Obstructive sleep apnea and heart disease: the biomarkers point of view

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1. ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disorder. Important risk factors for this disease are represented by obesity, male gender, smoking, some endocrinological disturbances, alcohol intake, use of benzodiazepines, and craniofacial alterations. It is well known that OSAS is a frequent comorbidity as well as a relevant risk factor for cardiovascular diseases (CVD), especially in patients with hypertension, coronary artery disease (CAD), arrhythmias, and heart failure. Furthermore, therapy with continuous positive airway pressure devices (CPAP) has been shown to significantly reduce the incidence of serious cardiovascular consequences. Interactions between OSAS and the cardiovascular system (CVS) can eventually result mainly in coronary atherosclerosis. These two conditions are connected by a complex biomarkers network. An extensive overview of these pathways could be helpful to better understand the causes of cardiovascular impairment in patients with OSAS.

2. INTRODUCTION

Sleep encompasses about a third of one's life. The reasons for this are mostly linked to its effects on the respiratory and cardiovascular system (CVS). During sleep physiological changes occur in the human body that lead to a resting status of cardiovascular, respiratory and metabolic systems. The importance of sleep within the human life has gathered a growing interest about sleep-related disordered breathing and their cardiovascular implications (1). This review will focus on the role of obstructive sleep disordered breathing in cardiovascular disease (CVD) through the activation of inflammatory pathways by inflammatory mediators.

3.OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

3.1. Epidemiological data, definition and clinical features

OSAS is a widespread disorder with an estimated prevalence ranging from 4.5%(2) to 17,6%(3) of adult
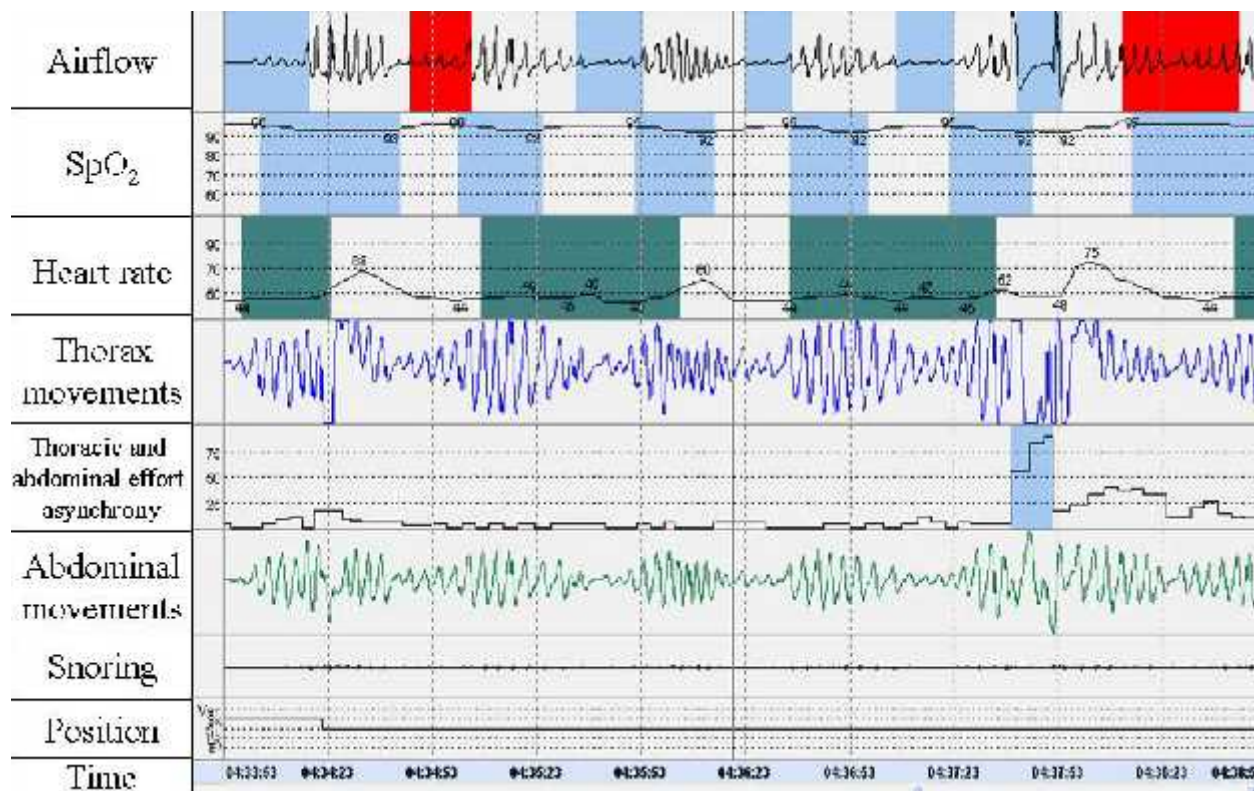
Figure 1. Typical cardiorespiratory monitoring of an OSA patient. SpO2: Blood oxygen saturation. (With the permission of the patient).

