

STATE-OF-THE-ART PAPER

Obstructive Sleep Apnea

A Cardiometabolic Risk in Obesity and the Metabolic Syndrome

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Obstructive sleep apnea (OSA) is an underdiagnosed condition characterized by recurrent episodes of obstruction of the upper airway leading to sleep fragmentation and intermittent hypoxia during sleep. Obesity predisposes to OSA, and the prevalence of OSA is increasing worldwide because of the ongoing epidemic of obesity. Recent evidence has shown that surrogate markers of cardiovascular risk, including sympathetic activation, systemic inflammation, and endothelial dysfunction, are significantly increased in obese patients with OSA versus those without OSA, suggesting that OSA is not simply an epiphenomenon of obesity. Moreover, findings from animal models and patients with OSA show that intermittent hypoxia exacerbates the metabolic dysfunction of obesity, augmenting insulin resistance and nonalcoholic fatty liver disease. In patients with the metabolic syndrome, the prevalence of moderate to severe OSA is very high (~60%). In this population, OSA is independently associated with increased glucose and triglyceride levels as well as markers of inflammation, arterial stiffness, and atherosclerosis. A recent randomized, controlled, crossover study showed that effective treatment of OSA with continuous positive airway pressure for 3 months significantly reduced several components of the metabolic syndrome, including blood pressure, triglyceride levels, and visceral fat. Finally, several cohort studies have consistently shown that OSA is associated with increased cardiovascular mortality, independent of obesity. Taken together, these results support the concept that OSA exacerbates the cardiometabolic risk attributed to obesity and the metabolic syndrome. Recognition and treatment of OSA may decrease the cardiovascular risk in obese patients. (J Am Coll Cardiol 2013;62:569–76) © 2013 by the American College of Cardiology Foundation

Obstructive sleep apnea (OSA) is a clinical condition characterized by recurrent episodes of complete obstruction (apnea) or partial obstruction (hypopnea) of the upper airway, leading to increased negative intrathoracic pressure, sleep fragmentation, and intermittent hypoxia during sleep (1). Research on the current prevalence of OSA indicated that one-third of sleep studies showed some degree of OSA (apnea-hypopnea index ≥ 5 events per hour of sleep) (2). Among adults 30 to 70 years of age, approximately 13% of men and 6% of women have moderate to severe forms of OSA (apnea-hypopnea index ≥ 15 events per hour of sleep) (2). Comparing data from 2 decades ago (3), the current estimates represent an increase of millions of additional afflicted persons and are mainly explained by the ongoing obesity epidemic. Overall, it is estimated that 50% to 60% of people who are obese and patients with the metabolic

syndrome have OSA (4,5). The prevalence of OSA is even higher in obese patients with diabetes mellitus (6) and morbid obesity (7). Despite such an overwhelming association, OSA remains unrecognized in the vast majority of these patients with high pre-test probability of OSA (8).

Why is OSA so common in patients with obesity and the metabolic syndrome? Several anatomic and functional factors predispose to OSA. Patients with OSA are able to compensate for the upper airway narrowing by increasing the activity of upper airway muscles that maintain airway patency during wakefulness (9). In contrast, this protective effect is lost during sleep, when relaxation of the muscles occurs and obstruction of the upper airways prevails. Obesity is a major risk factor for OSA because it promotes enlargement of soft tissue structures within and surrounding the airway, thereby contributing significantly to pharyngeal airway narrowing (10,11). An excess of fat deposition has also been observed under the mandible and in the tongue, soft palate, and uvula (9,12). Beyond the direct effects on the upper airway, obesity also contributes indirectly to upper airway narrowing during sleep. Lung volumes are markedly reduced by a combination of increased abdominal fat mass and recumbent posture. Reduction of lung volume may decrease longitudinal tracheal traction forces and pharyngeal wall tension, which

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**Abbreviations
and Acronyms**

BMI = body mass index
CPAP = continuous positive airway pressure
eNOS = endothelial nitric oxide synthase
NAFLD = nonalcoholic fatty liver disease
NO = nitric oxide
OSA = obstructive sleep apnea

predisposes to narrowing of the airway (Fig. 1) (13). In addition, obesity-related leptin resistance may impair the neuroanatomic interactions necessary for stable breathing, thereby contributing to the genesis of OSA (14).

