Sleep Breath (2010) 14:261–269
DOI 10.1007/s11325-010-0338-3

REVIEW

Inflammation accelerates atherosclerotic processes in obstructive sleep apnea syndrome (OSAS)

Alessandra Quercioli · François Mach · Fabrizio Montecucco

Received: 9 November 2009 / Revised: 26 January 2010 / Accepted: 31 January 2010 / Published online: 3 March 2010

Abstract Obstructive sleep apnea syndrome (OSAS) is an often underestimated sleep disorder that has been associated with cardiovascular disease. OSAS is characterized by cycles of apnea and/or hypopnea during sleep caused by the collapse of the upper airways. Intermittent hypoxia deriving from the cycles of apnea/arousals (to retrieve the ventilation) plays a pivotal role in the pathogenesis of the disease. Obesity is the most frequent predisposing condition of OSAS. Recent evidence suggests that OSAS could be considered as a pro-atherosclerotic disease, independently of visceral fat amount. Oxidative stress, cardiovascular inflammation, endothelial dysfunction, and metabolic abnormalities in OSAS could accelerate atherogenesis. The present review is focused on the possible pathophysiological mediators which could favor atherosclerosis in OSAS.

Keywords Obstructive sleep apnea syndrome · Inflammation · Oxidative stress · Atherosclerosis

A. Quercioli
Division of Cardiology,
Geneva University Hospital,
Avenue de la Roseraie 64,
1205 Geneva, Switzerland
e-mail: Alessandra.quercioli@hcuge.ch

F. Mach · F. Montecucco (✉)
Division of Cardiology, Foundation for Medical Researches,
Geneva University Hospital,
Avenue de la Roseraie 64,
1211 Geneva, Switzerland
e-mail: Fabrizio.Montecucco@unige.ch

F. Mach
e-mail: Francois.Mach@hcuge.ch

Introduction

Sleep apnea is an underdiagnosed syndrome, characterized by periods of breathing apnea and/or a marked reduction of the tidal volume (hypopnea) occurring during sleep. Obstructive sleep apnea syndrome (OSAS) is caused by the collapse of the upper airways. OSAS patients manifest excessive daytime sleepiness related to the fragmentation of the sleep by frequent arousal, which might favor the development of cognitive dysfunction and memory loss because of cerebral hypoxemia [1, 2]. Although it is still considered as a local and upper airway disorder, OSAS is now deemed a systemic disease that could involve not only the respiratory but also central nervous and cardiovascular systems. Intermittent hypoxemia (IH, intermittent periods of oxygen saturation below 90%) can increase oxidative stress, pro-inflammatory cytokine production, platelet aggregation, and metabolic dysregulation [1, 3–5]. Importantly, sleep-related IH was independently associated with all-cause mortality in 6,441 men and women participating in the Sleep Heart Health Study [6]. Several studies have demonstrated the association of OSAS with arterial hypertension [7, 8], stroke [9–12], coronary artery disease (CAD) [13–16], or pulmonary hypertension [17]. Sleep-disordered breathing was also significantly associated with coronary artery disease-related mortality [6]. The high mortality risk in untreated sleep-disordered breathing has been shown as independent of age, sex, and body mass index (BMI) [18]. Thus, recent evidence showed that OSAS should be considered as a condition predisposing cardiovascular disease [2, 15, 19–21]. Nevertheless, the elevated incidence of OSAS in the adult population (4% men and 2% women between 30 and 60 years of age manifest the severe form of the disorder, while these percentages go up to 5–15% considering all stages of the disease) [22–24] and the risk of

severe systemic complications confer to the diagnosis and treatment of OSAS a remarkable social importance.

OSAS-associated cardiovascular inflammation and its clinical relevance will be discussed in the present article.

Clinical relevance of OSAS

OSAS represents a systemic worldwide disease, mainly affecting obese subjects (up to 70% of OSAS patients are obese). This association renders difficult to define OSAS impact as an independent factor of risk [25, 26].

Subjects with OSAS have an increased comorbidity (CAD, stroke, arterial hypertension) and mortality, while continuous positive airway pressure (CPAP) treatment seems to improve survival [27, 28]. Marshall and co-workers recently showed that moderate to severe OSAS is independently associated with an increased risk of all-cause mortality in 397 residents of Busselton town (Western Australia) after up to a 14-year follow-up [29]. Doherty and co-workers observed that deaths for cardiovascular disease were more common in the untreated group of patients than in the CPAP-treated one during follow-up (14.8% vs. 1.9%, respectively) [30]. Cross-sectional associations from the Sleep Heart Health Study cohort (6,424 subjects) demonstrated that OSAS induces only modest to moderate effects on cardiovascular disease [15]. On the other hand, OSAS has high incidence among persons with known CAD (30–58%) [31, 32]. The relative risk for myocardial infarction in OSAS subjects for the upper quartile of the apnea index has been shown to be 23.3 compared with the lowest quartile, indicating a strong association between OSAS and the acute coronary syndrome. These studies suggest that OSAS is an independent risk factor for CAD [14]. Subjects with coexistent OSAS and CAD have higher mortality (38% vs. 9%), increased rate of restenose after percutaneous coronary intervention (24% vs. 5%), and increased rate of major adverse cardiac events (37% vs. 15%) as compared to CAD patients without OSAS [33]. Recent studies have shown early atherosclerotic lesions in OSAS subjects (such as the increase of intima–media thickness [IMT]), which can be reduced by CPAP treatment [34–36]. Furthermore, IMT is significantly correlated to levels of C-reactive protein (CRP), interleukin (IL)-6, and severity of OSAS [35]. OSAS is also associated with other signs of early atherosclerosis, such as increased arterial stiffness and heart remodeling (increased left atrial diameter, interventricular septal thickness, and left ventricle mass index), independently of other confounding factors [34, 37].