males and from 1.2%(4) to 3.2%(2) of women in industrialized countries (2-4). Its manifestations encompass both nocturnal (snoring, apnea, insomnia, nicturia, gasping) and daytime symptoms (sleepiness, headache at awakening, memory impairment) (4). The most frequent daytime symptom is sleepiness (5), which can be evaluated by means of scales (Stanford (6) and Epworth (7)), representing a subjective evaluation of the extent of the symptoms, or by laboratory exams (multiple sleep latency test [MSLT] (8) and maintenance of wakefulness test [MWT] (8)). Snoring is considered the most frequent nocturnal symptom (5-10). Predisposing factors are represented by male gender, obesity, smoking habit, endocrinological disturbances, alcohol intake, use of benzodiazepines and craniofacial alterations (11).

3.2. Diagnosis

Even though they are crucial to address clinical suspicion, medical history, symptoms and physical examination are not sufficient to establish the diagnosis of OSAS. Nowadays, full-montage polysomnography (PSG) (12) is still considered the gold standard investigation in order to diagnose OSAS, but it is complex and expensive, uncomfortable for the patients, and it requires a dedicated sleep laboratory with highly qualified personnel. For this reason simpler techniques such as cardiorespiratory monitoring (CRM) have been introduced to detect the presence of OSAS. Apnea, which is caused by collapse and consequent occlusion of upper airways during sleep, is defined as $\geq$

90% reduction of the airflow with respect to the baseline, lasting at least 10 seconds. Hypopnoea is $\geq$ 30-50% reduction of the airflow for 10 seconds or longer, associated with a significant oxygen desaturation or with an arousal. The number of apnea/hypopnoea episodes in one hour is defined as apnoea/hypopnoea index (AHI), which is considered pathological when exceeds 5 events/hour. The hypoxic burden of the disease is expressed by the oxygen desaturation index (ODI), which indicates the number of oxygen desaturations (4% reduction of SpO_2 compared to the baseline) in one hour of recording, and by the time span in which oxygen saturation stays below 90% (Figure 1) (13).

3.3. Treatment

The most common and effective treatment of OSAS is the application of a continuous positive pressure (CPAP) device, which keeps the upper airways open (14). This device is effective in reducing the AHI and it also helps to improve symptoms (15) and prevent the risk of systemic consequences such as hypertension (16), insulin resistance and cardiovascular events (17), especially in patients with moderate-to-severe OSAS (AHI > 15/h). Weight loss, the assumption of a lateral position during sleep, and life-style modifications should be always recommended in addition to CPAP therapy (11), since they concur to improve sleep parameters (18) in moderate-to-severe OSAS; moreover, they might be adopted as a stand-alone therapy in mild OSAS since they have been shown to be effective in this setting (19).

4. CVD AND OSAS

It is well established that OSAS, besides being an important cardiovascular risk factor, is also a relevant comorbidity in many patients with CVD. Over the last decades large studies have shown the high prevalence of sleep-related disordered breathing in patients suffering from hypertension, CAD, arrhythmias and heart failure. Since the earliest observational studies linking snoring, a surrogate for OSAS, with an increased risk of cardiac events (20), a growing evidence supporting this close relationship has been provided.

4.1. Prevalence of OSAS in hypertension

A crucial insight into the close relationship between CVD and sleep apnea diseases has been contributed by the Sleep Heart Health Study, which established a significant association between sleep disordered breathing (SDB) and systemic hypertension in middle-aged and older individuals of different gender and ethnicity (21). Similar conclusions were subsequently confirmed by other groups over a more extended follow-up.(22,23). It is estimated that about 50% of OSAS patients suffer from hypertension (24), and at the same time an estimated 30% of hypertensive patients also have OSAS, although frequently undiagnosed (25-30). Sleep disturbances due to obstructive apneic events often play a pivotal role for several patients with drug-refractory hypertension, defined as a blood pressure (BP) of 140/90 mmHg while taking a combination of 3 antihypertensive drugs titrated to maximally recommended doses (31,32).

