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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 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 intra-thoracic 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).

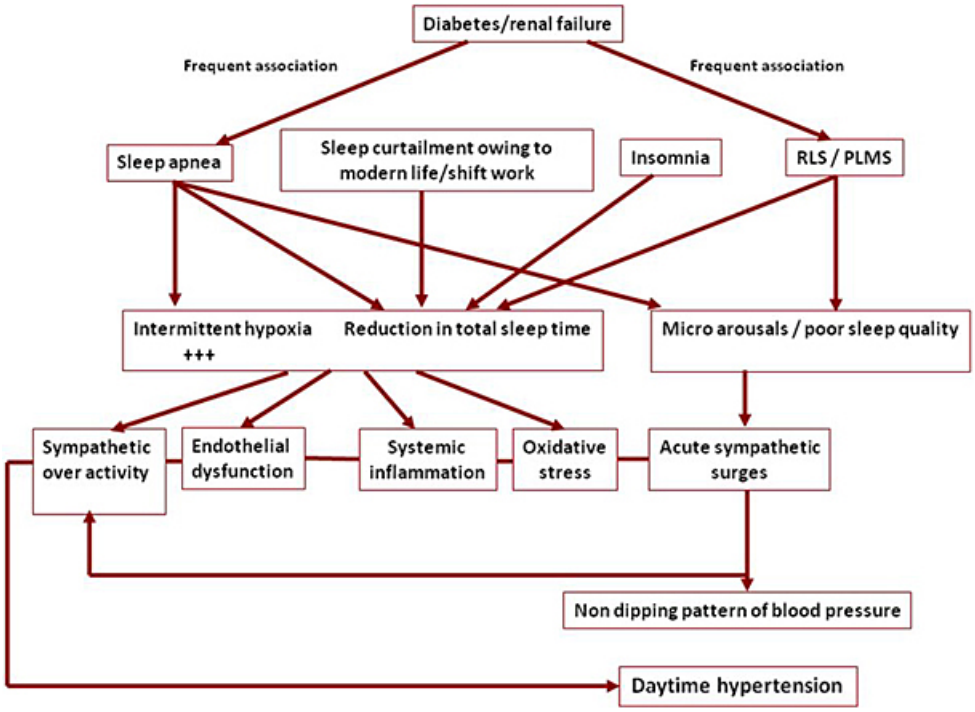

Figure 1. Relationships between sleep duration and various sleep anomalies and disorders and potential mechanisms ofypertension. The same mechanisms apply to other cardiovascular morbidities. Modified from Pépin *et al*, European Society of Hypertension Newsletter, 2010.

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 NFkB 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, down-stream 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

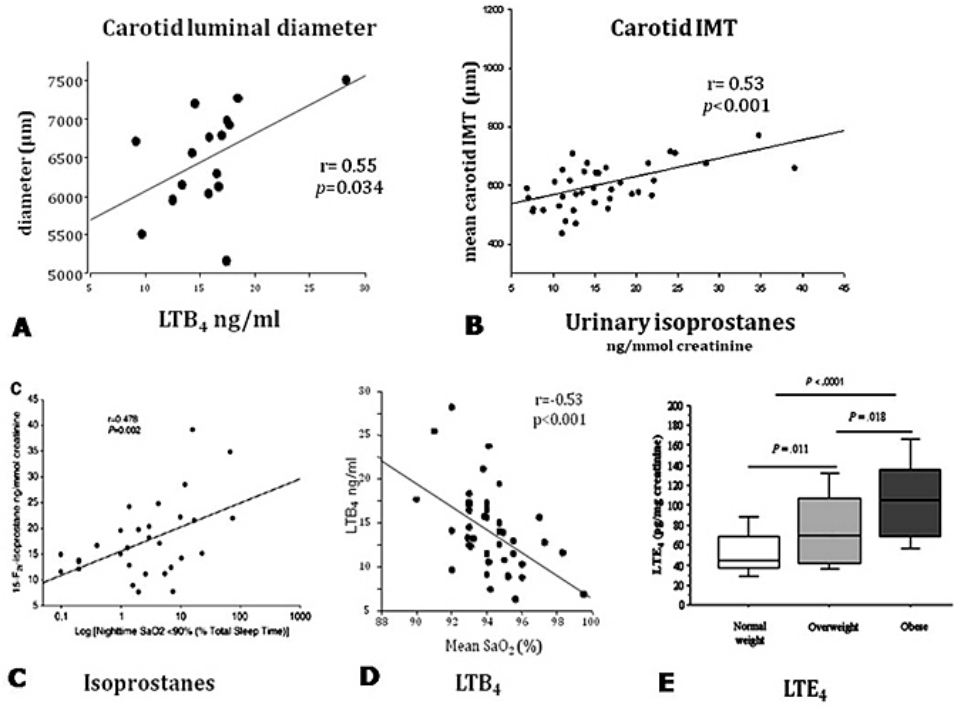

Figure 2. A. Correlation between Leukotrienes (LTB4) and vascular remodelling in OSA i.e. carotid luminal diameter (from reference 90). B Correlation between Urinary Isoprostanes, a marker of oxidative stress, and vascular remodelling in OSA i.e. Intima Media Thickness (IMT) (reproduced with permission from reference 91). C. Correlation between Isoprostanes and severity of OSA i.e. cumulative time spent below 90% SaO2 (from reference 91). D. Inverse correlation between Leukotrienes (LTB4) and mean SaO2 (issued from the data of reference 90). E. Influence of body weight on Leukotrienes (LTE4). (reproduced with permission from reference 83).

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 activation 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

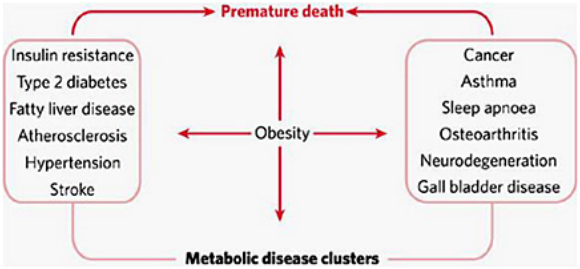

Figure 3. From reference 126. Clustering of metabolic diseases. Obesity is considered to be a central feature that increases the risk for a vast array of diseases, with significant morbidity and mortality.

