Sleep deprivation, sleep apnea and cardiovascular diseases

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1. ABSTRACT

Sleep dramatically influences cardiovascular regulation. Changes in sleep duration or quality as seen in sleep disorders may prevent blood pressure to fall during sleep as expected in human physiology. This supports the increased prevalence of hypertension and drug-resistant hypertension in those with sleep loss. Other cardiovascular outcomes i.e. coronary lesions seem to be associated with sleep duration. Systemic inflammation, oxidative stress and endothelial dysfunction seem to be associated with both sleep loss and sleep disorders. The most critical example is Obstructive Sleep Apnea (OSA). Sympathetic activation, oxidative stress and systemic inflammation are the main intermediary mechanisms associated with sleep apnea and intermittent hypoxia. There are now convincing data regarding the associations between hypertension, arrhythmias, stroke, coronary heart disease, increased cardiovascular mortality and OSA. There are also data in OSA and in animal models supporting the link between sleep apnea and atherosclerosis and dysmetabolism. Whether treating sleep apnea enables the reversal of chronic cardiovascular and metabolic consequences of OSA, remains to be studied in adequately designed studies, particularly in comparison with usual treatment strategies.

2. INTRODUCTION

Sleep represents approximately one third of our lives. It is now well established that sleep alters the autonomic nervous system (1, 2) and thus modifies cardiovascular regulation (3). It has also been shown that sleep deprivation may trigger sympathetic activation (4, 5) although this has been discussed (6) and systemic inflammation (7). This may partly support the increased prevalence of hypertension (HT) (8) and drug-resistant HT (9) in those with sleep loss.

Obstructive sleep apnoea (OSA) syndrome corresponds to recurrent episodes of partial or complete pharyngeal collapse occurring during sleep. It is a growing health concern affecting up to 5% of middle-aged men and women in the general population (10). This is a serious health hazard being recognized as an independent risk factor for HT, arrhythmias, stroke, coronary heart disease and heart failure (11-15). People with OSA have a peak in sudden death during night-time and an increased rate of cardiovascular morbidity and mortality (11, 12). OSA is also associated with several cardiovascular sub-clinical or clinical conditions including diastolic HT (16), diastolic ventricular dysfunction (17-20) early atherosclerosis (21) as well as conditions requiring long-term cardiac pacing (22).
Sleep apnea and cardiovascular

Sleep apnea syndrome comprises different types of respiratory events occurring during sleep. According to the severity of upper airway obstruction, the obstructive events may lead to various stimuli e.g. oxygen and carbon dioxide cyclical changes, progressive negative intrathoracic pressure changes occurring during the obstructive event and lastly arousal terminating the obstructive event. The desaturation – reoxygenation sequence, however, is a typical pattern coupled with a majority of respiratory events and thought to be responsible for most of the associated cardiovascular morbidity. This sequence leads to oxidative stress with production of reactive oxygen species (ROS) (23). Numerous studies have shown an increased oxidative stress using various biological markers although co-morbidities such as diabetes, HT, or obesity may account for part of these results (23-27). The increased levels of reactive oxygen species (ROS) contribute to generate adhesion molecules (28, 29), to activate leukocytes (30, 31), and to produce vascular and systemic inflammation (32-34). All these mechanisms are presumably responsible for vascular endothelium damage.