4.2. Prevalence of OSAS in CAD

Apneic events during the night cause a rise in the heart rate (HR) and BP with a consistent hemodinamical stress occurring when such parameters are supposed to be the at their lowest level and quite stable. The nightly peripheral sympathetic activation due to OSAS persists during wakefulness, settling at approximately twice the normal levels, and it may be even higher in the early hours of the morning, with an increased potential to provoke acute coronary events (33). Further studies confirmed the role of OSAS as an independent predictor of CAD (34,35) after the first clinical observation of an association between snoring and myocardial infarction in men (36). A relationship between OSAS and cardiovascular mortality has been found in a studies analyzing patients with known CAD and Respiratory disturbances index (RDI) > 10 events/hour: these patients were reported to be much more likely to experience cardiovascular death over a 5-yr period than those with lower RDIs after adjusting for age, weight, and smoking (35,37,38). A role for sleep apnea in nocturnal angina pectoris has been also suggested since dynamic ST segment depression has been demonstrated to be relatively common in patients with severe OSAS during sleep (39), however nightly episodes of myocardial injury has not been detected by measurements of cardiac troponin T (40). Moreover, neither oxygen desaturation index nor AHI independently predicts single endpoints such as myocardial infarction or death (41).

4.3. Prevalence of OSAS in patients with cardiac arrhythmias

Nocturnal arrhythmias occur in up to 50% of OSAS patients (42), and in particular, the presence of ectopic ventricular beats is documented in up to 66% of patients with sleep apnea (42,43). In the Sleep Heart Health Study, a significant association was noted between SDB and several types of arrhythmias, such as atrial fibrillation, complex ventricular ectopies, non-sustained ventricular tachycardia, ventricular bigeminy and trigeminy (44). Current data show that the incidence of atrial fibrillation and ventricular tachycardia is significantly higher in patients with AHI > 10/h than in healthy subjects (45-48). On the other hand, the burden of premature ventricular contractions can be reduced by CPAP therapy both in patients with normal left ventricular function and in those with heart failure (49,50). In a retrospective cohort study of >3500 adults with history of atrial fibrillation undergoing complete overnight polysomnography, both obesity and nocturnal oxygen desaturation were independent predictors of atrial fibrillation, but only in subjects > 65 years of age (51). Regarding bradyarrhytmias, in a minority of OSAS patients events such as various degree atrio-ventricular block and asystole may arise, even in the absence of preexisting cardiac conduction disease (42,52). Interestingly, CPAP therapy may play an important role in reversing electrical disturbances in these patients, thus avoiding unnecessary pacemaker therapy (53-56). The mechanisms of OSAS-induced arrhythmias are unknown. However, the sympathetic activation induced by hypoxemia and by apneic events, with its rebound on systemic stress mechanisms, may play a pivotal role.

4.4. Prevalence of OSAS in heart failure

While SDB affects 2 to 5% of general population, its prevalence among patients with chronic heart failure (CHF) can be as high as 12-53%, as documented by polysomnography;(57-59). On the other hand, more than 55% of patients with OSAS have diastolic dysfunction (60). Javaheri et al. showed the presence of OSAS in approximately 11-12% of ambulatory male patients with systolic CHF and low ejection fraction (EF) in two different studies (45,61). Similar results were found by Vazir et al. (59), who reported a 15% prevalence of OSAS in CHF patients. In a prospective study including female patients, Wang et al. (62) found a 26% prevalence of OSAS among 218 CHF patients with a left ventricular EF of less than 45%,. Two retrospective studies showed an higher prevalence of OSAS. The first one by Sin et al. included 450 patients with systolic CHF (63) and a prevalence of OSAS of 37%. In a smaller population of 53 stable CHF outpatients, (58) the prevalence of OSAS reached 53% in. Such a variable prevalence of OSAS among heart failure patients, ranging from 11 to 53%, might be at least partially explained by the different study designs. In fact, in the last two studies a minimum AHI cutoff of 10/h was used and the mean EF was higher. Further data supporting these high prevalence were provided by Oldenburg et al. (64), who studied 700 CHF patients with NYHA Class II or higher and set a relatively low AHI cutoff of 5/h, nevertheless found that 36% of patients were affected by OSAS.