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 morbid 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 Forced 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 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 reports have indicated that the majority of patients with type 2 diabetes also have OSA (166, 172, 173). Rapidly accumulating data from both epidemiologic and clinical studies (173, 174) suggest that OSA is independently associated with alterations in glucose metabolism and places patients at an increased risk of the development of 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.

7. REFERENCES

1. Smith, R. P., D. Veale, J. L. Pepin & P. A. Levy: Obstructive sleep apnoea and the autonomic nervous system. *Sleep Med Rev* 2, 69-92 (1998)

2. Somers, V. K., M. E. Dyken, A. L. Mark & F. M. Abboud: Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* 328, 303-7 (1993)

3. Murali, N. S., A. Svatikova & V. K. Somers: Cardiovascular physiology and sleep. *Front Biosci* 8, s636-52 (2003)

4. Irwin, M., J. Thompson, C. Miller, J. C. Gillin & M. Ziegler: Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. *J Clin Endocrinol Meta*b 84, 1979-85 (1999)

5. Irwin, M. R. & M. Ziegler: Sleep deprivation potentiates activation of cardiovascular and catecholamine responses in abstinent alcoholics. *Hypertension* 45, 252-7 (2005)

6. Kato, M., B. G. Phillips, G. Sigurdsson, K. Narkiewicz, C. A. Pesek & V. K. Somers: Effects of sleep deprivation on neural circulatory control. *Hypertension* 35, 1173-5 (2000)

7. Irwin, M. R., M. Wang, C. O. Campomayor, A. Collado-Hidalgo & S. Cole: Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med* 166, 1756-62 (2006)

8. Gangwisch, J. E., S. B. Heymsfield, B. Boden-Albala, R. M. Buijs, F. Kreier, T. G. Pickering, A. G. Rundle, G. K. Zammit & D. Malaspina: Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 47, 833-9 (2006)

9. Friedman, O., T. D. Bradley, P. Ruttanaumpawan & A. G. Logan: Independent association of drug-resistant hypertension to reduced sleep duration and efficiency. *Am J Hypertens* 23, 174-9 (2010)

10. Young, T., P. E. Peppard & D. J. Gottlieb: Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 165, 1217-39 (2002)

11. Gami, A. S., D. E. Howard, E. J. Olson & V. K. Somers: Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med* 352, 1206-14 (2005)

12. Marin, J. M., S. J. Carrizo, E. Vicente & A. G. Agusti: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 365, 1046-53 (2005)

13. Arzt, M., T. Young, L. Finn, J. B. Skatrud & T. D. Bradley: Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 172, 1447-51 (2005)

14. Mehra, R., E. J. Benjamin, E. Shahar, D. J. Gottlieb, R. Nawabit, H. L. Kirchner, J. Sahadevan & S. Redline: Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med* 173, 910-6 (2006)

15. Gottlieb, D. J., G. Yenokyan, A. B. Newman, G. T. O'Connor, N. M. Punjabi, S. F. Quan, S. Redline, H. E. Resnick, E. K. Tong, M. Diener-West & E. Shahar: Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 122, 352-60 (2010)

16. Baguet, J. P., L. Hammer, P. Levy, H. Pierre, E. Rossini, S. Mouret, O. Ormezzano, J. M. Mallion & J. L. Pepin: Night-time and diastolic hypertension are common and underestimated conditions in newly diagnosed apnoeic patients. *J Hypertens* 23, 521-7 (2005)

17. Alchanatis, M., G. Tourkohoriti, E. N. Kosmas, G. Panoutsopoulos, S. Kakouros, K. Papadima, M. Gaga & J. B. Jordanoglou: Evidence for left ventricular dysfunction in patients with obstructive sleep apnoea syndrome. *Eur Respir J* 20, 1239-45 (2002)

18. Arias, M. A., F. Garcia-Rio, A. Alonso-Fernandez, O. Mediano, I. Martinez & J. Villamor: Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. *Circulation* 112, 375-83 (2005)

19. Chami, H. A., R. B. Devereux, J. S. Gottdiener, R. Mehra, M. J. Roman, E. J. Benjamin & D. J. Gottlieb: Left ventricular morphology and systolic function in sleep-disordered breathing: the Sleep Heart Health Study. *Circulation* 117, 2599-607 (2008)

20. Baguet, J. P., G. Barone-Rochette, P. Levy, E. Vautrin, H. Pierre, O. Ormezzano & J. L. Pepin: Left ventricular diastolic dysfunction is linked to severity of obstructive sleep apnoea. *Eur Respir J* 36, 1323-9 (2010)

21. Baguet, J. P., L. Hammer, P. Levy, H. Pierre, S. Launois, J. M. Mallion & J. L. Pepin: The severity of oxygen desaturation is predictive of carotid wall thickening and plaque occurrence. *Chest* 128, 3407-12 (2005)

22. Garrigue, S., J. L. Pepin, P. Defaye, F. Murgatroyd, Y. Poezevara, J. Clementy & P. Levy: High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. *Circulation* 115, 1703-9 (2007)

23. Lavie, L.: Obstructive sleep apnoea syndrome--an oxidative stress disorder. *Sleep Med Rev* 7, 35-51 (2003)

24. Lavie, L., A. Vishnevsky & P. Lavie: Evidence for lipid peroxidation in obstructive sleep apnea. *Sleep* 27, 123-8 (2004)

25. Barcelo, A., C. Miralles, F. Barbe, M. Vila, S. Pons & A. G. Agusti: Abnormal lipid peroxidation in patients with sleep apnoea. *Eur Respir J* 16, 644-7 (2000)

26. Svatikova, A., R. Wolk, L. O. Lerman, L. A. Juncos, E. L. Greene, J. P. McConnell & V. K. Somers: Oxidative stress in obstructive sleep apnoea. *Eur Heart J* 26, 2435-9 (2005)

27. Barcelo, A., F. Barbe, M. de la Pena, M. Vila, G. Perez, J. Pierola, J. Duran & A. G. Agusti: Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment. *Eur Respir J* 27, 756-60 (2006)

28. Ohga, E., T. Tomita, H. Wada, H. Yamamoto, T. Nagase & Y. Ouchi: Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. *J Appl Physiol* 94, 179-84 (2003)

