (22.2 events/h), and very high levels of hyperlipidemia, cardiovascular diseases and chronic diseases, like gastrointestinal diseases, neurological and psychiatric diseases;

• cluster 4: overweight older men (72.9%), with BMI 28.4 kg/m^2, moderate AHI (22.2 events/h), low ESS (8/24), and an intermediate level of comorbidities;

• cluster 5: middle-aged, obese, men (67.5%), with few comorbidities except pulmonary disease, AHI 24.1 events/h, and a low ESS score (9/24).

Clusters vary not only by symptoms, OSA se-

verity and comorbidities but also by polysomnographic features; clusters 1 and 2 had the highest hypoxic burden with most time spent with nocturnal oxygen saturation (SpO_2) <90% (67.6 min for cluster 1 and 65 min for cluster 2), meanwhile clusters 6 and 7 shown little nocturnal hypoxia. Sleep efficiency varied from 77.6% for cluster 2 to 85.9% for clusters 6 and 7.[105]

Zinchuk *et al.*[106] summarized all the existing data from cluster analysis studies in OSA. They identified a subtype 'C' of middle-aged females with insomnia or complaints of poor sleep and medium AHI, a medium prevalence of comorbidities, and low CPAP adherence. This subtype corresponds to cluster 7 and it is characterized by low CPAP acceptance and the highest percentage of MAD prescriptions and adherence.[105] Data proposed by Bailly *et al.*[105] present a high concordance with Zinchuk's data, but ESADA analysis has allowed describing for the first time a cluster (cluster 5) characterized by pulmonary diseases, almost always asthma. According to this clinical evidence, Turino *et al.*,[107] identified six clusters of comorbidities in a very large population (72,217 subjects), of CPAP-treated Spanish patients, using 30 diagnoses in an administrative database. A predominantly female subgroup of patients with asthma was identified, exhibiting high rates of hospitalization. Such findings are consistent with previous studies suggesting a bidirectional OSA-asthma relationship, with a combined adverse impact on health outcomes.[108] In addition, a cluster with cancer and one with cardiovascular disease (*i.e.* hypertension, heart failure, stroke), both oldest and with previously reported associations with hypoxemia in OSA[109] exhibited the highest rates of mortality and healthcare resource use. Some studies have attempted to identify comorbidity patterns among patients with OSA. In one study, Vavougios *et al.*[110] used the AHI and 19 comorbidities, including cardiovascular, metabolic, liver, renal, pulmonary disorders, and malignancies. They found high and low comorbidity burden clusters within both moderate and severe OSA groups. Age, BMI, daytime oxygen saturation, and hypertension predicted inclusion in the high *versus* low comorbidity clusters. Quan *et al.*[111] used cardiovascular and cerebrovascular comorbidity data, in addition to other clinical features, from the Sleep Apnea Cardiovascular Endpoints (SAVE) trial to identify four clusters: coronary artery disease (CAD), CAD and diabetes, cerebrovascular disease, and cerebrovascular disease and diabetes. The risk of incident composite cardiac and stroke outcomes was increased in all clusters, compared with those with cerebrovascular disease alone.[112, 113] The findings highlight the importance of recognizing gender-based phenotypes, of stratifying risks correlated with OSA and associated comorbidities and the impact of these subtypes on treatment prescription.

Conclusions

OSA is an independent risk factor for diurnal hypertension and has been implicated as a risk factor for the first stroke, recurrent stroke, and post-stroke mortality. There are a lot of factors that contribute to developing a hypertensive state in patients suffering from Obstructive Sleep Apnea (OSA), some more decisive, others less.[112, 113] It is important to discover the mechanisms that might be responsible for this association, clustering the patients and aimed at deciding the better treatment in OSA patients affected also by hypertension. In clinical practice, allocating patients to one of these clusters also might help in implementing personalized medicine in OSA. We try to analyze the most important factors that underline the pathogenesis of OSA-related hypertension, through a narrative review according to the most recent literature. The limit of our work is represented by the fact that we have not led one systematic review, which can lead to an incomplete analysis of the multiple sides of the same coin "OSA and hypertension". In the end, the link between OSA hypertension and cardiovascular risk represents an issue under constant evaluation.

More evidence from longitudinal studies is needed on the impact of OSA on cardiovascular risk in females, on the causal link between OSAS and arterial hypertension or metabolic diseases, like diabetes and glucose intolerance, and the effect of different kinds of OSA treatment (CPAP, MAD, surgery, positional therapies) on the reduction of blood pressure levels and cardiovas-

cular, neurological, and metabolic risks. A broad clinical approach could allow clinicians to better control nocturnal and diurnal blood pressure values, while treating the underlining sleep disorders, ameliorating sleep quality, quality of life, and cardiovascular outcomes and re-evaluating the current therapeutic schemes of antihypertensive medications.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Elvia Battaglia and Antonello Nicolini have given substantial contributions to the conception or the design of the manuscript, and Elena Compalati, Teresa Diaz de Teran, Monica Gonzales and Paolo Solidoro contributed to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, author Paolo Banfi revised it critically. All authors read and approved the final version of the manuscript.

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