5. PATHOPHYSIOLOGICAL MECHANISMS

The pathophysiological mechanisms underlying the relationship between OSAS and CVD are still debated and only partially known. However, several studies suggest a multifactorial process involving a wide range of mechanisms including enhanced sympathetic activity, metabolic dysregulation, alteration of the coagulation pathways and most of all the involvement of systemic and vascular inflammation through mechanisms of injury which are still under investigation. Particularly, apnoeic events cause intermittent hypoxia and subsequent re-oxygenation, and this typical sequence might be the key feature in the pathophysiology of the disorder, in fact the desaturation-reoxygenation pattern leads to oxidative stress through the production of reactive oxygen species (ROS) (65,66). Thus, reperfusion injury in association with changes in the intra-thoracic pressure, and the consequent arousal with sleep fragmentation, which is necessary to restore the normal condition of breathing, could play as a trigger for several further mechanisms, including sympathetic activation, systemic and vascular inflammation pathways, atherosclerosis, endothelial dysfunction, oxidative stress and alteration of the coagulation (67).

5.1. Role of inflammation

The inflammation processes are critical in the pathogenesis of atherosclerosis. Serum levels of several biomarkers have been associated with cardiovascular risk. Recent findings underline the important role that the inflammatory cascade might play in the cardiovascular pathophysiology of OSAS. The inflammatory cascade involves different pathways by the activation of a large number of humoral mediators and there is plenty of evidence supporting its pivotal role in all phases of atherosclerosis.

A lot of studies have showed the role of leukocytes in atherosclerosis, and in their interesting works Dyugovskaya *et al.* have demonstrated augmented expression of adhesion molecules (e.g. ICAM-1) and cytotoxicity of leukocytes in OSAS patients (68-71).

Findings from a cell-culture model showed that intermittent hypoxia sustain inflammation through the activation of transcription of the nuclear factor kB (NF-kB) and the hypoxia-inducible factor-1 (HIF-1). Particularly, HIF-1 is activated by a high burden of intermittent hypoxia, and it increases systemic inflammation by modifying the levels of inflammation mediators (e.g. TNF- and IL-8) and prolongs the natural life of myeloyd cells (72). In this pathway, an important role is played by p38 mitogen-activated protein kinase (MAPK) which could increase systemic inflammation by activating HIF-1 (73).

This evidence is also corroborated by clinical studies which have demonstrated higher levels of IL-8 and TNF- in OSAS patients, as well as their direct correlation with the severity of the disease. For this reason ODI, rather than AHI, might be the best predictor of the systemic inflammatory burden (74).

A recent review describes a relevant implication of reactive oxygen species (ROS), also induced by intermittent hypoxia and the subsequent activation of NF-kB and HIF-1 (75), but the data are discordant and further studies are necessary (76).

Through well-defined mechanisms, it has been shown an increased expression of a number of genes encoding proteins such as erythropoietin, vascular endothelial growth factor, and inducible nitric oxide synthase, which increase tissue oxygenation. Moreover, OSAS increases, through the reduction of serum oxygen levels, inflammatory cell adhesion to the vascular endothelium, and at the same time it promotes the activation of proinflammatory cytokines and other inflammation markers involved in atherosclerosis (65). A brief summary of the potential mechanisms of cardiovascular disease in OSAS is shown in Figure 2.