29. Lavie, L., L. Dyugovskaya & P. Lavie: Sleep-apnea-related intermittent hypoxia and atherogenesis: adhesion molecules and monocytes/endothelial cells interactions. *Atherosclerosis* 183, 183-4 (2005)

30. Schulz, R., S. Mahmoudi, K. Hattar, U. Sibelius, H. Olschewski, K. Mayer, W. Seeger & F. Grimminger: Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med* 162, 566-70 (2000)

31. Dyugovskaya, L., P. Lavie & L. Lavie: Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* 165, 934-9 (2002)

32. Carpagnano, G. E., S. A. Kharitonov, O. Resta, M. P. Foschino-Barbaro, E. Gramiccioni & P. J. Barnes: Increased 8-isoprostane and interleukin-6 in breath condensate of obstructive sleep apnea patients. *Chest* 122, 1162-7. (2002)

33. Minoguchi, K., T. Yokoe, A. Tanaka, S. Ohta, T. Hirano, G. Yoshino, C. P. O'Donnell & M. Adachi: Association between lipid peroxidation and inflammation in obstructive sleep apnoea. *Eur Respir J* 28, 378-85 (2006)

34. Shamsuzzaman, A. S., M. Winnicki, P. Lanfranchi, R. Wolk, T. Kara, V. Accurso & V. K. Somers: Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 105, 2462-4 (2002)

35. Kronholm, E., T. Partonen, T. Laatikainen, M. Peltonen, M. Harma, C. Hublin, J. Kaprio, A. R. Aro, M. Partinen, M. Fogelholm, R. Valve, J. Vahtera, T. Oksanen, M. Kivimaki, M. Koskenvuo & H. Sutela: Trends in self-reported sleep duration and insomnia-related symptoms in Finland from 1972 to 2005: a comparative review and re-analysis of Finnish population samples. *J Sleep Res* 17, 54-62 (2008)

36. Phillips, B. & D. M. Mannino: Does insomnia kill? *Sleep* 28, 965-71 (2005)

37. Gottlieb, D. J., S. Redline, F. J. Nieto, C. M. Baldwin, A. B. Newman, H. E. Resnick & N. M. Punjabi: Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 29, 1009-14 (2006)

38. Choi, K. M., J. S. Lee, H. S. Park, S. H. Baik, D. S. Choi & S. M. Kim: Relationship between sleep duration and the metabolic syndrome: Korean National Health and Nutrition Survey 2001. *Int J Obes (Lond)* 32, 1091-7 (2008)

39. Javaheri, S., A. Storfer-Isser, C. L. Rosen & S. Redline: Sleep quality and elevated blood pressure in adolescents. *Circulation* 118, 1034-40 (2008)

40. van den Berg, J. F., J. H. Tulen, A. K. Neven, A. Hofman, H. M. Miedema, J. C. Witteman & H. Tiemeier: Sleep duration and hypertension are not associated in the elderly. *Hypertension* 50, 585-9 (2007)

41. Cappuccio, F. P., S. Stranges, N. B. Kandala, M. A. Miller, F. M. Taggart, M. Kumari, J. E. Ferrie, M. J. Shipley, E. J. Brunner & M. G. Marmot: Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. *Hypertension* 50, 693-700 (2007)

42. Vgontzas, A. N., D. Liao, E. O. Bixler, G. P. Chrousos & A. Vela-Bueno: Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 32, 491-7 (2009)

43. Gangwisch, J. E., D. Malaspina, K. Posner, L. A. Babiss, S. B. Heymsfield, J. B. Turner, G. K. Zammit & T. G. Pickering: Insomnia and sleep duration as mediators of the relationship between depression and hypertension incidence. *Am J Hypertens* 23, 62-9 (2010)

44. Kripke, D. F., L. Garfinkel, D. L. Wingard, M. R. Klauber & M. R. Marler: Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 59, 131-6 (2002)

45. Winkelman, J. W., L. Finn & T. Young: Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med* 7, 545-52 (2006)

46. King, C. R., K. L. Knutson, P. J. Rathouz, S. Sidney, K. Liu & D. S. Lauderdale: Short sleep duration and incident coronary artery calcification. *Jama* 300, 2859-66 (2008)

47. Naska, A., E. Oikonomou, A. Trichopoulou, T. Psaltopoulou & D. Trichopoulos: Siesta in healthy adults and coronary mortality in the general population. *Arch Intern Med* 167, 296-301 (2007)

48. Stang, A., N. Dragano, C. Poole, S. Moebus, S. Mohlenkamp, A. Schmermund, J. Siegrist, R. Erbel & K. H. Jockel: Daily siesta, cardiovascular risk factors, and measures of subclinical atherosclerosis: results of the Heinz Nixdorf Recall Study. *Sleep* 30, 1111-9 (2007)

49. Campos, H. & X. Siles: Siesta and the risk of coronary heart disease: results from a population-based, case-control study in Costa Rica. *Int J Epidemiol* 29, 429-37 (2000)

50. Borel, A. L., P. Y. Benhamou, J. P. Baguet, I. Debaty, P. Levy, J. L. Pepin & J. M. Mallion: Short sleep duration is associated with a blood pressure nondipping pattern in type 1 diabetes: the DIAPASOM study. *Diabetes Care* 32, 1713-5 (2009)

51. Spiegel, K., E. Tasali, P. Penev & E. Van Cauter: Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 141, 846-50 (2004)

52. Spiegel, K., K. Knutson, R. Leproult, E. Tasali & E. Van Cauter: Sleep loss: a novel risk factor for insulin

resistance and Type 2 diabetes. *J Appl Physiol* 99, 2008-19 (2005)

53. Tasali, E., R. Leproult, D. A. Ehrmann & E. Van Cauter: Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A* 105, 1044-9 (2008)

54. Spiegel, K., E. Tasali, R. Leproult & E. Van Cauter: Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol* 5, 253-61 (2009)

55. Taheri, S., L. Lin, D. Austin, T. Young & E. Mignot: Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 1, e62 (2004)

56. Marshall, N. S., N. Glozier & R. R. Grunstein: Is sleep duration related to obesity? A critical review of the epidemiological evidence. *Sleep Med Rev* 12, 289-98 (2008)