In the last decades, increasing evidence showed that OSAS is also associated with arterial hypertension [8, 38–40]. Large clinical studies have demonstrated that OSAS is an independent risk factor for hypertension [7, 20, 41] with an adjusted odds ratio for baseline hypertension, non-modifiable risk factors, obesity, and smoke of 2.9 [20]. Several studies have also demonstrated that CPAP treatment not only reduces nocturnal blood pressure [42] but also decreases daytime diastolic blood pressure [43–45]. On the other hand, some authors failed to find any beneficial effect on blood pressure when investigating hypertensive OSAS patients [46].

OSAS has been also related to an increased risk of stroke. The Sleep Heart Health Study showed a small but significant increase in stroke prevalence among OSAS subjects [15]. Yaggi and co-workers showed that OSAS subjects have a 2-fold increased risk of stroke as compared with non-OSAS subjects in a 3.5-year follow-up [12]. Moreover, OSAS is associated with a more serious prognosis after stroke [11, 47].

Other known cardiovascular complications are different types of arrhythmias (brady- and tachyarrhythmias) [48, 49], pulmonary hypertension [50–52], and congestive heart failure [53, 54].

The nasal CPAP is the gold-standard treatment; it significantly improves oxygen saturation and general symptoms. In spite of the existing debate, some studies have shown that CPAP reduces the levels of systemic inflammatory markers such as TNF-α, IL-6, CRP, and IL-8 [55–58].

Several pathogenetic mechanisms have been proposed to explain the possible association between OSAS and cardiovascular disease.

Cardiovascular inflammation in OSAS

Oxidative stress

IH is a key element in the pathophysiology of OSAS and its complications. It consists of cycles of short periods of oxygen desaturation followed by retrieval of the ventilation with normalized oxygenation. It has been postulated that IH is a harmful mechanism analogous to ischemia–reperfusion injury. In ischemia–reperfusion injury, the damage occurs when the blood flow to an ischemic or hypoxic tissue is restored [1, 3, 5, 59, 60] and overproduction of reactive oxygen species (ROS) is induced. The same mechanism might be implicated in intermittent hypoxia during sleep. During reperfusion, ROS are generated through the xanthine oxidase pathway, the NADPH oxidase pathway, and the incomplete oxidative phosphorylation in the mitochondria [22, 61–63]. Accordingly, several oxidative stress markers are increased in OSAS [62, 64–68] and are reduced after CPAP treatment [69, 70]. An increased level of ROS, such as superoxide anion (O_2^-), hydroxyl radical (OH^-), and peroxynitrite ($ONOO^-$), provides cell membrane damage by lipid peroxidation, protein oxidation, depletion of

intracellular adenosine triphosphate, alteration in calcium homeostasis, cellular apoptosis, and oxidative DNA damage. These events finally could increase endothelial dysfunction and inflammation [60, 62, 71].

ROS production is associated with the upregulation of different genes regulated by the pro-inflammatory nuclear factor kappa B (NF-κB) pathway [3, 72, 73]. NF-κB mediates the production of inducible NO synthase (iNOS) [74] and cyclooxygenase (COX)-2. NF-κB also activates the overexpression of adhesion molecules involved in leukocyte recruitment and migration to the inflammatory site, i.e., intercellular adhesion molecule-1 (ICAM-1), E-selectin, and vascular cell adhesion molecule-1 (VCAM-1) [73, 75, 76]. Accordingly, NF-κB is highly activated in OSAS patients as compared to healthy controls. Furthermore, CPAP treatment strongly reduces NF-κB activation [77]. Interestingly, IH does not seem to activate protective hypoxia-inducible factor-1 (HIF-1), a key regulator of the adaptive pathway to chronic hypoxia [72, 78]. The short duration of hypoxia in IH does not allow the stabilization of HIF-1 and the cyclic re-oxygenation induces mitochondria dysfunction. Thus, it results in the activation of the NF-κB pathway alone [78, 79]. These results are controversial and need further confirmations. Indeed, it is well known that HIF-1 downstream proteins, such as the vascular endothelial growth factor (VEGF, which regulates the oxygen homeostasis), iNOS, and endothelin-1 (a potent vasoconstrictor), are increased in OSAS, suggesting a possible activation of HIF-1 pathway [80–87].

Systemic inflammatory mediators

Several evidences suggest that OSAS might be considered as a systemic inflammatory disease (Table 1). The levels of the pro-inflammatory cytokine TNF-α are correlated with the severity of OSAS. TNF-α modulates physiological sleep [88]

Table 1 Clinical studies investigating the association between inflammatory cardiovascular risk markers and OSAS

Author	Year	Number of patients	Marker	Effect
Vgontzas et al. [91]	2000	14 OSAS; 11 obese; 12 controls	TNF-α and IL-6	Increased TNF-α and IL-6 in OSAS vs. controls
Minoguchi et al. [56]	2004	24 OSAS; 15 obese; 12 controls	TNF-α	Increased TNF-α serum levels in severe OSAS vs. controls and vs. mild OSAS
Ryan et al. [28]	2006	67 OSAS male; 30 controls male	TNF-α and IL-8	Increased TNF-α and IL-8 in OSAS vs. controls
Yokoe et al. [58]	2003	30 OSAS; 14 obese	IL-6	Increased IL-6 in OSAS vs. obese
Al Lawati et al. [99]	2009	176 OSAS (80.1% AHI≥5 events/h and 25% AHI≥30 events/h)	IL-6	No correlation between IL-6 and OSAS severity
Minoguchi et al. [35]	2005	36 OSAS; 16 obese	IL-6 and CRP	Increase IL-6 and CRP in OSAS vs. obese
Can et al. [102]	2006	62 OSAS male (30 subjects with AHI>5 [group 1] and 32 subjects with AHI<5 [group 2]); 30 controls	CRP and homocysteine	Increased CRP and homocysteine in OSAS group 1 vs. group 2. Increased CRP and homocysteine in OSAS groups vs. control
Taheri et al. [115]	2007	907 OSAS (68.7% AHI<5; 19.1%5 ≤ AHI15; 12.2% AHI≥15)	CRP	Positive association between CRP and the AHI (AHI 5–15, AHI≥15). No significant association after adjustment for age, sex, and BMI
Kapsimalis et al. [110]	2008	52 OSAS (26 severe; 26 mild–moderate); 15 non-OSAS	CRP and leptin	Increased CRP in severe OSAS vs. non-OSAS. Increased leptin in severe OSAS and moderate OSAS vs. non-OSAS
Hayashi et al. [103]	2006	60 OSAS; 30 controls	CRP and MCP-1	Increased CRP and MCP-1 in OSAS vs. control
Ohga et al. [117]	2003	20 OSAS male; 10 control male	MCP-1	Increased MCP-1 in OSAS vs. controls
Ip et al. [133]	2000	30 OSAS; 30 non-OSAS matched for BMI, age, sex, and menopausal status	Leptin	Increased leptin in OSAS subjects vs. controls
Phillips et al. [129]	2000	32 OSAS vs. 32 obese	Leptin	Increased leptin in OSAS vs. controls
Schafer et al. [134]	2002	55 OSAS (8 patients with 10AHI15; 4 patients with 15AHI20; 22 patients with 20AHI40; 21 patients with AHI>40); 26 controls	Leptin	Leptin levels correlate with AHI (r=0.39, p<0.0003). No significant correlation (r=0.25) after adjustment for body fat content
Kuramoto et al. [121]	2008	35 patients with 20 ≤ AHI40, 46 patients with AHI≥40, 35 non-OSAS (AHI<20).	SAA	Increased SAA in AHI>40 group vs. AHI<20 group
Tazaki et al. [120]	2004	44 OSAS; 18 controls	MMP-9	Increased MMP-9 in OSAS vs. controls