5.2. C-Reactive protein

C-reactive protein (CRP) is an acute phase pentameric protein of 23kD constituted by 5 subunits, produced under cytokine stimulus, especially IL-6, synthesized in the inflammation site by different types of cells, in particular monocytes and macrophages (77). Even though increased CRP levels lack specificity, this biomarker is one of the most significant predictors of cardiovascular risk and prognosis because atherosclerosis is nowadays recognized as a chronic inflammatory disease (78-81). The potential association between this protein and cardiovascular prognosis was first underlined in patients with acute coronary syndrome (80,81). Recently it is shown that CPR has pro-atherogenic proprieties through different pathways: 1) inducing endothelial cells to express adhesion molecules, ICAM-1(intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1), E-selectine 11 and chemokine MCP (monocyte chemotactic protein-1) (82); 2) inducing secretion of IL-6 and endothelin 1 and reducing the expression e bioavailability of NO synthetase and consequent reduction of NO production that is able to inhibit platelets adhesion and aggregation, to induce vasodilation and to reduce leucocytes adhesion to endothelium and proliferation of vascular smooth muscle cells (83); 3) activating macrophages to express cytokine and tissue factor remarking the uptake of opsonized LDL-CRP (78); 4) amplifying pro-inflammatory effects of other mediators including endotoxin (78); 5) activating complement inside atherosclerotic plaque so inducing potential instability (78). Hypoxemia as well as sleep deprivation appear to be important triggers for systemic inflammation (84,85). The combination of reduced serum oxygen levels and reduced sleeping time engenders increased levels of CRP (86-88). In their study, Yokoe *et al.* (89) found that CRP was significantly higher in 30 patients with newly diagnosed OSAS than in 14 obese subjects with no evidence of OSAS, and there was a direct relationship between OSAS severity and CRP levels. Similarly, in a recent study Basoglu *et al.* (90) have shown that the mean levels of high sensitivity CRP were significantly higher in OSAS patients than the control group.
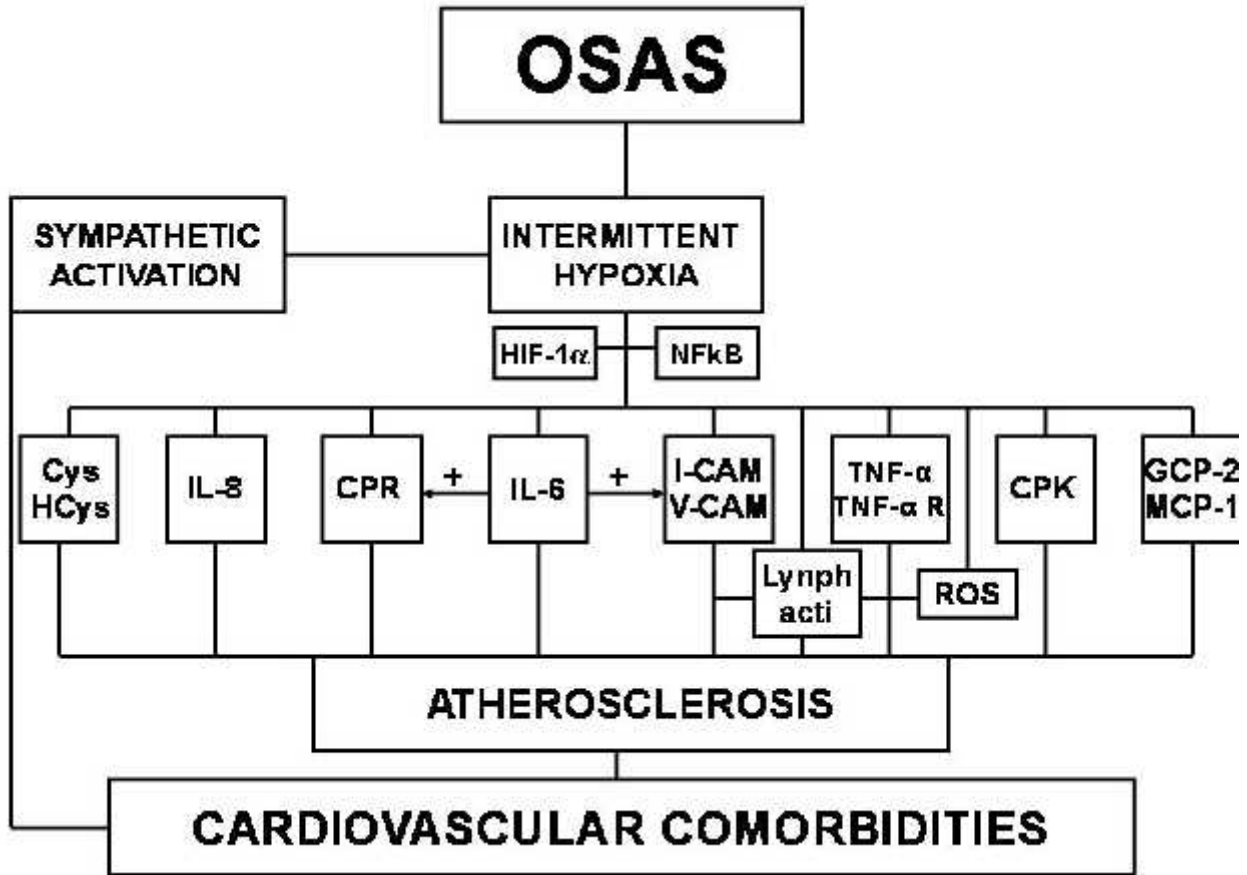
Figure 2. Simplified diagram of interactions among OSAS, cardiovascular diseases and biomarkes. IL: interleukine; HIF-1: hypoxia inducible factor-1; NFkB: nuclear factor kB; Cys: cysteine; HCys: homocysteine; CPR: C-reactive protein; I-CAM: intercellular adhesion molecule; V-CAM : vascular cell adhesion molecule; TNF- α : Tumor necrosis factor- alpha; TNF- α R: Tumor necrosis factor- alpha Receptor; CPK: creatinine phosphokinase; GCP-2: granulocyte chemotactic protein 2; MCP-1: monocyte chemoattractant protein 1; ROS: reactive oxygen species; Lymph act: lymphocytes activation.