57. Gottlieb, D. J., N. M. Punjabi, A. B. Newman, H. E. Resnick, S. Redline, C. M. Baldwin & F. J. Nieto: Association of Sleep Time With Diabetes Mellitus and Impaired Glucose Tolerance. *Arch Intern Med* 165, 863-867 (2005)

58. Chaput, J. P., J. P. Despres, C. Bouchard & A. Tremblay: Association of sleep duration with type 2 diabetes and impaired glucose tolerance. *Diabetologia* 50, 2298-304 (2007)

59. Levy, P., M. R. Bonsignore & J. Eckel: Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J* 34, 243-60 (2009)

60. Young, T.: Increasing sleep duration for a healthier (and less obese?) population tomorrow. *Sleep* 31, 593-4 (2008)

61. Cappuccio, F. P., F. M. Taggart, N. B. Kandala, A. Currie, E. Peile, S. Stranges & M. A. Miller: Meta-analysis of short sleep duration and obesity in children and adults. *Sleep* 31, 619-26 (2008)

62. Knutson, K. L. & E. Van Cauter: Associations between sleep loss and increased risk of obesity and diabetes. *Ann N Y Acad Sci* 1129, 287-304 (2008)

63. Pepin, J. L., G. Ferretti, D. Veale, P. Romand, M. Coulomb, C. Brambilla & P. A. Levy: Somnofluoroscopy, computed tomography, and cephalometry in the assessment of the airway in obstructive sleep apnoea. *Thorax* 47, 150-6 (1992)

64. Mayer, P., J. L. Pepin, G. Bettega, D. Veale, G. Ferretti, C. Deschaux & P. Levy: Relationship between body mass index, age and upper airway measurements in snorers and sleep apnoea patients. *Eur Respir J* 9, 1801-9 (1996)

65. Schwartz, A. R., N. Schubert, W. Rothman, F. Godley, B. Marsh, D. Eisele, J. Nadeau, L. Permutt, I. Gleadhill & P. L. Smith: Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 145, 527-32 (1992)

66. Sforza, E., C. Petiau, T. Weiss, A. Thibault & J. Krieger: Pharyngeal critical pressure in patients with obstructive sleep apnea syndrome. Clinical implications. *Am J Respir Crit Care Med* 159, 149-57 (1999)

67. Gold, A. R., C. L. Marcus, F. Dipalo & M. S. Gold: Upper airway collapsibility during sleep in upper airway resistance syndrome. *Chest* 121, 1531-40 (2002)

68. Morrell, M. J., Y. Arabi, B. Zahn & M. S. Badr: Progressive retropalatal narrowing preceding obstructive apnea. *Am J Respir Crit Care Med* 158, 1974-81 (1998)

69. Tamisier, R., J. L. Pepin, B. Wuyam, C. Deschaux & P. Levy: Expiratory changes in pressure: flow ratio during sleep in patients with sleep-disordered breathing. *Sleep* 27, 240-8 (2004)

70. Horner, R. L.: Motor control of the pharyngeal musculature and implications for the pathogenesis of obstructive sleep apnea. *Sleep* 19, 827-53 (1996)

71. Mezzanotte, W. S., D. J. Tangel & D. P. White: Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism*). J Clin Invest* 89, 1571-9 (1992)

72. Berry, R. B., D. P. White, J. Roper, G. Pillar, R. B. Fogel, M. Stanchina & A. Malhotra: Awake negative pressure reflex response of the genioglossus in OSA patients and normal subjects. *J Appl Physiol* 94, 1875-82 (2003)

73. Carrera, M., F. Barbe, J. Sauleda, M. Tomas, C. Gomez & A. G. Agusti: Patients with obstructive sleep apnea exhibit genioglossus dysfunction that is normalized after treatment with continuous positive airway pressure. *Am J Respir Crit Care Med* 159, 1960-6 (1999)

74. Dematteis, M., P. Levy & J. L. Pepin: A simple procedure for measuring pharyngeal sensitivity: a contribution to the diagnosis of sleep apnoea. *Thorax* 60, 418-26 (2005)

75. Boyd, J. H., B. J. Petrof, Q. Hamid, R. Fraser & R. J. Kimoff: Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Me*d 170, 541-6 (2004)

76. Ciftci, T. U., O. Kokturk, N. Bukan & A. Bilgihan: The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. *Cytokine* 28, 87-91 (2004)

77. Nieto, F. J., D. M. Herrington, S. Redline, E. J. Benjamin & J. A. Robbins: Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. *Am J Respir Crit Care Med* 169, 354-60 (2004)

78. Itzhaki, S., L. Lavie, G. Pillar, G. Tal & P. Lavie: Endothelial dysfunction in obstructive sleep apnea

measured by peripheral arterial tone response in the finger to reactive hyperemia. *Sleep* 28, 594-600 (2005)

79. Borel, J. C., P. Roux-Lombard, R. Tamisier, C. Arnaud, D. Monneret, N. Arnol, J. P. Baguet, P. Levy & J. L. Pepin: Endothelial dysfunction and specific inflammation in obesity hypoventilation syndrome. *PLoS One* 4, e6733 (2009)

80. Marin, J. M., J. B. Soriano, S. J. Carrizo, A. Boldova & B. R. Celli: Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 182, 325-31 (2010)

81. Jelic, S., D. J. Lederer, T. Adams, M. Padeletti, P. C. Colombo, P. H. Factor & T. H. Le Jemtel: Vascular inflammation in obesity and sleep apnea. *Circulation* 121, 1014-21 (2010)

82. Pierce, G. L., L. A. Lesniewski, B. R. Lawson, S. D. Beske & D. R. Seals: Nuclear factor-{kappa}B activation contributes to vascular endothelial dysfunction via oxidative stress in overweight/obese middle-aged and older humans. *Circulation* 119, 1284-92 (2009)

83. Stanke-Labesque, F., M. Back, B. Lefebvre, R. Tamisier, J. P. Baguet, N. Arnol, P. Levy & J. L. Pepin: Increased urinary leukotriene E4 excretion in obstructive sleep apnea: effects of obesity and hypoxia. *J Allergy Clin Immunol* 124, 364-70 (2009)