TNF-α tumor necrosis factor-alpha, *AHI* apnea–hypopnea index, *CRP* C-reactive protein, *MCP-1* monocyte chemoattractant protein-1, *BMI* body mass index, *SAA* serum amyloid A, *MMP-9* matrix metalloproteinase-9

and is produced by monocytes and T cells through a transcriptional pathway involving NF-κB and up-regulates VCAM-1, E- and L-selectin, and ICAM-1 expression. TNF-α is involved in the increase of NREM sleep [89] and induces somnolence and fatigue [90]. Accordingly, its levels are significantly higher in OSAS patients as compared to healthy controls and lower after treatment with CPAP, independently of obesity [56, 57, 90–92]. Moreover, in OSAS subjects, the nocturnal peak of secretion of TNF-α is replaced by an abnormal daytime peak, thus altering the secretion rhythm of TNF-α [93]. As these alterations persist after a 3-month treatment with CPAP, it is likely that they require much more time to regress. TNF-α might cause the apneic events by promoting the dysfunction of the upper airway muscles [59]. On the other hand, interleukin (IL)-6 is also produced by the adipose tissue and circulating monocytes through the NF-κB pathway during nocturnal hypoxia [58, 94]. IL-6 represents a major stimulant of CRP production in the liver [95] and might modulate inflammatory processes in sleep disorders. Differently from TNF-α, IL-6 circadian rhythm is not altered in OSAS [93]. Although elevated levels of IL-6 has been shown in OSAS subjects as compared to healthy controls and a significant improvement after CPAP treatment [35, 58, 90, 91, 96], other studies did not confirm the potential role of this cytokine (mainly after covariate analysis and adjustment for BMI) probably because of a less severe OSAS included in the studies (mean apnea–hypopnea index, AHI=22.8/h) [57, 97–99]. Nevertheless, Zhang and co-workers have recently showed that genetic variants of the IL-6 gene confer different susceptibility to develop OSAS, thus suggesting a potential approach to assess the risk for OSAS [100].

The alteration of CRP levels in OSAS obese patients remains controversial, mainly because of the relationship between CRP and BMI [101]. Nevertheless, studies showed that in OSAS subjects, CRP levels are independently associated with the severity of the disease [35, 55, 58, 69, 102–108]. Importantly, 1-month treatment with CPAP significantly reduces CRP levels. More recently, increased levels of CRP were associated with OSAS in obese men independently of adiposity [109]. CRP levels also correlate with the degree of nocturnal hypoxemia independently of obesity [110]. Larkin and co-workers recently showed that an AHI ≥5 is associated with increased CRP serum levels in adolescents without known cardiovascular diseases. The relationship between CRP and sleep-disordered breathing was also confirmed after adjustment of important covariates (including BMI, hypertension, waist-to-hip ratio, and lipid profile) [104]. Conversely, these interesting associations were not confirmed by other studies [96, 111–116]. Larger and controlled studies are needed to better understand the role of CRP-mediated effects in the OSAS pathophysiology.

Elevated levels of IL-8 and monocytes chemoattractant protein (MCP)-1 have been shown in patients with OSAS [57, 76, 114, 117]. IL-8 is also reduced by 6-week treatment with CPAP [57]. Chemokines might play a pivotal role in the pathogenesis of the cardiovascular complications of OSAS through their crucial activation of neutrophils and monocytes [118, 119]. In particular, increased serum levels of leukocyte proteases (such as matrix metalloproteinase [MMP]-9) have been found in OSAS [120].

A relationship between the acute phase reactant serum amyloid A (SAA) and the degree of OSAS has been also shown. Furthermore, SAA levels have been reduced by CPAP treatment [121].

Leptin is the product of the *obese* gene in the adipocytes and mediates several functions such as the regulation of food intake, the energy balance, and the regulation of lipid and glucose metabolism [122, 123]. In obesity (a condition known as leptin resistance), leptin levels are increased [124, 125]. Leptin activates inflammation and mediates cellular damage synergistically with IH in a rabbit model of OSAS [78]. Although the major inducing factor for leptin production is visceral obesity [112], hypoxia might increase leptin production [126–128]. Furthermore, leptin correlates with OSAS independently of obesity [129–133]. Kapsimalis and co-workers confirmed that nocturnal hypoxemia is associated with leptin independently of obesity [112]. Conversely, other studies did not show a significant association between leptin levels and OSAS after adjustment for obesity [134–137].