The concept that OSA may be part of the metabolic syndrome is not new. In 1998, Wilcox *et al.* proposed the name “syndrome Z” for the combination of the metabolic syndrome (syndrome X) and OSA to reflect the close

association of components of the metabolic syndrome with OSA (15). Since then, a major challenge to the field has been to understand whether OSA is a mere epiphenomenon or an additional burden that exacerbates the cardiometabolic risk of obesity and the metabolic syndrome. In the present review, we discuss recent evidence supporting the independent role of OSA in these scenarios. Because of space limitations, the cardiometabolic risk of obesity and the metabolic syndrome *per se* are not discussed in this review.

Can OSA Have Independent Effects on the Cardiometabolic Risk Attributed to Obesity and the Metabolic Syndrome?

Clinical and epidemiological studies have reported an independent association between OSA and cardiovascular events, suggesting that OSA may lead to cardiometabolic dysregulation (16–18). Studies in mice showed that a short-term regimen of intermittent hypoxia (a hallmark of OSA) caused large-amplitude oxygen swings in the liver, mirroring swings of SpO₂, whereas fluctuations of oxygen levels were attenuated in muscle and nearly abolished in adipose tissue

in both lean and obese mice (19). The data in the animal model suggest that OSA exacerbates hypoxia at the tissue level (19). The amplification of hypoxia in the adipose tissue may represent an important mechanism of cardiometabolic dysfunction in OSA because it is a major trigger of lipolysis, chronic inflammation, macrophage infiltration, reduction of adiponectin level, elevation of leptin level, adipocyte death, endoplasmic reticulum stress, and mitochondrial dysfunction (20). Despite clinical and experimental evidence, the vast majority of clinical studies that evaluated the impact of obesity and the metabolic syndrome on cardiovascular burden failed to consider OSA a potential confounding factor. Reflecting this gap, the American Heart Association Scientific Statement on metabolic syndrome referred to OSA in the section of “other fields of medicine,” with the same attention given to cholesterol gallstones and lipodystrophies (21). This may reflect a low awareness of OSA in the cardiovascular field associated with the perception that OSA is merely an epiphenomenon of obesity. For didactic purposes, we present the evidence linking OSA to cardiometabolic dysregulation in separate sections.

Metabolic dysregulation. An independent association between OSA, insulin resistance, and type 2 diabetes has been consistently demonstrated by a number of cross-sectional studies, observational studies, and large population-based studies (22–25). Moreover, the development of insulin resistance and pancreatic beta cell dysfunction has been linked to chronic intermittent hypoxemia observed in OSA (26). Even mild recurrent oxyhemoglobin desaturations (>2%) were independently associated with metabolic dysfunction (27). The causal role of intermittent hypoxia in insulin resistance has been further proven in a mouse model of OSA. Lean C57BL/6J mice developed insulin resistance acutely after several hours of hypoxic exposure (28). Chronic intermittent hypoxia exacerbated fasting hyperglycemia, glucose intolerance, and insulin resistance in both mice with

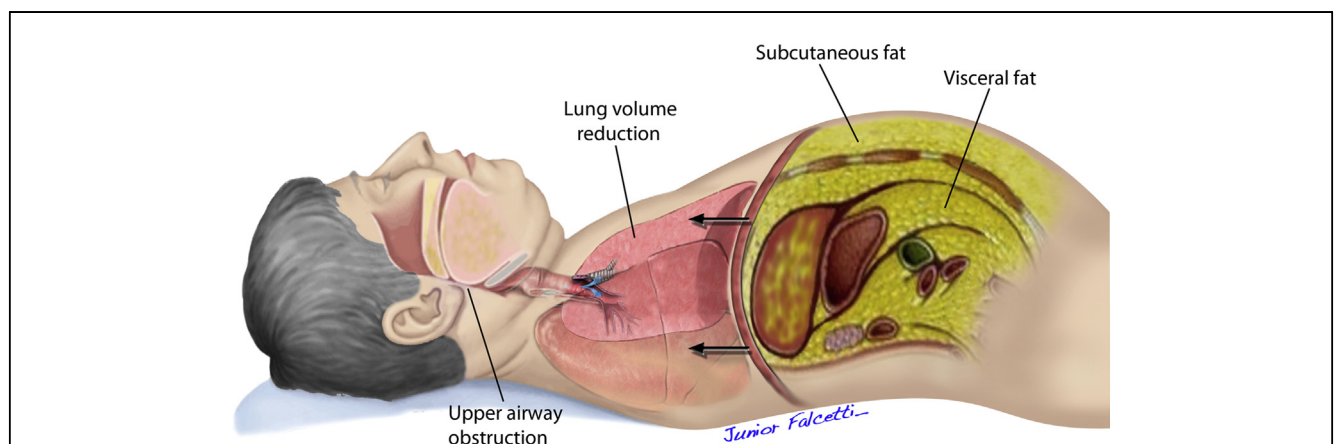


Figure 1. Obesity Predisposes to Obstructive Sleep Apnea

Anatomic factors that predispose obese patients to obstructive sleep apnea.