84. Ryan, S., C. T. Taylor & W. T. McNicholas: Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 112, 2660-7 (2005)

85. Yokoe, T., K. Minoguchi, H. Matsuo, N. Oda, H. Minoguchi, G. Yoshino, T. Hirano & M. Adachi: Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 107, 1129-34 (2003)

86. Larkin, E. K., C. L. Rosen, H. L. Kirchner, A. Storfer-Isser, J. L. Emancipator, N. L. Johnson, A. M. Zambito, R. P. Tracy, N. S. Jenny & S. Redline: Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. *Circulation* 111, 1978-84 (2005)

87. Lui, M. M.-s., J. C.-m. Lam, H. K.-F. Mak, A. Xu, C. Ooi, D. C.-l. Lam, J. C.-w. Mak, P. L. Khong & M. S.-M. Ip: C-Reactive Protein Is Associated With Obstructive Sleep Apnea Independent of Visceral Obesity. *Chest* 135, 950-956 (2009)

88. Guilleminault, C., C. Kirisoglu & M. M. Ohayon: C-reactive protein and sleep-disordered breathing. *Sleep* 27, 1507-11 (2004)

89. Kohler, M., L. Ayers, J. C. T. Pepperell, K. L. Packwood, B. Ferry, N. Crosthwaite, S. Craig, M. M. Siccoli, R. J. O. Davies & J. R. Stradling: Effects of continuous positive airway pressure on systemic inflammation in patients with moderate to severe obstructive sleep apnoea: a randomised controlled trial. *Thorax* 64, 67-73 (2009)

90. Lefebvre, B., J. L. Pepin, J. P. Baguet, R. Tamisier, M. Roustit, K. Riedweg, G. Bessard, P. Levy & F. Stanke-Labesque: Leukotriene B4: early mediator of atherosclerosis in obstructive sleep apnoea? *Eur Respir J* 32, 113-120 (2008)

91. Monneret, D., J.-L. Pepin, D. Godin-Ribuot, V. Ducros, J.-P. Baguet, P. Levy & P. Faure: Association of urinary 15-F2t-isoprostane level with oxygen desaturation and carotid intima-media thickness in nonobese sleep apnea patients. *Free Radical Biology and Medicine* 48, 619-625 (2010)

92. Dyugovskaya, L., P. Lavie & L. Lavie: Phenotypic and functional characterization of blood gammadelta T cells in sleep apnea. *Am J Respir Crit Care Med* 168, 242-9 (2003)

93. El Solh, A. A., M. E. Akinnusi, F. H. Baddoura & C. R. Mankowski: Endothelial Cell Apoptosis in Obstructive Sleep Apnea: A Link to Endothelial Dysfunction. *Am. J. Respir. Crit. Care Med* 175, 1186-1191 (2007)

94. Priou, P., F. Gagnadoux, A. Tesse, M. L. Mastronardi, A. Agouni, N. Meslier, J. L. Racineux, M. C. Martinez, W. Trzepizur & R. Andriantsitohaina: Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. *Am J Pathol* 177, 974-83 (2010)

95. Nanduri, J., G. Yuan, G. K. Kumar, G. L. Semenza & N. R. Prabhakar: Transcriptional responses to intermittent hypoxia. *Respir Physiol Neurobiol* 164, 277-81 (2008)

96. Prabhakar, N. R.: Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. *J Appl Physiol* 90, 1986-94 (2001)

97. Vgontzas, A. N., D. A. Papanicolaou, E. O. Bixler, A. Kales, K. Tyson & G. P. Chrousos: Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 82, 1313-6 (1997)

98. Teramoto, S., H. Yamamoto & Y. Ouchi: Increased C-reactive protein and increased plasma interleukin-6 may synergistically affect the progression of coronary atherosclerosis in obstructive sleep apnea syndrome. *Circulation* 107, E40-0 (2003)

99. Vgontzas, A. N., E. O. Bixler & G. P. Chrousos: Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Med Rev* 9, 211-24 (2005)

100. Peng, Y., G. Yuan, J. L. Overholt, G. K. Kumar & N. R. Prabhakar: Systemic and cellular responses to intermittent hypoxia: evidence for oxidative stress and mitochondrial dysfunction. *Adv Exp Med Bio*, 536, 559-64 (2003)

101. Dematteis, M., D. Godin-Ribuot, C. Arnaud, C. Ribuot, F. Stanke-Labesque, J. L. Pepin & P. Levy: Cardiovascular consequences of sleep-disordered breathing: contribution of animal models to understanding the human disease. *Ilar J* 50, 262-81 (2009)

102. Kimoff, R. J., H. Makino, R. L. Horner, L. F. Kozar, F. Lue, A. S. Slutsky & E. A. Phillipson: Canine model of obstructive sleep apnea: model description and preliminary application. *J Appl Physiol* 76, 1810-7 (1994)

103. Brooks, D., R. L. Horner, L. F. Kozar, C. L. Render-Teixeira & E. A. Phillipson: Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 99, 106-9. (1997)

104. Brooks, D., R. L. Horner, R. J. Kimoff, L. F. Kozar, C. L. Render-Teixeira & E. A. Phillipson: Effect of obstructive sleep apnea versus sleep fragmentation on responses to airway occlusion. *Am J Respir Crit Care Med* 155, 1609-17. (1997)

105. Neubauer, J. A.: Invited review: Physiological and pathophysiological responses to intermittent hypoxia. *J Appl Physiol* 90, 1593-9. (2001)

106. Fletcher, E. C., J. Lesske, W. Qian, C. C. Miller, 3rd & T. Unger: Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension* 19, 555-61. (1992)

107. Fletcher, E. C., G. Bao & R. Li: Renin activity and blood pressure in response to chronic episodic hypoxia. *Hypertension* 34, 309-14. (1999)

108. Julien, C., S. Bayat & P. Levy: Vascular reactivity to norepinephrine and acetylcholine after chronic intermittent hypoxia in mice. *Respir Physiol Neurobiol* 139, 21-32 (2003)

109. Lefebvre, B., D. Godin-Ribuot, M. Joyeux-Faure, F. Caron, G. Bessard, P. Levy & F. Stanke-Labesque: Functional assessment of vascular reactivity after chronic intermittent hypoxia in the rat. *Respir Physiol Neurobiol* 150, 278-86 (2006)