Homocysteine is a product of the metabolism of the aminoacid methionine and increases the risk of arterial occlusive disease [138] causing endothelial dysfunction [3, 139–141]. Controversial data have been reported on homocysteine levels in OSAS. Some studies indicate that homocysteine is increased in OSAS subjects with cardiovascular disease (CAD) in comparison with OSAS subjects without CAD and with healthy controls [102, 142]. Accordingly, CPAP treatment reduces homocysteine concentrations [143]. Conversely, other studies did not confirm this association [62, 144]. Finally, studies on insulin [110, 145–147] and adiponectin [132, 147–150] also showed controversial results. Further studies are needed to better address the role of these inflammatory cardiovascular risk markers in OSAS.

Endothelial dysfunction

Endothelium regulates the vascular tone and maintains the pro-/anti-inflammatory equilibrium in the vessel wall. Alterations of the normal homeostasis of the vascular wall represent early signs of cardiovascular diseases [151]. Recent studies have demonstrated that OSAS significantly affects the endothelial function. Indeed, endothelium-

dependent vasodilation in response to acetylcholine is reduced in OSAS patients in comparison with age- and BMI-matched healthy subjects [152, 153]. Flow-mediated vasodilation is impaired in OSAS with a direct correlation with the severity of the hypoxemia [154]. The normal function of the endothelium depends on the bioavailability of NO. In OSAS, reduced levels of circulating NO [155, 156] and elevated concentrations of endothelial NO synthase inhibitor have been shown, as compared to healthy controls [157].

The mechanisms by which OSAS might affect the endothelial function are dependent on IH and sleep fragmentation [158]. As mentioned above, IH causes a reduction of NO production by affecting the transcriptional and post-transcriptional pathways and by increasing the production of ROS. ROS could react with NO, further reducing its availability and enhance the oxidative stress. Moreover, IH up-regulates cyclooxygenase-2 (COX-2), VEGF, endothelin-1, and iNOS, which might further alter the functional integrity of the endothelium [80–87]. Sleep fragmentation is associated with 50% reduction of the flow-mediated vasodilation [159]. Several studies show increased inflammation, activation of the sympathetic tone, and hypercoagulability during repetitive arousals from sleep during OSAS [160–162]. Accordingly, treatment with CPAP reverses endothelial dysfunction [163].

Endothelial dysfunction could be a key element in atheroprogression in OSAS. Further efforts should be done in order to better understand and possibly prevent endothelial dysfunction in OSAS.

Conclusions

Despite its underestimation, OSAS should be considered a serious disease involving not only the respiratory system but also having cardiovascular and cerebral implications. The promotion of atherogenesis through oxidative stress, inflammation, and endothelial dysfunction is still a matter of debate. Intermittent hypoxia is the distinctive element of OSAS and could play a pivotal role in triggering cardiovascular inflammation. The treatment with CPAP represents a very promising therapeutic strategy to clinically improve OSAS and reduce the associated oxidative stress, cardiovascular inflammation, and endothelial dysfunction. Larger randomized clinical studies are still needed to identify more selective cardiovascular risk markers in OSAS.

Acknowledgments François Mach and Fabrizio Montecucco equally contributed as last authors to this work. This work was funded by EU FP7, Grant Number 201668, AtheroRemo and supported by a grant from the Swiss National Science Foundation to Dr. F. Mach (#310030-118245).

References

1. Shamsuzzaman AS, Gersh BJ, Somers VK (2003) Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 290:1906–1914
2. Phillipson EA (1993) Sleep apnea—a major public health problem. N Engl J Med 328:1271–1273
3. Yamauchi M, Kimura H (2008) Oxidative stress in obstructive sleep apnea: putative pathways to the cardiovascular complications. Antioxid Redox Signal 10:755–768
4. Ryan S, McNicholas WT (2008) Intermittent hypoxia and activation of inflammatory molecular pathways in OSAS. Arch Physiol Biochem 114:261–266
5. McNicholas WT (2009) Obstructive sleep apnea and inflammation. Prog Cardiovasc Dis 51:392–399
6. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM (2009) Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 6:e1000132
7. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG (2000) Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 283:1829–1836
8. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, Leung RS, Bradley TD (2001) High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 19:2271–2277
9. Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G (2006) Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 37:2317–2321
10. Yaggi H, Mohsenin V (2004) Obstructive sleep apnoea and stroke. Lancet Neurol 3:333–342
11. Portela PC, Fumado JC, Garcia HQ, Borrego FR (2009) Sleep-disordered breathing and acute stroke. Cerebrovasc Dis 27(Suppl 1):104–110
12. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V (2005) Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 353:2034–2041
13. Peker Y, Hedner J, Kraiczi H, Loth S (2000) Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med 162:81–86
14. Hung J, Whitford EG, Parsons RW, Hillman DR (1990) Association of sleep apnoea with myocardial infarction in men. Lancet 336:261–264
15. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O'Connor GT, Boland LL, Schwartz JE, Samet JM (2001) Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the sleep heart health study. Am J Respir Crit Care Med 163:19–25
16. Marin JM, Carrizo SJ, Vicente E, Agusti AG (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365:1046–1053
17. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD (1994) Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 149:416–422
18. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM (2008) Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 31:1071–1078
19. Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB (1996) Investigating the relationship between stroke and obstructive sleep apnea. Stroke 27:401–407

20. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 342:1378–1384
21. Lorenzi-Filho G, Drager LF (2007) Obstructive sleep apnea and atherosclerosis: a new paradigm. Am J Respir Crit Care Med 175:1219–1221
22. Kyzer S, Charuzi I (1998) Obstructive sleep apnea in the obese. World J Surg 22:998–1001
23. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328:1230–1235
24. Flemons WW (2002) Clinical practice. Obstructive sleep apnea. N Engl J Med 347:498–504
25. Wysocka E, Cofta S, Cymerys M, Gozdzik J, Torlinski L, Batura-Gabryel H (2008) The impact of the sleep apnea syndrome on oxidant–antioxidant balance in the blood of overweight and obese patients. J Physiol Pharmacol 59(Suppl 6):761–769
26. Young T, Peppard PE, Gottlieb DJ (2002) Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 165:1217–1239
27. He J, Kryger MH, Zorick FJ, Conway W, Roth T (1988) Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. Chest 94:9–14
28. Partinen M, Jamieson A, Guilleminault C (1998) Long-term outcome for obstructive sleep apnea syndrome patients. Mortality Chest 94:1200–1204
29. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR (2008) Sleep apnea as an independent risk factor for all-cause mortality: the Busselton health study. Sleep 31:1079–1085
30. Doherty LS, Kiely JL, Swan V, McNicholas WT (2005) Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest 127:2076–2084
31. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M (1999) An independent association between obstructive sleep apnoea and coronary artery disease. Eur Respir J 14:179–184
32. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U (2001) Sleep-disordered breathing and coronary artery disease: long-term prognosis. Am J Respir Crit Care Med 164:1910–1913
33. Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H (2007) Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. Am J Cardiol 99:26–30
34. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G (2005) Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 172:613–618
35. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, Okada S, Ohta S, Naito H, Adachi M (2005) Increased carotid intima–media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med 172:625–630
36. Baguet JP, Hammer L, Levy P, Pierre H, Launois S, Mallion JM, Pepin JL (2005) The severity of oxygen desaturation is predictive of carotid wall thickening and plaque occurrence. Chest 128:3407–3412
37. Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G (2007) Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. Chest 131:1379–1386
38. Guilleminault C, Simmons FB, Motta J, Cummiskey J, Rosekind M, Schroeder JS, Dement WC (1981) Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. Arch Intern Med 141:985–988
39. Kales A, Bixler EO, Cadieux RJ, Schneck DW, Shaw LC 3rd, Locke TW, Vela-Bueno A, Soldatos CR (1984) Sleep apnoea in a hypertensive population. Lancet 2:1005–1008
40. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB (1985) Undiagnosed sleep apnea in patients with essential hypertension. Ann Intern Med 103:190–195
41. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A (2000) Association of hypertension and sleep-disordered breathing. Arch Intern Med 160:2289–2295
42. Parish JM, Somers VK (2004) Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 79:1036–1046
43. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ (2002) Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 359:204–210
44. Faccenda JF, Mackay TW, Boon NA, Douglas NJ (2001) Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea–hypopnea syndrome. Am J Respir Crit Care Med 163:344–348
45. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH (2003) Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 107:68–73
46. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J, Merino-Sanchez M, Gonzalez-Benitez MA, Beltran-Robles M, Almeida-Gonzalez C (2006) Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. Chest 129:1459–1467
47. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S (1996) Sleep-disordered breathing and poor functional outcome after stroke. Stroke 27:252–259
48. Guilleminault C, Connolly SJ, Winkle RA (1983) Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 52:490–494
49. Shepard JW Jr, Garrison MW, Grither DA, Dolan GF (1985) Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. Chest 88:335–340
50. Weitzenblum E, Krieger J, Apprill M, Vallee E, Ehrhart M, Ratomaharo J, Oswald M, Kurtz D (1988) Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 138:345–349
51. Sanner BM, Doberauer C, Konermann M, Sturm A, Zidek W (1997) Pulmonary hypertension in patients with obstructive sleep apnea syndrome. Arch Intern Med 157:2483–2487
52. Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S, Jordanoglou JB (2001) Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics. Respiration 68:566–572
53. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD (1991) Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 338:1480–1484
54. Naughton MT (1998) Impact of treatment of sleep apnoea on left ventricular function in congestive heart failure. Thorax 53(Suppl 3):S37–S40
55. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK (2002) Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 105:2462–2464
56. Minoguchi K, Tazaki T, Yokoe T, Minoguchi H, Watanabe Y, Yamamoto M, Adachi M (2004) Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome. Chest 126:1473–1479