3. SLEEP DEPRIVATION AND CARDIOVASCULAR OUTCOMES

3.1. Scientific evidence

The onset of sleep is associated with marked cardiorespiratory changes. Depending on the stage of sleep, different patterns of hemodynamic and autonomic responses are observed (1). During non-REM sleep there is a fall in heart rate, in systolic blood pressure and in cardiac output of up to 15%. These changes are most marked in slow wave sleep, and thought to occur as a result of changes in autonomic activity. Data on autonomic function during sleep in humans are limited but sympathetic traffic measured by microneurography has been correlated to the blood pressure changes observed in humans during sleep (2). Parasympathetic activity tends to increase during non-REM sleep and is largely responsible for the fall in heart rate and accentuation of any sinus arrhythmia (1). Quite striking changes have been documented during REM sleep. This stage of sleep is characterized by generalized muscle atonia punctuated by muscle twitching, irregular breathing and bursts of rapid eye movement. The hemodynamic changes include erratic rises in pulse rate and blood pressure. Somers et al., in their study of normal human subjects, recorded instability in heart rate and blood pressure which was associated with a level of sympathetic traffic significantly higher than that observed during wakefulness (2). These increases in blood pressure and muscle sympathetic activity tend to coincide with the phasic eye movements of REM sleep and become less pronounced as the duration of REM sleep increased. REM sleep is thus a period of labile sympathetic and hemodynamic activity. Overall, non-REM sleep is associated with significant rest of the cardiovascular system e.g. dipping of blood pressure whilst the increase in sympathetic activity occurring during REM sleep has been discussed as a possible cardiovascular risk factor (1, 2).

We have recently reviewed the relationship between sleep duration and cardiovascular outcomes (Pepin et al, European Society of Hypertension Scientific Newsletter: Update on Hypertension Management 2010; 11:46). Sleep duration has decreased in general population over the last 30 years (35). In the US, the National Sleep Foundation reported between 1998 and 2005 an increase from 12% to 16% of subjects sleeping less than 6 hours on workdays, as a marker of voluntary sleep restriction. Also, prevalence of insomnia complaints was 23% in The Atherosclerosis Risk in Communities Study (ARIC), a prospective observational cohort involving 13,563 middle aged participants (36). Two large community-based cohort studies, the Sleep Heart Health Study (SHHS) (37) and the National Health and Nutrition Examination Survey (NHANES) (8) have evidenced a relationship between self-reported short sleep duration and prevalence and incidence of HT. Actually, Gottlieb et al (37) have demonstrated in the SHHS that both short and long habitual sleep durations are associated with a higher prevalence of HT when compared with subjects sleeping between 7 to 8 hours per night after adjustment for possible confounders such as age, sex, race, obesity, apnea-hypopnea index or lifestyle habits. Short sleep duration was also associated with a higher prevalence of HT in the Korean National Health and Nutrition survey 2001 (38). Subjects participating in theNHANES, who slept less than 5 hours per night, demonstrated a higher incidence of HT after 8 to 10 years follow-up (8). This association persisted, even though attenuated, when adjusted for confounders i.e. body weight.

The relationship between sleep duration and HT is age and gender dependent. Adolescents with shorter sleep duration assessed by actigraphy demonstrated higher prevalence of borderline HT (39). Conversely, the association between sleep restriction and incident HT was not found in subjects between 60 and 86 years-old in the NHANES study (8). HT was not associated with sleep duration assessed by either self-report or actigraphy in a cross-sectional study of 5058 participants, aged 58 to 98 years-old of the Rotterdam Study (40). Finally, considering short sleep duration, HT was both more prevalent and more incident in women only, in the Whitehall II Study (41).

Short sleep duration and insomnia although are classically related but of different entities. Insomnia entails dissatisfaction with the quality of sleep that can be explained or not by a true reduction in sleep duration. Whether insomnia is associated with increased somatic disorders, cardiovascular in particular, is still controversial in the literature. Recently, Vgontzas et al (42) have demonstrated, in a population based study, that only insomnia associated with sleep duration < 5 hours (as evidenced by polysomnography) was associated with a five-fold increased risk of HT after adjustment for any other sleep disorder. Accordingly, in middle-aged subjects of the NHANES, depression was associated with increased incidence of HT, but the strength of this link was weakened by 33% after adjustment for both sleep duration and insomnia, suggesting that these conditions may explain the relationship between depression and HT (43). Lastly, there is evidence that mortality is only slightly increased in insomnia when sleep duration is reduced to less than 4 hours (44).
Sleep apnea and cardiovascular

Figure 1. Relationships between sleep duration and various sleep anomalies and disorders and potential mechanisms of hypertension. The same mechanisms apply to other cardiovascular morbidities. Modified from Pépin et al, European Society of Hypertension Newsletter, 2010.