diet-induced obesity and mice with genetic obesity (29,30). Thus, animal data suggest that intermittent hypoxia of OSA and obesity may interact to cause metabolic dysfunction. The role of intermittent hypoxia has also been shown in humans. Healthy volunteers were exposed to 6 h of intermittent hypoxia and developed insulin resistance and impaired beta cell function (31). Regarding lipid metabolism, consistent evidence from animal models of OSA has shown that chronic intermittent hypoxia induces fasting dyslipidemia in both lean and obese mice due to activation of the transcription factor sterol regulatory element-binding protein 1 and an important downstream enzyme of triglyceride and phospholipid biosynthesis, stearoyl-CoA desaturase-1 (32–34). Moreover, chronic intermittent hypoxia also impaired clearance of triglyceride-rich lipoproteins, inactivating adipose lipoprotein lipase (35,36). In humans, a randomized study showed that treatment of OSA with continuous positive airway pressure (CPAP) improves postprandial triglyceride and total cholesterol levels (37). Despite this evidence, there are no consistent data suggesting that OSA is a major risk factor for dyslipidemia (38).

In the metabolic syndrome scenario, occult OSA is common and independently associated with increased serum levels of triglycerides and glucose as well as with several metabolic and inflammatory parameters not included in the criteria for metabolic syndrome (cholesterol/high-density lipoprotein cholesterol ratio, uric acid, and C-reactive protein) (4).

Regarding the pathogenic adipose tissue endocrine responses, inappropriate secretion of several adipokines that have anti-inflammatory, antiatherogenic, and insulin-sensitizing properties have been described in OSA (39) but obesity per se is a potential confounding factor (40). Therefore, the relative role of OSA in adipokines remains to be established.

Nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of progressive stages of liver disease ranging from simple steatosis to nonalcoholic steatohepatitis manifested by hepatic inflammation, necrosis, and fibrosis. NAFLD is strongly linked to obesity and independently associated with incident and prevalent cardiovascular disease (41).

Despite the well-known heterogeneous disease spectrum of NAFLD, the potential triggers for the progression of NAFLD are not fully understood. Consistent evidence from both humans and mice suggests that OSA is a potential candidate for exacerbation of NAFLD in obesity (42). Polotsky et al. (43) examined whether OSA and nocturnal hypoxemia predict the severity of steatohepatitis in severely obese individuals presenting for bariatric surgery. Taking advantage of the availability of liver biopsy specimens, the investigators found that patients with moderate to severe OSA and severe hypoxemia exhibited more severe hepatic lobular inflammation than patients with mild OSA (Fig. 2). Severe nocturnal hypoxemia was associated with ballooning of hepatocytes and pericellular fibrosis in the liver. Similar findings were described in patients with OSA

by another group of investigators (44). Animal studies confirmed the role of chronic intermittent hypoxia in the progression of fatty liver in obesity (29).

Sympathetic activity. Previous evidence showed that variations in sympathetic tone in obese patients are largely explained by their OSA status. In 1998, Narkiewicz et al. (45) reported provocative data on muscle sympathetic nerve activity in healthy normal-weight subjects and healthy sedentary obese subjects. Polysomnography revealed that 1 of 25 normal-weight subjects and 9 of 30 obese subjects had occult OSA. Interestingly, muscle sympathetic nerve activity was similar in normal-weight subjects and obese subjects without OSA. Muscle sympathetic nerve activity in obese subjects with OSA was significantly higher than that in obese subjects without OSA. The investigators concluded that obesity alone, in the absence of OSA, is not accompanied by increased sympathetic activity. The major limitation of this pivotal study was the small sample size and the lack of a control lean group. Seven years later, Grassi et al. evaluated muscle sympathetic nerve activity in 86 middle-aged normotensive subjects classified according to body mass index (BMI) and apnea/hypopnea index as lean and obese subjects with and without OSA (46). Subjects with and without OSA were matched for age, sex, and blood pressure values within the lean and obese groups. Compared with the non-OSA lean group, there were similar increases in muscle sympathetic nerve activity in the OSA lean and the non-OSA obese groups, whereas a further increase was detected in obese patients with OSA (Fig. 3). These results suggested that sympathetic activation in obesity occurs independently of OSA but OSA has an additive sympathostimulating effect (46).