The importance of CPR, and related cytokines (*see figure 2*), is true not only in adults, but also in caucasic children, and for same authors, in the future, it could be used as a marker of metabolic syndrome for an early diagnosis in young obese OSA patients (91). Although the exact links between OSAS and CVD are not well known, there is growing evidence that OSAS is associated with proinflammatory pattern with the release of inflammatory factors in the blood stream that are deemed to be important in the development of atherosclerosis and other manifestations of CVD. The presence of high CRP levels have been associated with increased cardiovascular mortality in OSAS patients.

5.3. Brain natriuretic peptide (BNP)

The pro-hormone (Pro-BNP) is predominantly synthesized by myocytes of the left ventricle in response to wall distension and is then cleaved into a biologically active peptide (BNP) and a N-terminal pro-BNP fragment (NT-proBNP),. NT-ProBNP, for its stability and relatively long half-life, is preferred as a more sensitive diagnostic measure of BNP secretion (92,93). Several studies have

shown that elevated levels of BNP have been associated with reduced left ventricular function and a poor prognosis (94,95). The role of natriuretic peptides in OSAS still remains controversial. Kita *et al.* (96) found in a small population of patients with severe OSAS and without heart failure increased plasma BNP levels during the night, and this situation was reversed by nasal CPAP therapy. Nevertheless in a later study Hubner *et al.* (97) found that NT-proBNP is not useful to detect myocardial stress caused by OSAS, in fact changes of NT-proBNP in the study population were not documented, nasal CPAP therapy showed a non-significant trend towards a reduction of NT-proBNP levels in a small subgroup of patients, in agreement with the other study.

5.4. Cysteine and homocysteine

Homocysteine is a sulfur-containing aminoacid, and it is considered a cardiovascular risk biomarker (98,99). It has been related to the risk of developing myocardial infarction, hypertension and atherosclerosis (99). This correlation is significant also in mild level of homocysteinemia (100), where homocysteine action is

mediated by endothelial injury, altered coagulation and platelet activation (99). Ozkan *et al.* (101) hypothesized a possible involvement of nitric oxide in this pathway, successively confirmed in elderly patients (102). The relationship between this biomarker and OSAS has been studied in few works, but their results are discordant. Indeed some authors reported that homocysteine blood levels are increased in OSAS patients regardless the presence of echocardiographic abnormalities (103-106), and they show a significant positive correlation with the oxygen desaturation index (ODI) and the number of respiratory arousals (106). These data were confirmed by Chen *et al.* (107), who showed a significant increase of this aminoacid in OSAS patients with ischemic stroke. For these reasons homocysteine is considered a promising marker of this syndrome by several authors. However, homocysteinemia was not influenced by CPAP therapy in another study (108). On the contrary, other groups (90,109) did not find any difference in homocysteinemia between OSAS patients and normal subjects. Like homocysteine, cysteine levels are considered as a cardiovascular risk factor as well (110). Interestingly Cintra *et al.* (111) did not notice any difference in homocysteine levels between patients with moderate/severe OSAS (mean AHI: 31.73 ± 23.23) and healthy subjects, but demonstrated a significant difference in cysteine plasma levels between the two groups. The increase of cysteine levels in OSAS patients was significantly reduced after 6 months of CPAP therapy. These results suggest that cysteine might be considered an important mediator of endothelial damage in OSA.