Winkelman et al. (45) studying 2821 participants in the Wisconsin Sleep Cohort found a non significant trend for the association between Restless Leg Syndrome (RLS) and HT. The relationship seemed to be more robust only in those with severe as opposed to moderate RLS. This was expected since only RLS and Periodic Leg Movements (PLMS) result in significant impairment in sleep duration and quality and thus may lead to HT.

There is also a relationship between sleep duration and coronary heart disease. This has been evidenced in a study evaluating prospectively coronary artery calcification measured by computed tomography in 2000-2001 and 2005-2006 and incidence of new calcification over that time as primary outcome (46). Longer measured sleep was associated with lower calcification incidence independent of examined potential mediators and confounders (46). Amazingly, this is also supported by a study evidencing that after controlling for potential confounders, siesta in apparently healthy individuals was inversely associated with coronary mortality, and the association was particularly evident among working men (47). It should be mentioned however that long duration siestas may reflect comorbidities and thus be associated with poor cardiovascular outcomes (48, 49).

3.2. What are the mechanisms linking sleep duration and cardiovascular outcomes?

Among the pathophysiological mechanisms associated with sleep restriction and sleep disturbances, nocturnal sympathetic activation is likely to be the key mechanism (Figure 1). This nocturnal sympathetic over activity limits the nocturnal BP fall and in turn leads to persistent diurnal increase in sympathetic tone. Hypertensive subjects in whom nocturnal BP fall is blunted (non dipping pattern) are likely to develop a higher degree of target organ damage and significant cardiovascular morbidity-mortality. Systemic inflammation, oxidative stress and endothelial dysfunction are also linked with sleep and may influence the development and progression of HT as well as other cardiovascular anomalies. We recently demonstrated that, in type 1 diabetic subjects, shorter sleep duration was associated with non dipping pattern of BP (50). A similar association with sleep duration occurs in drug-resistant HT. In this condition, OSA is highly prevalent i.e. more than 80%. However, OSA with shorter sleep duration exhibit higher BP values (9). In summary, both alterations in sleep quality and sleep disorders are associated with intermediary mechanisms that favor the development of HT and other cardiovascular impairments.

3.3. Sleep deprivation and metabolic dysregulation

In addition to the cardiovascular changes that have been described during sleep deprivation, there is accumulating evidence that sleep deprivation favors metabolic dysregulation, obesity and type II diabetes both from an experimental (51-54) and a public health (55-58) perspective (59). As regards the relationship between sleep duration and obesity, causality is difficult to establish owing to biological complexity and multiple interactions (60). Moreover, a modest effect size, such as the average decrease in BMI by 0.35 units associated with one extra
hour of sleep in the general population (32), may be unimportant on an individual basis but of major significance in public health (61). From the available relative risk ratios and short sleep prevalence, Young (60) calculated that 5–13% of the total proportion of obesity in children and 3–5% in adults could be attributable to short sleep. The mechanisms that are possibly involved are of interest (59). Sleep deprivation has been found to induce a pro-inflammatory state, with increased release of interleukin (IL)-6 and production of IL-6 and tumour necrosis factor (TNF)-α by circulating monocytes. Nuclear factor (NF)κB activation has been identified as a molecular pathway by which sleep restriction may influence leukocyte inflammatory gene expression and the risk of inflammation-related disease. The pro-inflammatory effects of sleep restriction may, at least partly, be mediated by stress activation, i.e. sympathetic and/or cortisol activation (59). In addition, the group of Knutson and Van Cauter (62) speculated that the adverse impact of sleep deprivation on appetite regulation is likely to be driven by activity in neuronal populations expressing the excitatory peptides orexins, which promote both waking and feeding.