110. Greenberg, H. E., A. Sica, D. Batson & S. M. Scharf: Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. J Appl Phys*iol* 86, 298-305 (1999)

111. Brooks, D., R. L. Horner, J. S. Floras, L. F. Kozar, C. L. Render-Teixeira & E. A. Phillipson: Baroreflex control of heart rate in a canine model of obstructive sleep apnea. *Am J Respir Crit Care Med* 159, 1293-7 (1999)

112. McGuire, M. & A. Bradford: Chronic intermittent hypercapnic hypoxia increases pulmonary arterial pressure and haematocrit in rats. *Eur Respir J* 18, 279-85 (2001)

113. Kraiczi, H., J. Magga, X. Y. Sun, H. Ruskoaho, X. Zhao & J. Hedner: Hypoxic pressor response, cardiac size, and natriuretic peptides are modified by long-term intermittent hypoxia. *J Appl Physiol* 87, 2025-31 (1999)

114. Phillips, S. A., E. B. Olson, B. J. Morgan & J. H. Lombard: Chronic intermittent hypoxia impairs endothelium-dependent dilation in rat cerebral and skeletal muscle resistance arteries. *Am J Physiol Heart Circ Physiol* 286, H388-93 (2004)

115. Allahdadi, K. J., B. R. Walker & N. L. Kanagy: Augmented endothelin vasoconstriction in intermittent hypoxia-induced hypertension. *Hypertension* 45, 705-9 (2005)

116. Belaidi, E., M. Joyeux-Faure, C. Ribuot, S. H. Launois, P. Levy & D. Godin-Ribuot: Major role for hypoxia inducible factor-1 and the endothelin system in promoting myocardial infarction and hypertension in an animal model of obstructive sleep apnea. *J Am Coll Cardiol* 53, 1309-17 (2009)

117. Beguin, P. C., M. Joyeux-Faure, D. Godin-Ribuot, P. Levy & C. Ribuot: Acute intermittent hypoxia improves rat myocardium tolerance to ischemia. *J Appl Physiol* 99, 1064-9 (2005)

118. Joyeux-Faure, M., F. Stanke-Labesque, B. Lefebvre, P. Beguin, D. Godin-Ribuot, C. Ribuot, S. H. Launois, G. Bessard & P. Levy: Chronic intermittent hypoxia increases infarction in the isolated rat heart. *J Appl Physiol* 98, 1691-1696 (2005)

119. Li, J., L. N. Thorne, N. M. Punjabi, C. K. Sun, A. R. Schwartz, P. L. Smith, R. L. Marino, A. Rodriguez, W. C. Hubbard, C. P. O'Donnell & V. Y. Polotsky: Intermittent hypoxia induces hyperlipidemia in lean mice. *Circ Res* 97, 698-706 (2005)

120. Jun, J., C. Reinke, D. Bedja, D. Berkowitz, S. Bevans-Fonti, J. Li, L. A. Barouch, K. Gabrielson & V. Y. Polotsky: Effect of intermittent hypoxia on atherosclerosis in apolipoprotein E-deficient mice. *Atherosclerosis* 209, 381-6 (2010)

121. Arnaud, C., P. C. Beguin, S. Lantuejoul, J. L. Pepin, C. Guillermet, G. Pelli, F. Burger, V. Buatois, C. Ribuot, J. P. Baguet, F. Mach, P. Levy & M. Dematteis: The Inflammatory Pre-Atherosclerotic Remodeling Induced by Intermittent Hypoxia is Attenuated by RANTES/CCL5 Inhibition. *Am J Respir Crit Care Med* (2011) in press

122. Dematteis, M., C. Julien, C. Guillermet, N. Sturm, S. Lantuejoul, M. Mallaret, P. Levy & E. Gozal: Intermittent hypoxia induces early functional cardiovascular remodeling in mice. *Am J Respir Crit Care Med* 177, 227-35 (2008)

123. Savransky, V., A. Nanayakkara, J. Li, S. Bevans, P. L. Smith, A. Rodriguez & V. Y. Polotsky: Chronic intermittent hypoxia induces atherosclerosis. *Am J Respir Crit Care Med* 175, 1290-7 (2007)

124. Li, J., V. Savransky, A. Nanayakkara, P. L. Smith, C. P. O'Donnell & V. Y. Polotsky: Hyperlipidemia and lipid

peroxidation are dependent on the severity of chronic intermittent hypoxia. *J Appl Physiol* 102, 557-63 (2007)

125. Iiyori, N., L. C. Alonso, J. Li, M. H. Sanders, A. Garcia-Ocana, R. M. O'Doherty, V. Y. Polotsky & C. P. O'Donnell: Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. *Am J Respir Crit Care Med* 175, 851-7 (2007)

126. Hotamisligil, G. S.: Inflammation and metabolic disorders. *Nature* 444, 860-7 (2006)

127. Devouassoux, G., P. Levy, E. Rossini, I. Pin, M. Fior-Gozlan, M. Henry, D. Seigneurin & J. L. Pepin: Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness. *J Allergy Clin Immunol* 119, 597-603 (2007)

128. Veale, D., E. Chailleux, A. Hoorelbeke-Ramon, O. Reybet-Degas, M. P. Humeau-Chapuis, F. Alluin-Aigouy, B. Fleury, O. Jonquet & P. Michard: Mortality of sleep apnoea patients treated by nasal continuous positive airway pressure registered in the ANTADIR observatory. Association Nationale pour le Traitement A Domicile de l'Insuffisance Respiratoire chronique. *Eur Respir J* 15, 326-31 (2000)

129. Mehra, R., F. Xu, D. C. Babineau, R. P. Tracy, N. S. Jenny, S. R. Patel & S. Redline: Sleep-disordered breathing and prothrombotic biomarkers: cross-sectional results of the Cleveland Family Study. *Am J Respir Crit Care Med* 182, 826-33 (2010)

130. Marin, J. M., S. J. Carrizo, E. Vicente & A. G. Agusti: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *The Lancet* 365, 1046-1053 (2005)