5.5. TNF-alpha, IL-6 and IL-8

TNF-alpha, one of the most important mediators of inflammation, plays a paramount role in heart disease. The main source of this molecule remains unclear (67). In particular, TNF-alpha can induce the leucocytes' adhesion receptors involved in early atherosclerosis in clinically healthy men and it is a reliable marker of cardiovascular events (112). The core of its action is NF-kB (74) which is activated through the HIF-1 (113). This could be one of the molecular mechanism responsible for the atherogenic potential of OSAS (67). Recently, also p38 MAPK has been shown to be involved in this pathway (73). Moreover, TNF-alpha-308 G/A polymorphism is a risk factor for OSAS, especially in adults (114), and it is significantly increased in OSAS patients even after adjustment for other variables such as age, body mass index and sleepiness (67,74,113), and correlates positively with OSAS severity (74). Arias *et al.* (115) confirmed these data; moreover, even although they did not find any difference in TNF-alpha levels before and after CPAP therapy, they were able to demonstrate a significant reduction of its soluble urinary receptor. Nevertheless, Sarac *et al.* found discordant results, with no difference between OSAS patients and normal subjects (116). Vgontzas et. al (85) confirmed the relationship between OSAS and TNF-alpha. In their pilot, placebo-controlled, double blind study on 8 patients receiving etanercept, a protein which can inhibit the interaction between TNF-alpha and its specific cellular receptor (117), subjects who received etanercept showed, along with an expected reduction of TNF-alpha and IL-6 levels, also an improvement of daytime sleepiness and a reduction in AHI.

As TNF-alpha, IL-6 is under investigation as a marker of heart disease, and its relationship with CRP is well known (67). Some studies (85,89,118) have found High levels of IL-6 have been detected in OSAS patients, but those studies bore some methodological limitations such as selection biases, small number of subjects enrolled and inclusion of patients with cardiovascular comorbidities (67,85,89,118). Conversely Ryan *et al.* (74) did not obtain any correlation between IL-6 and OSAS parameters. Moreover, in a larger study a correlation between OSAS severity and IL-6 was no longer detectable after adjusting for antropometric features (gender, age, race, waist circumference) and cardiovascular comorbidities, while IL-6 soluble receptor still maintained a correlation with OSAS severity(119).

Interleukin 8 (IL-8) is also associated with an increased cardiovascular risk (120) by promoting leukocytes adhesion (121). IL-8 levels are increased in OSAS patients and CPAP therapy can reverse this enhanced production (74,122,123), as well as for TNF-alpha (115).

5.6 Other biomarkers

There is strong evidence of the role played by the ICAM-1 and the VCAM-1 in atherosclerosis and consequent heart diseases (124,125). Earlier small studies found an association between these markers (126,127) and OSAS severity and demonstrated the efficacy of CPAP therapy in reducing their levels (128). The association between ICAM-1 and VCAM-1 levels and OSAS has been further confirmed by more recent case-control studies (129,130). Some authors demonstrated increased levels of fibrinogen in OSAS patients, which were improved by CPAP therapy (131), but also discordant results have been reported (132). Granulocyte chemotactic protein 2 (123), monocyte chemoattractant protein 1 (132), creatinine phosphokinase (133), lymphocyte's CD40 ligand (71) and circulating cell-derived microparticles (134) are also increased in OSAS patients, but larger studies are required to confirm these findings.

6. CONCLUSIONS

By reviewing the literature regarding OSAS available so far, it comes evident that a close relationship exists between this condition and several features of CVD such as hypertension, atherosclerosis and CAD, arrhythmias, CHF. The exact pathophysiological mechanisms of this link are still mostly under investigation, however growing evidence is emerging about the role of systemic inflammation. The levels of several mediators of inflammation have been shown to be increased among patients with OSAS, which may trigger the production of such biomarkers by sympathetic hyperactivation or other pathways. On the other hand, most of those mediators have an established or at least suspected role in the pathogenesis of cardiovascular conditions such as hypertension, endothelial dysfunction, thrombosis, atherosclerosis. On the basis of these findings, inflammation might play a crucial role in this pathogenetic process, thus representing the critical bridge between OSAS and CVD. Further evidence

is still warranted to better understand the implication of OSAS in the development and progression of CVD.

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