4. PATHOPHYSIOLOGY OF OSA AND ASSOCIATED CARDIOVASCULAR AND METABOLIC CONSEQUENCES

4.1. Overall mechanisms

Upper airway (UA) collapse characterises OSA (63). Pharyngeal collapse occurrence is multifactorial, including reduction in UA volume (64), increase in pharyngeal collapsibility (65-67), cyclical changes in upper airway resistance during sleep (68, 69), changes in pharyngeal muscle activity (70-73) and alteration in upper airway protective reflex (74), possibly resulting from denervation induced by prolonged heavy snoring and associated vibratory lesions of the pharynx (75). Obesity is present in about 50% of OSA patients. The biological factors linking upper airway patency and obesity remain largely unknown although leptin and leptin resistance may play a role.

The desaturation-reoxygenation sequence is a typical pattern coupled with a majority of respiratory events, resulting in intermittent hypoxia. This leads to oxidative stress and production of ROS (23). This has been shown using various biological markers although co-morbidities such as diabetes, HT and obesity per se may contribute (23-26). Increased ROS levels lead to increase expression of adhesion molecules (28), to activate leukocytes (30), and to produce systemic inflammation (76). Taken all together, these mechanisms lead to vascular endothelium damage and dysfunction (77, 78). Both systemic inflammation and endothelial dysfunction are aggravated when sleep-disordered breathing is associated with other co-morbid conditions such as morbid obesity and chronic respiratory failure i.e Obesity Hypoventilation Syndrome (OHS) (79), or COPD i.e. Overlap Syndrome (80). The role of obesity per se remains highly controversial since in some papers, OSA seems to be the only contributing factor to vascular inflammation and dysfunction (81) whilst obesity has been evidenced as a source of oxidative stress and inflammation (82, 83).

4.2. Oxidative stress and inflammation

Oxidative stress generates an inflammatory cascade via NFκB activation (82, 84). However, inflammatory markers have not been found consistently increased in OSA. Obesity and the various associated co-morbidities may account for the conflicting results regarding high-sensitivity CRP in OSA. Although CRP is found elevated in several studies (34, 85-87), other reports failed to demonstrate any linear relationship with the severity of OSA (88). Moreover, a randomized controlled trial (RCT) (89) did not evidence any significant effect of Continuous Positive Airway Pressure (CPAP), the reference treatment of OSA, on CRP when compared with sham-CPAP, a system delivering very low pressure with no impact on sleep-disordered breathing. Obesity however remains a major confounding factor. We evidenced a correlation between both leukotrienes and urinary isoprostanes production with vascular remodelling in OSA (90, 91). However, urinary leukotriene E (4) (U-LTE (4)), a validated marker of pro-inflammatory cysteinyl leukotriene production, was mainly related with obesity, and to a lesser extent with hypoxia severity (83) (figure 2).

This inflammatory cascade increases adhesion molecules expression (31) and further activates monocytes and lymphocytes (29, 92). An impairment of endothelial-dependent vasodilation correlated with the degree of endothelial cell apoptosis has been evidenced. In this study, CPAP therapy significantly reduced circulating apoptotic endothelial cells (93, 94).

Studies on cell culture have revealed that IH is a more potent stimulus for transcriptional activation than continuous hypoxia (CH) at a comparable level of hypoxia intensity and duration. HIF-1 has been shown to be more activated during CH than during IH in some studies (84, 95) but not all (95, 96). Indeed, several experimental factors may be critical for explaining these discrepancies i.e. cellular type, intensity and duration of the hypoxic stimulus. As a consequence, downstream end products such as erythropoietin and VEGF on one hand and TNF-alpha or other pro-inflammatory interleukins on the other hand have been shown to be differently affected (84, 97-99). IH applied to cellular models lead to demonstrate NFkB selective activation (84), ROS production and mitochondrial dysfunction (100).