131. McNicholas, W. T., M. R. Bonsignore & M. C. COST action B26: Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 29, 156-78 (2007)

132. Punjabi, N. M., B. S. Caffo, J. L. Goodwin, D. J. Gottlieb, A. B. Newman, G. T. O'Connor, D. M. Rapoport, S. Redline, H. E. Resnick, J. A. Robbins, E. Shahar, M. L. Unruh & J. M. Samet: Sleep-Disordered Breathing and Mortality: A Prospective Cohort Study. *PLoS Med* 6, e1000132 (2009)

133. Levy, P., J. L. Pepin, C. Arnaud, R. Tamisier, J. C. Borel, M. Dematteis, D. Godin-Ribuot & C. Ribuot: Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. *Eur Respir J* 32, 1082-95 (2008)

134. Baguet, J. P., K. Narkiewicz & J. M. Mallion: Update on Hypertension Management: obstructive sleep apnea and hypertension. *J Hypertens* 24, 205-8 (2006)

135. Chobanian, A. V., G. L. Bakris, H. R. Black, W. C. Cushman, L. A. Green, J. L. Izzo, Jr., D. W. Jones, B. J. Materson, S. Oparil, J. T. Wright, Jr. & E. J. Roccella: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* 289, 2560-72 (2003)

136. Tamisier, R., G. S. Gilmartin, S. H. Launois, J. L. Pepin, H. Nespoulet, R. Thomas, P. Levy & J. W. Weiss: A new model of chronic intermittent hypoxia in humans: effect on ventilation, sleep, and blood pressure. *J Appl Physiol* 107, 17-24 (2009)

137. Tamisier, R., J. L. Pepin, J. Remy, J. P. Baguet, J. A. Taylor, J. W. Weiss & P. Levy: 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. *Eur Respir J* 37, 119-28 (2011)

138. Pepperell, J. C., S. Ramdassingh-Dow, N. Crosthwaite, R. Mullins, C. Jenkinson, J. R. Stradling & R. J. Davies: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *The Lancet* 359, 204-210 (2002)

139. Becker, H. F., A. Jerrentrup, T. Ploch, L. Grote, T. Penzel, C. E. Sullivan & J. H. Peter: Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 107, 68-73 (2003)

140. Haentjens, P., A. Van Meerhaeghe, A. Moscariello, S. De Weerdt, K. Poppe, A. Dupont & B. Velkeniers: The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. *Arch Intern Med* 167, 757-64 (2007)

141. Barbe, F., L. R. Mayoralas, J. Duran, J. F. Masa, A. Maimo, J. M. Montserrat, C. Monasterio, M. Bosch, A. Ladaria, M. Rubio, R. Rubio, M. Medinas, L. Hernandez, S. Vidal, N. J. Douglas & A. G. N. Agusti: Treatment with Continuous Positive Airway Pressure Is Not Effective in Patients with Sleep Apnea but No Daytime Sleepiness: A Randomized, Controlled Trial. *Ann Intern Med* 134, 1015-1023 (2001)

142. Robinson, G. V., D. M. Smith, B. A. Langford, R. J. Davies & J. R. Stradling: Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *Eur Respir J* 27, 1229-35 (2006)

143. Barbe, F., J. Duran-Cantolla, F. Capote, M. de la Pena, E. Chiner, J. F. Masa, M. Gonzalez, J. M. Marin, F. Garcia-Rio, J. D. de Atauri, J. Teran, M. Mayos, C. Monasterio, F. del Campo, S. Gomez, M. S. de la Torre, M. Martinez & J. M. Montserrat: Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 181, 718-26 (2010)

144. Pepin, J.-L., R. Tamisier, G. Barone-Rochette, S. H. Launois, P. Levy & J.-P. Baguet: Comparison of Continuous Positive Airway Pressure and Valsartan in Hypertensive Patients with Sleep Apnea. *Am. J. Respir. Crit. Care Med* 182, 954-960 (2010)

145. Levy, P., J. L. Pepin, C. Arnaud, J. P. Baguet, M. Dematteis & F. Mach: Obstructive sleep apnea and atherosclerosis. *Prog Cardiovasc Dis* 51, 400-10 (2009)

146. Minoguchi, K., T. Yokoe, T. Tazaki, H. Minoguchi, A. Tanaka, N. Oda, S. Okada, S. Ohta, H. Naito & M. Adachi: Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. *Am J Respir Crit Care Med* 172, 625-30 (2005)

147. Drager, L. F., L. A. Bortolotto, M. C. Lorenzi, A. C. Figueiredo, E. M. Krieger & G. Lorenzi-Filho: Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 172, 613-8 (2005)

148. Drager, L. F., L. A. Bortolotto, E. M. Krieger & G. Lorenzi-Filho: Additive Effects of Obstructive Sleep Apnea and Hypertension on Early Markers of Carotid Atherosclerosis. *Hypertension* 53, 64-69 (2009)

149. Drager, L. F., L. A. Bortolotto, C. Maki-Nunes, I. C. Trombetta, M. J. Alves, R. F. Fraga, C. E. Negrao, E. M. Krieger & G. Lorenzi-Filho: The incremental role of obstructive sleep apnoea on markers of atherosclerosis in patients with metabolic syndrome. *Atherosclerosis* 208, 490-5 (2010)

150. Drager, L. F., H. F. Lopes, C. Maki-Nunes, I. C. Trombetta, E. Toschi-Dias, M. J. Alves, R. F. Fraga, J. C. Jun, C. E. Negrao, E. M. Krieger, V. Y. Polotsky & G. Lorenzi-Filho: The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. *PLoS One* 5, e12065 (2010)

151. Drager, L. F., L. A. Bortolotto, A. C. Figueiredo, E. M. Krieger & G. F. Lorenzi: Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 176, 706-12 (2007)

152. Pedrosa, R. P., L. F. Drager, P. R. Genta, A. C. Amaro, M. O. Antunes, A. Y. Matsumoto, E. Arteaga, C. Mady & G. Lorenzi-Filho: Obstructive sleep apnea is common and independently associated with atrial fibrillation in patients with hypertrophic cardiomyopathy. *Chest* 137, 1078-84 (2010)