57. Ryan S, Taylor CT, McNicholas WT (2006) Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 174:824–830
58. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T, Adachi M (2003) 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 107:1129–1134
59. Dean RT, Wilcox I (1993) Possible atherogenic effects of hypoxia during obstructive sleep apnea. Sleep 16:S15–S21
60. Hatipoglu U, Rubinstein I (2003) Inflammation and obstructive sleep apnea syndrome pathogenesis: a working hypothesis. Respiration 70:665–671
61. Lattimore JD, Celermajer DS, Wilcox I (2003) Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 41:1429–1437
62. Lavie L (2003) Obstructive sleep apnoea syndrome—an oxidative stress disorder. Sleep Med Rev 7:35–51
63. Asehnoune K, Strassheim D, Mitra S, Kim JY, Abraham E (2004) Involvement of reactive oxygen species in Toll-like receptor 4-dependent activation of NF-kappa B. J Immunol 172:2522–2529
64. Christou K, Markoulis N, Moulas AN, Pastaka C, Gourgoulianis KI (2003) Reactive oxygen metabolites (ROMs) as an index of oxidative stress in obstructive sleep apnea patients. Sleep Breath 7:105–110
65. Suzuki YJ, Jain V, Park AM, Day RM (2006) Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. Free Radic Biol Med 40:1683–1692
66. Barcelo A, Miralles C, Barbe F, Vila M, Pons S, Agusti AG (2000) Abnormal lipid peroxidation in patients with sleep apnoea. Eur Respir J 16:644–647
67. Lavie L, Vishnevsky A, Lavie P (2004) Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 27:123–128
68. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ (2003) 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. Chest 124:1386–1392
69. Minoguchi K, Yokoe T, Tanaka A, Ohta S, Hirano T, Yoshino G, O'Donnell CP, Adachi M (2006) Association between lipid peroxidation and inflammation in obstructive sleep apnoea. Eur Respir J 28:378–385
70. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F (2000) Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. Am J Respir Crit Care Med 162:566–570
71. Yamamoto H, Teramoto S, Yamaguchi Y, Ouchi Y (2007) Effect of nasal continuous positive airway pressure treatment on plasma adrenomedullin levels in patients with obstructive sleep apnea syndrome: roles of nocturnal hypoxia and oxidant stress. Hypertens Res 30:1065–1076
72. Ryan S, Taylor CT, McNicholas WT (2005) Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 112:2660–2667
73. Greenberg H, Ye X, Wilson D, Htoo AK, Hendersen T, Liu SF (2006) Chronic intermittent hypoxia activates nuclear factor-kappaB in cardiovascular tissues in vivo. Biochem Biophys Res Commun 343:591–596
74. Ayas NT, Mancini GB, Fleetham J (2006) Does CPAP delay the development of cardiovascular disease in patients with obstructive sleep apnoea hypopnoea? Thorax 61:459–460
75. Htoo AK, Greenberg H, Tongia S, Chen G, Henderson T, Wilson D, Liu SF (2006) Activation of nuclear factor kappaB in obstructive sleep apnea: a pathway leading to systemic inflammation. Sleep Breath 10:43–50
76. Alzoghaibi MA, Bahammam AS (2005) Lipid peroxides, superoxide dismutase and circulating IL-8 and GCP-2 in patients with severe obstructive sleep apnea: a pilot study. Sleep Breath 9:119–126
77. Yamauchi M, Tamaki S, Tomoda K, Yoshikawa M, Fukuoka A, Makinodan K, Koyama N, Suzuki T, Kimura H (2006) Evidence for activation of nuclear factor kappaB in obstructive sleep apnea. Sleep Breath 10:189–193
78. Feng J, Chen BY, Cui LY, Wang BL, Liu CX, Chen PF, Guo MN, Dong LX, Li S (2009) Inflammation status of rabbit carotid artery model endothelium during intermittent hypoxia exposure and its relationship with leptin. Sleep Breath 13:277–283
79. Schofield CJ, Ratcliffe PJ (2004) Oxygen sensing by HIF hydroxylases. Nat Rev Mol Cell Biol 5:343–354
80. Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F (2002) Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. Am J Respir Crit Care Med 165:67–70
81. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK (1999) Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens 17:61–66
82. Manalo DJ, Rowan A, Lavoie T, Natarajan L, Kelly BD, Ye SQ, Garcia JG, Semenza GL (2005) Transcriptional regulation of vascular endothelial cell responses to hypoxia by HIF-1. Blood 105:659–669
83. Semenza G (2000) Oxygen-regulated transcription factors and their role in pulmonary disease. Respir Res 1:159–162
84. Gjorup PH, Sadauskiene L, Wessels J, Nyvad O, Strunge B, Pedersen EB (2007) Abnormally increased endothelin-1 in plasma during the night in obstructive sleep apnea: relation to blood pressure and severity of disease. Am J Hypertens 20:44–52
85. Saarelainen S, Seppala E, Laasonen K, Hasan J (1997) Circulating endothelin-1 in obstructive sleep apnea. Endothelium 5:115–118
86. Imagawa S, Yamaguchi Y, Higuchi M, Neichi T, Hasegawa Y, Mukai HY, Suzuki N, Yamamoto M, Nagasawa T (2001) Levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea–hypopnea syndrome. Blood 98:1255–1257
87. Lavie L, Kraiczi H, Hefetz A, Ghandour H, Perelman A, Hedner J, Lavie P (2002) Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. Am J Respir Crit Care Med 165:1624–1628
88. Moldofsky H, Lue FA, Eisen J, Keystone E, Gorczynski RM (1986) The relationship of interleukin-1 and immune functions to sleep in humans. Psychosom Med 48:309–318
89. Krueger JM, Obal F Jr (1994) In: Saunders NA, Sullivan CE (eds) Sleep factors. Sleep and breathing. Marcel Dekker, New York, pp 79–112
90. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP (1997) Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 82:1313–1316
91. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP (2000) Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 85:1151–1158
92. Steiropoulos P, Kotsianidis I, Nena E, Tsara V, Gounari E, Hatzizisi O, Kyriazis G, Christaki P, Froudarakis M, Bouros D (2009) Long-term effect of continuous positive airway pressure therapy on inflammation markers of patients with obstructive sleep apnea syndrome. Sleep 32:537–543
93. Entzian P, Linnemann K, Schlaak M, Zabel P (1996) Obstructive sleep apnea syndrome and circadian rhythms of hormones and cytokines. Am J Respir Crit Care Med 153:1080–1086

94. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW (1997) Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 82:4196–4200
95. Heinrich PC, Castell JV, Andus T (1990) Interleukin-6 and the acute phase response. Biochem J 265:621–636
96. Kobayashi K, Nishimura Y, Shimada T, Yoshimura S, Funada Y, Satouchi M, Yokoyama M (2006) Effect of continuous positive airway pressure on soluble CD40 ligand in patients with obstructive sleep apnea syndrome. Chest 129:632–637
97. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP (2004) Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. J Clin Endocrinol Metab 89:4409–4413
98. Ueda K, Takahashi M, Ozawa K, Kinoshita M (1999) Decreased soluble interleukin-6 receptor in patients with acute myocardial infarction. Am Heart J 138:908–915
99. Al Lawati N, Mulgrew A, Cheema R, Vaneeden S, Butt A, Fleetham J, Ryan F, Ayas N (2009) Pro-atherogenic cytokine profile of patients with suspected obstructive sleep apnea. Sleep Breath 13:391–395
100. Zhang X, Liu RY, Lei Z, Zhu Y, Huang JA, Jiang X, Liu Z, Liu X, Peng X, Hu H, Zhang HT (2009) Genetic variants in interleukin-6 modified risk of obstructive sleep apnea syndrome. Int J Mol Med 23:485–493
101. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB (1999) Elevated C-reactive protein levels in overweight and obese adults. JAMA 282:2131–2135
102. Can M, Acikgoz S, Mungan G, Bayraktaroglu T, Kocak E, Guven B, Demirtas S (2006) Serum cardiovascular risk factors in obstructive sleep apnea. Chest 129:233–237
103. Hayashi M, Fujimoto K, Urushibata K, Takamizawa A, Kinoshita O, Kubo K (2006) Hypoxia-sensitive molecules may modulate the development of atherosclerosis in sleep apnoea syndrome. Respirology 11:24–31
104. Larkin EK, Rosen CL, Kirchner HL, Storfer-Isser A, Emancipator JL, Johnson NL, Zambito AM, Tracy RP, Jenny NS, Redline S (2005) Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. Circulation 111:1978–1984
105. Tauman R, Ivanenko A, O'Brien LM, Gozal D (2004) Plasma C-reactive protein levels among children with sleep-disordered breathing. Pediatrics 113:e564–e569
106. Yao M, Tachibana N, Okura M, Ikeda A, Tanigawa T, Yamagishi K, Sato S, Shimamoto T, Iso H (2006) The relationship between sleep-disordered breathing and high-sensitivity C-reactive protein in Japanese men. Sleep 29:661–665
107. Zouaoui Boudjeltia K, Van Meerhaeghe A, Doumit S, Guillaume M, Cauchie P, Brohee D, Vanhaeverbeek M, Kerkhofs M (2006) Sleep apnoea–hypopnoea index is an independent predictor of high-sensitivity C-reactive protein elevation. Respiration 73:243–246
108. Kokturk O, Ciftci TU, Mollarecep E, Ciftci B (2005) Elevated C-reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome. Int Heart J 46:801–809
109. Punjabi NM, Beamer BA (2007) C-reactive protein is associated with sleep disordered breathing independent of adiposity. Sleep 30:29–34
110. Kapsimalis F, Varouchakis G, Manousaki A, Daskas S, Nikita D, Kryger M, Gourgoulianis K (2008) Association of sleep apnea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea. Lung 186:209–217
111. Chung S, Yoon IY, Lee CH, Kim JW (2010) The effects of nasal continuous positive airway pressure on vascular functions and serum cardiovascular risk factors in obstructive sleep apnea syndrome. Sleep Breath. doi:10.1007/s11325-009-0323-x
112. Ryan S, Nolan GM, Hannigan E, Cunningham S, Taylor C, McNicholas WT (2007) Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. Thorax 62:509–514
113. Guilleminault C, Kirisoglu C, Ohayon MM (2004) C-reactive protein and sleep-disordered breathing. Sleep 27:1507–1511
114. Kaditis AG, Alexopoulos EI, Kalampouka E, Kostadima E, Germenis A, Zintzaras E, Gourgoulianis K (2005) Morning levels of C-reactive protein in children with obstructive sleep-disordered breathing. Am J Respir Crit Care Med 171:282–286
115. Taheri S, Austin D, Lin L, Nieto FJ, Young T, Mignot E (2007) Correlates of serum C-reactive protein (CRP)—no association with sleep duration or sleep disordered breathing. Sleep 30:991–996
116. Kohler M, Ayers L, Pepperell JC, Packwood KL, Ferry B, Crosthwaite N, Craig S, Siccoli MM, Davies RJ, Stradling JR (2009) 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
117. Ohga E, Tomita T, Wada H, Yamamoto H, Nagase T, Ouchi Y (2003) Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. J Appl Physiol 94:179–184
118. Gerszten RE, Garcia-Zepeda EA, Lim YC, Yoshida M, Ding HA, Gimbrone MA Jr, Luster AD, Luscinskas FW, Rosenzweig A (1999) MCP-1 and IL-8 trigger firm adhesion of monocytes to vascular endothelium under flow conditions. Nature 398:718–723
119. Aukrust P, Yndestad A, Smith C, Ueland T, Gullestad L, Damås JK (2007) Chemokines in cardiovascular risk prediction. Thromb Haemost 97:748–754
120. Tazaki T, Minoguchi K, Yokoe T, Samson KT, Minoguchi H, Tanaka A, Watanabe Y, Adachi M (2004) Increased levels and activity of matrix metalloproteinase-9 in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 170:1354–1359
121. Kuramoto E, Kinami S, Ishida Y, Shiotani H, Nishimura Y (2009) Continuous positive nasal airway pressure decreases levels of serum amyloid A and improves autonomic function in obstructive sleep apnea syndrome. Int J Cardiol 135:338–345
122. Klein S, Coppack SW, Mohamed-Ali V, Landt M (1996) Adipose tissue leptin production and plasma leptin kinetics in humans. Diabetes 45:984–987
123. Schwartz MW, Seeley RJ (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Neuroendocrine responses to starvation and weight loss. N Engl J Med 336:1802–1811
124. Münzberg H, Björnholm M, Bates SH, Myers MG Jr (2005) Leptin receptor action and mechanisms of leptin resistance. Cell Mol Life Sci 62:642–652
125. Cinaz P, Bideci A, Camurdan MO, Güven A, Gönen S (2005) Leptin and soluble leptin receptor levels in obese children in fasting and satiety states. J Pediatr Endocrinol Metab 18:303–307
126. Grosfeld A, Andre J, Hauguel-De Mouzon S, Berra E, Pouyssegur J, Guerre-Millo M (2002) Hypoxia-inducible factor 1 transactivates the human leptin gene promoter. J Biol Chem 277:42953–42957
127. Meissner U, Hänisch C, Ostreicher I, Knerr I, Hofbauer KH, Blum WF, Allabauer I, Rascher W, Dötsch J (2005) Differential regulation of leptin synthesis in rats during short-term hypoxia and short-term carbon monoxide inhalation. Endocrinology 146:215–220
128. Finck BN, Johnson RW (2000) Tumor necrosis factor-alpha regulates secretion of the adipocyte-derived cytokine, leptin. Microsc Res Tech 50:209–215
129. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK (2000) Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. Am J Physiol Heart Circ Physiol 279: H234–H237

130. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M (1999) Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 100:706–712
131. Ozturk L, Unal M, Tamer L, Celikoglu F (2003) The association of the severity of obstructive sleep apnea with plasma leptin levels. Arch Otolaryngol Head Neck Surg 129:538–540
132. Tokuda F, Sando Y, Matsui H, Koike H, Yokoyama T (2008) Serum levels of adipocytokines, adiponectin and leptin, in patients with obstructive sleep apnea syndrome. Intern Med 47:1843–1849
133. Ip MS, Lam KS, Ho C, Tsang KW, Lam W (2000) Serum leptin and vascular risk factors in obstructive sleep apnea. Chest 118:580–586
134. Schafer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S, Berthold HK (2002) Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest 122:829–839
135. Sanner BM, Kollhosser P, Buechner N, Zidek W, Tepel M (2004) Influence of treatment on leptin levels in patients with obstructive sleep apnoea. Eur Respir J 23:601–604
136. Barcelo A, Barbe F, Llompart E, de la Pena M, Duran-Cantolla J, Ladaria A, Bosch M, Guerra L, Agusti AG (2005) Neuropeptide Y and leptin in patients with obstructive sleep apnea syndrome: role of obesity. Am J Respir Crit Care Med 171:183–187
137. Harsch IA, Konturek PC, Koebnick C, Kuehnlein PP, Fuchs FS, Pour Schahin S, Wiest GH, Hahn EG, Lohmann T, Ficker JH (2003) Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. Eur Respir J 22:251–257
138. Townend J, O'Sullivan J, Wilde JT (1998) Hyperhomocysteinaemia and vascular disease. Blood Rev 12:23–34
139. Dudman NP, Hicks C, Lynch JF, Wilcken DE, Wang J (1991) Homocysteine thiolactone disposal by human arterial endothelial cells and serum in vitro. Arterioscler Thromb 11:663–670
140. Wall RT, Harlan JM, Harker LA, Striker GE (1980) Homocysteine-induced endothelial cell injury in vitro: a model for the study of vascular injury. Thromb Res 18:113–121
141. Jamler JS, Osborne JA, Jaraki O, Rabbani LE, Mullins M, Singel D, Loscalzo J (1993) Adverse vascular effects of homocysteine are modulated by endothelium-derived relaxing factor and related oxides of nitrogen. J Clin Invest 91:308–318
142. Kokturk O, Ciftci TU, Mollarecep E, Ciftci B (2006) Serum homocysteine levels and cardiovascular morbidity in obstructive sleep apnea syndrome. Respir Med 100:536–541
143. Jordan W, Berger C, Cohrs S, Rodenbeck A, Mayer G, Niedmann PD, von Ahsen N, Ruther E, Kornhuber J, Bleich S (2004) CPAP-therapy effectively lowers serum homocysteine in obstructive sleep apnea syndrome. J Neural Transm 111:683–689
144. Svatikova A, Wolk R, Magera MJ, Shamsuzzaman AS, Phillips BG, Somers VK (2004) Plasma homocysteine in obstructive sleep apnoea. Eur Heart J 25:1325–1329
145. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS (2002) Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 165:670–676
146. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL (2002) Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 165:677–682
147. Makino S, Handa H, Suzukawa K, Fujiwara M, Nakamura M, Muraoka S, Takasago I, Tanaka Y, Hashimoto K, Sugimoto T (2006) Obstructive sleep apnoea syndrome, plasma adiponectin levels, and insulin resistance. Clin Endocrinol (Oxf) 64:12–19
148. Harsch IA, Wallaschofski H, Koebnick C, Pour Schahin S, Hahn EG, Ficker JH, Lohmann T (2004) Adiponectin in patients with obstructive sleep apnea syndrome: course and physiological relevance. Respiration 71:580–586
149. Masserini B, Morpurgo PS, Donadio F, Baldessari C, Bossi R, Beck-Peccoz P, Orsi E (2006) Reduced levels of adiponectin in sleep apnea syndrome. J Endocrinol Invest 29:700–705
150. Kanbay A, Kokturk O, Ciftci TU, Tavil Y, Bukan N (2008) Comparison of serum adiponectin and tumor necrosis factor-alpha levels between patients with and without obstructive sleep apnea syndrome. Respiration 76:324–330
151. Aird WC (2007) Phenotypic heterogeneity of the endothelium: II. Representative vascular beds. Circ Res 100:174–190
152. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK (2000) Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 102:2607–2610
153. Carlson JT, Rangemark C, Hedner JA (1996) Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. J Hypertens 14:577–584
154. Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA (2004) Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. Am J Respir Crit Care Med 169:354–360
155. Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, Lam WK (2000) Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med 162:2166–2171
156. Schulz R, Schmidt D, Blum A, Lopes-Ribeiro X, Lucke C, Mayer K, Olschewski H, Seeger W, Grimminger F (2000) Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy. Thorax 55:1046–1051
157. Ohike Y, Kozaki K, Iijima K, Eto M, Kojima T, Ohga E, Santa T, Imai K, Hashimoto M, Yoshizumi M, Ouchi Y (2005) Amelioration of vascular endothelial dysfunction in obstructive sleep apnea syndrome by nasal continuous positive airway pressure—possible involvement of nitric oxide and asymmetric NG, NG-dimethylarginine. Circ J 69:221–226
158. Atkeson A, Yeh SY, Malhotra A, Jelic S (2009) Endothelial function in obstructive sleep apnea. Prog Cardiovasc Dis 51:351–362
159. Takase B, Akima T, Uehata A, Ohsuzu F, Kurita A (2004) Effect of chronic stress and sleep deprivation on both flow-mediated dilation in the brachial artery and the intracellular magnesium level in humans. Clin Cardiol 27:223–227
160. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM (2004) Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol 43:678–683
161. Mausbach BT, Ancoli-Israel S, von Känel R, Patterson TL, Aschbacher K, Mills PJ, Ziegler MG, Dimsdale JE, Calleran S, Grant I (2006) Sleep disturbance, norepinephrine, and D-dimer are all related in elderly caregivers of people with Alzheimer disease. Sleep 29:1347–1352
162. von Känel R, Loredo JS, Ancoli-Israel S, Mills PJ, Natarajan L, Dimsdale JE (2007) Association between polysomnographic measures of disrupted sleep and prothrombotic factors. Chest 131:733–739
163. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK (2004) Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med 169:348–353