Animal models have been extensively used in the field. The most frequently used has been the chronic intermittent hypoxia model, which mimics the major consequence of OSA (101). Using animal models, it was evidenced in a canine model that upper airway obstruction led to sustained increase in blood pressure (BP) whilst sleep fragmentation produced only acute but not chronic changes in BP (102-104). Much more research has been done, however, in rodents (105). Starting from the early evidence provided by Fletcher et al. that IH during night time resulted in daytime increase in blood pressure (106), there have been many reports on IH effects, mainly on the
Sleep apnea and cardiovascular system. Vascular reactivity has been shown to be altered in rodents (107-110). Many biological and pathophysiological changes have been linked to IH i.e. alteration in baroreflex activity (111), increase in pulmonary arterial pressure and haematocrit (112), changes in heart structure and function (113), alteration in endothelial dependent vasodilation in cerebral and muscular arteries (114). An increased response to endothelin-1 was also evidenced (109), presumably almost exclusively mediated by ET-A receptors (115). We recently confirmed the role of the ET-A receptors, overexpressed in the heart during IH in Spontaneously Hypertensive Rats (SHR) which were responsible for both increase in blood pressure (BP) and in heart sensitivity to ischemia (116). Sensitivity to ischemia is altered during IH, being reduced when IH is acute, acting as a preconditioning stimulus (117) whilst increased when chronic (118). Endothelin-1 receptors might be an adequate pharmacological target needing to be further tested.

More recently, metabolic and atherosclerotic changes have been shown in mice exposed to IH (119, 120). At the arterial level, there is significant systemic inflammation, as evidenced by T-cell activation, characterized by spleen-derived T-cell proliferation and chemokine mRNA expression. This occurs from day 5 of IH. In mesenteric resistance arteries, Inter-Cellular Adhesion Molecule-1 (ICAM-1) protein expression increases at 14 days of IH and is associated with an increased leukocyte rolling. Aorta from hypoxic mice exhibits at 14-day both upregulation of the pro-inflammatory transcription factor NF-κB and increased intima-media thickness (121). Thus, there is both systemic and localized inflammation of small and large arteries due to intermittent hypoxia. Moreover, we evidenced recovery of lymphocyte proliferation, chemokines expression and NF-κB activation after oxygen fraction normalisation for several days (121). We also demonstrated a reduction in Platelet Endothelial Cell Adhesion Molecules (PECAM-1), a marker of the endothelial cell, with a specific gradient, without loss of endothelial cells, suggesting a role for shear forces applied to both the heart and the aorta (122). In both studies, there was thus vascular remodelling resulting from either hemodynamic or inflammatory changes. From these two studies and others published in the literature (84, 119, 121-125), it can be suggested that there are strong interactions in response to intermittent hypoxia between hemodynamic alterations, systemic inflammation and metabolic changes, modulated by the genetic background.

5. OSA IS A MAJOR CAUSE OF CARDIOVASCULAR AND METABOLIC MORBIDITY

5.1. Overall mechanisms

OSA is clearly identified as being part of the cluster of chronic metabolic disorders linked to obesity and
Sleep apnea and cardiovascular disease

Figure 3. From reference 126. Clustering of metabolic diseases. Obesity is considered to be a central feature that increases the risk for a vast array of diseases, with significant morbidity and mortality.

associated with low grade inflammation (126). The overall conception is that immune response and metabolic response are highly integrated in ensuring metabolic homeostasis and that its dysfunction leads to morbidity chronic conditions particularly obesity, type 2 diabetes and cardiovascular diseases (figure 3) (126).

There is evidence for inflammation at various levels in OSA. Inflammation is present at the systemic level and at the upper airway level (75) but also at the bronchial level as reflected by neutrophilia and increase in IL-8 in the sputum supernatant (127). The exact significance of the bronchial neutrophilia remains unknown. However, it should be noted that in sleep apneic cohorts, the presence of COPD as well as decreased Forc ed Expiratory Volume (FEV1) and Vital Capacity (VC) are the main predicting factors for mortality (80, 128).

Also, it has been shown that OSA is associated with increase in pro-thrombotic factors: in a recent analysis of the Cleveland Family Study, Plasminogen activator inhibitor-1 (PAI-1) and fibrinogen levels increased monotonically with AHI at degrees of Sleep Disordered Breathing (SDB) considered mildly to moderately abnormal, suggesting that even mild SDB levels may increase pro-thrombotic processes (129).