153. Monahan, K., A. Storfer-Isser, R. Mehra, E. Shahar, M. Mittleman, J. Rottman, N. Punjabi, M. Sanders, S. F. Quan, H. Resnick & S. Redline: Triggering of nocturnal arrhythmias by sleep-disordered breathing events. *J Am Coll Cardiol* 54, 1797-804 (2009)

154. Yaggi, H. K., J. Concato, W. N. Kernan, J. H. Lichtman, L. M. Brass & V. Mohsenin: Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 353, 2034-41 (2005)

155. Arzt, M., T. Young, L. Finn, J. B. Skatrud & T. D. Bradley: Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 172, 1447-51 (2005)

156. Redline, S., G. Yenokyan, D. J. Gottlieb, E. Shahar, G. T. O'Connor, H. E. Resnick, M. Diener-West, M. H. Sanders, P. A. Wolf, E. M. Geraghty, T. Ali, M. Lebowitz & N. M. Punjabi: Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 182, 269-77 (2010)

157. Martinez-Garcia, M. A., J. J. Soler-Cataluna, L. Ejarque-Martinez, Y. Soriano, P. Roman-Sanchez, F. B. Illa, J. M. Canal & J. Duran-Cantolla: Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. *Am J Respir Crit Care Med* 180, 36-41 (2009)

158. Parra, O., Ã. Sánchez-Armengol, M. Bonnin, A. Arboix, F. Campos-Rodriguez, J. Pérez-Ronchel, J. Duran-Cantolla, G. de la Torre, J. R. Gonzalez Marcos, M. de la Pena, M. Carmen Jiménez, F. Masa, I. Casado, M. Luz Alonso & J. L. Macarron: Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J* 37, 1128-1136 (2011)

159. Lévy, P. & J. L. Pépin: CPAP treatment of sleep apnoea in the early phase of stroke: growing evidence of effectiveness. *Eur Respir J* 37, 997-999 (2011)

160. He, J., M. H. Kryger, F. J. Zorick, W. Conway & T. Roth: Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. *Chest* 94, 9-14 (1988)

161. Lavie, P., P. Herer, R. Peled, I. Berger, N. Yoffe, J. Zomer & A. H. Rubin: Mortality in sleep apnea patients: a multivariate analysis of risk factors. *Sleep* 18, 149-57 (1995)

162. Young, T., L. Finn, P. E. Peppard, M. Szklo-Coxe, D. Austin, F. J. Nieto, R. Stubbs & K. M. Hla: Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 31, 1071-8 (2008)

163. Lavie, P., L. Lavie & P. Herer: All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *Eur Respir J* 25, 514-20 (2005)

164. Lavie, L. & P. Lavie: Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. *Med Hypotheses* 66, 1069-73 (2006)

165. Steiner, S., P. O. Schueller, V. Schulze & B. E. Strauer: Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion. *Chest* 137, 516-20 (2010)

166. Levy, P., M. R. Bonsignore & J. Eckel: Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J* 34, 243-60 (2009)

167. Tasali, E. & M. S. Ip: Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc*, 5, 207-17 (2008)

168. Coughlin, S. R., L. Mawdsley, J. A. Mugarza, P. M. Calverley & J. P. Wilding: Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* 25, 735-41 (2004)

169. Tan, K. C., W. S. Chow, J. C. Lam, B. Lam, W. K. Wong, S. Tam & M. S. Ip: HDL dysfunction in obstructive sleep apnea. *Atherosclerosis* 184, 377-82 (2006)

170. Ford, E. S.: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 28, 1769-78 (2005)

171. Sundstrom, J., U. Riserus, L. Byberg, B. Zethelius, H. Lithell & L. Lind: Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *Bmj* 332, 878-82 (2006)

172. West, S. D., D. J. Nicoll & J. R. Stradling: Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 61, 945-50 (2006)

173. Shaw, J. E., N. M. Punjabi, J. P. Wilding, K. G. Alberti & P. Z. Zimmet: Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 81, 2-12 (2008)

174. Tasali, E., B. Mokhlesi & E. Van Cauter: Obstructive sleep apnea and type 2 diabetes: interacting epidemics. *Chest* 133, 496-506 (2008)

175. Xu, J., Y. S. Long, D. Gozal & P. N. Epstein: Beta-cell death and proliferation after intermittent hypoxia: role of oxidative stress. *Free Radic Biol Med* 46, 783-90 (2009)

176. Savransky, V., A. Nanayakkara, A. Vivero, J. Li, S. Bevans, P. L. Smith, M. S. Torbenson & V. Y. Polotsky: Chronic intermittent hypoxia predisposes to liver injury. *Hepatology* 45, 1007-13 (2007)

177. Savransky, V., S. Bevans, A. Nanayakkara, J. Li, P. L. Smith, M. S. Torbenson & V. Y. Polotsky: Chronic intermittent hypoxia causes hepatitis in a mouse model of diet-induced fatty liver. *Am J Physiol Gastrointest Liver Physiol* 293, G871-877 (2007)

178. Tanne, F., F. Gagnadoux, O. Chazouilleres, B. Fleury, D. Wendum, E. Lasnier, B. Lebeau, R. Poupon & L. Serfaty: Chronic liver injury during obstructive sleep apnea. *Hepatology* 41, 1290-6 (2005)

179. Harsch, I. A., S. P. Schahin, M. Radespiel-Troger, O. Weintz, H. Jahreiss, F. S. Fuchs, G. H. Wiest, E. G. Hahn, T. Lohmann, P. C. Konturek & J. H. Ficker: Continuous Positive Airway Pressure Treatment Rapidly Improves Insulin Sensitivity in Patients with Obstructive Sleep Apnea Syndrome. *Am. J. Respir. Crit. Care Med* 169, 156-162 (2004)

180. Coughlin, S. R., L. Mawdsley, J. A. Mugarza, J. P. Wilding & P. M. Calverley: Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J* 29, 720-7 (2007)

181. West, S. D., D. J. Nicoll, T. M. Wallace, D. R. Matthews & J. R. Stradling: Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 62, 969-74 (2007)

182. Lam, J. C., B. Lam, T. J. Yao, A. Y. Lai, C. G. Ooi, S. Tam, K. S. Lam & M. S. Ip: A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. *Eur Respir J* 35, 138-45 (2010)

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