5.2. Clinical data

Cardiovascular morbidity and mortality associated with OSA have been extensively studied in the last decade. There are data supporting association between sleep apnea and HT, stroke, arrhythmias, coronary heart disease as well as overall cardiovascular mortality (130-132). The mechanisms supporting these relationships are essentially those having been described regarding intermittent hypoxia in animal or cellular models (105, 133).

5.2.1. Hypertension

Hypertension can be caused by OSA as now recognized as a risk factor for the development of HT in International Guidelines (134, 135). Although not fully understood, the role of hypoxia in promoting increase in BP seems prominent, as evidenced both in animal models (104) and more recently in a model that we developed in healthy human volunteers (136, 137). BP response to CPAP appears to be dependent on OSA severity (138-140). Whether sleepiness is critical in predicting the CPAP reduction in BP is still discussed (140-142), but probably not the case (143). In any case, the magnitude of BP reduction obtained when treating OSA with CPAP seems relatively small (140, 144) but we recently evidenced a synergistic treatment effect of CPAP and anti-hypertensive drugs (144).

5.2.2. Atherosclerosis

There are several reports establishing that OSA, without significant cardiovascular risk factors otherwise, may lead to early atherosclerosis as reflected by increased Intima Media Thickness and development of plaques at the carotid arteries level (145, 21, 146, 147). In a group of OSA patients without known cardiovascular disease, severity of oxygen desaturation and BP status were the best predictors for carotid wall hypertrophy and plaques occurrence which was also strictly related to the amount of oxygen desaturation (21). As previously mentioned, vascular remodelling correlated with both OSA severity and biological markers of atherosclerosis (90, 91). It has been shown that both HT and the metabolic syndrome have an additive effect on OSA vascular remodelling (148, 149). This is consistent with previous reports on OSA contributing to metabolic dysregulation and systemic inflammation in patients with metabolic syndrome (150). Drager et al also suggested that CPAP treatment may reverse early atherosclerosis in OSA (151).

5.2.3. Arrhythmias and stroke

Increased prevalence of arrhythmias has been reported in OSA since the late seventies. A high prevalence of sleep apnea in patients with AF, i.e. 5% in severe OSA versus 1% in the absence of OSA, has been more recently evidenced in a prospective general population cohort (14), as well as an independent association between the two conditions (14). Also, OSA has been shown as highly prevalent in patients with hypertrophic cardiomyopathy and associated with left atrial and aortic enlargement. In this subgroup, OSA is independently associated with AF, a risk factor for cardiovascular death in these patients (152). Moreover, in the Sleep Heart Health Study, although the absolute arrhythmia rate was low, the relative risk of paroxysmal atrial fibrillation and non-sustained ventricular tachycardia during sleep was markedly increased shortly after a respiratory disturbance. These results support a direct temporal link between SDB events and the development of arrhythmias (153). Lastly, all these findings may explain why OSA patients are at increased risk of nocturnal sudden death (11).

OSA has been found associated with stroke in several studies. This has been found both in clinical cohorts (154) and in the general population (155). Specifically, the Wisconsin Sleep Cohort provided prospective evidence that sleep-disordered breathing precedes stroke and may contribute to the development of stroke (155). The prospective analysis of the Sleep Heart and Health Study also evidenced in men below 70 years a strong adjusted association between ischemic stroke and AHI in mild to moderate sleep apnoea (156). The evidence supporting OSA treatment in stroke remains relatively weak, supporting further randomized controlled trials (157-159).
5.2.4. Heart failure, systolic and diastolic dysfunction

Several conditions including HT, ischemic heart disease and myocardiopathy have been found associated with OSA. Thus it was expected to found OSA as a determinant for heart failure (15). Also, diastolic dysfunction has been evidenced in OSA (18, 20).

5.2.5. Cardiovascular mortality

An excess in mortality has been evidenced for a long time in OSA. It has been evidenced both in clinical populations (129, 160, 161) and in general population cohorts (132, 162). This increased mortality is mainly cardiovascular. It has been suggested however that this only true before 70-year old at least regarding ischemic cardiovascular. It has been suggested however that this only true before 70-year old at least regarding ischemic heart disease. This has been evidenced in clinical cohorts (163) but was recently confirmed by the Sleep Heart and Health Study (132). This is not fully understood e.g. previous deaths of comorbid or sensitive subjects, selection of subjects being resistant to apneas and to intermittent hypoxia, adaptive phenomena occurring during chronic exposure to intermittent hypoxia e.g. preconditioning (101, 164). Actually, a recent study has evidenced that OSA seem to develop more coronary collaterals than controls (165).

5.2.6. Metabolic changes

There have been several studies reporting an independent association of OSA with several components of the Metabolic Syndrome (MS), particularly insulin resistance and abnormal lipid metabolism (166-169). This association may further increase cardiovascular risk since the syndrome is recognised to be a risk factor for cardiovascular morbidity and mortality (170, 171). Recent studies (173, 174) suggest that OSA is independently associated with alterations in glucose metabolism and type 2 diabetes. OSA-related factors that may contribute to metabolic dysregulation include increased sympathetic activity, due to both sleep fragmentation and intermittent hypoxia. However, IH contributes to decrease glucose utilisation of oxidative muscle fibres, independent of autonomic nervous system activation (125). IH seems also to be responsible for increased beta-cell proliferation and cell death, the later being attributable to oxidative stress (175). IH results in increase in serum cholesterol and phospholipids levels, up-regulated triglycerides and phospholipids biosynthesis, and inhibited cholesterol uptake in the liver (119). Lastly, inflammation and fibrosis of the liver appears to result from intermittent or nocturnal hypoxia (176-178).

Even though there is emerging evidence that the relationship between type 2 diabetes and OSA is at least partially independent of adiposity (166, 172), there are several important limitations in the published literature that do not allow to establish causality i.e. cross-sectional studies; use of snoring as a surrogate marker of OSA; various assessments of glucose metabolism and type 2 diabetes; different criteria or cut-offs for fasting blood glucose to define type 2 DM. Also CPAP treatment assessment suggests that in obese individuals insulin sensitivity is likely to be determined primarily by obesity and, to a lesser extent, by OSA (179). This was confirmed in two RCT evaluating metabolic outcomes with therapeutic or sham CPAP in non-diabetic (180) and diabetic patients (181). In both studies, there was no change in glucose, lipids, insulin resistance or the proportion of patients with metabolic syndrome in obese subjects; There is however a recent RCT providing conflicting data at least in case of moderate obesity, with a significant improvement in insulin sensitivity after 1 and 12-week CPAP treatment (182).

6. CONCLUSIONS

There is accumulating evidence that sleep deprivation and sleep disorders may profoundly affect cardiovascular control. Increase in sympathetic activity, oxidative stress, systemic inflammation and endothelial dysfunction may result from sleep loss, sleep fragmentation and SDB. This may explain at least partly an increase prevalence of HT in these conditions. OSA, presumably mainly through IH, is associated with oxidative stress, systemic inflammation, vascular endothelium damage and dysfunction. Both systemic inflammation and endothelial dysfunction are aggravated when OSA is associated with other co-morbid conditions such as morbid obesity. OSA is clearly identified as being part of the cluster of chronic metabolic disorders linked to obesity and associated with low-grade inflammation. There are data supporting associations between OSA and HT, stroke, arrhythmias, coronary heart disease as well as overall cardiovascular mortality. There is also evidence that CPAP, the most effective treatment of OSA, may improve cardiovascular outcomes. Patients with OSA usually need anti-HT drugs for better BP control in addition to CPAP treatment”. Atherosclerosis and metabolic anomalies are present in OSA even in the absence of any significant co-morbidity. Their regression with OSA treatment remains however less well established.

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