Two independent groups of investigators recently explored whether the sympathetic hyperactivity observed in the metabolic syndrome is further exacerbated by the presence of OSA (47,48). Both groups reported that patients with the metabolic syndrome and comorbid OSA have higher sympathetic drive and diminished baroreflex sensitivity compared with patients with the metabolic syndrome without OSA. CPAP therapy reduces muscle sympathetic nerve activity in patients with OSA (49).

Overall, current evidence implicates OSA in potentiating sympathetic activity in obese patients. It is conceivable that the sympathetic activation is induced by hypoxia via peripheral chemoreceptors (50).

Endothelial dysfunction, surrogate markers of atherosclerosis, and arterial stiffness. Several reports consistently showed that OSA is independently associated with endothelial dysfunction (51,52) and that treatment of OSA with CPAP significantly improved endothelial function (53,54). However, a systematic analysis of endothelial dysfunction in obese patients with and without OSA was performed only recently. Jelic et al. (55) measured brachial artery flow-mediated dilation, an indirect marker of endothelial nitric oxide (NO)-mediated reactivity, in 71 subjects with a BMI ranging from normal to obese who

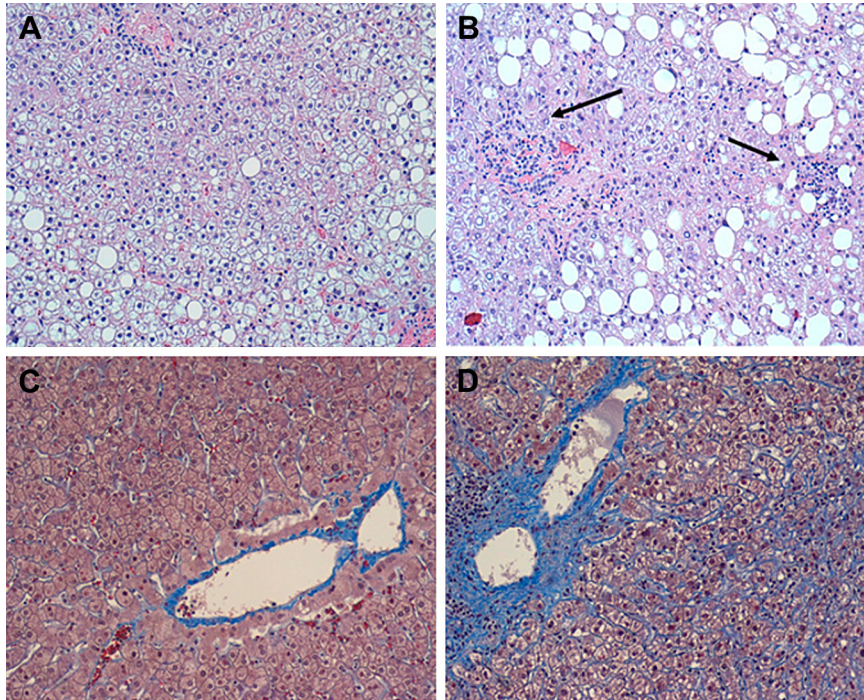


Figure 2 Nonalcoholic Fatty Liver Disease in Severely Obese Individuals According to the Presence or Absence of OSA

(A) Representative image of the liver without inflammation in a subject without OSA. Macrovesicular hepatic steatosis is evident, but inflammation is absent (hematoxylin-eosin; original magnification $\times 100$). (B) Representative image of the liver in a subject with OSA and severe nocturnal oxyhemoglobin desaturation. Macrovesicular hepatic steatosis is evident, and lobular inflammation is present (arrows) (hematoxylin-eosin; original magnification $\times 100$). (C) Representative image of liver without pericellular fibrosis in an individual without OSA (Masson trichrome; original magnification $\times 100$). (D) Representative image of liver in a subject with OSA and severe nocturnal oxyhemoglobin desaturation. Prominent pericellular perisinusoidal fibrosis is present. Collagen depositions are stained blue and have a chicken-wire appearance (Masson trichrome; original magnification $\times 100$). Reprinted with permission from Polotsky et al. (43). Abbreviation as in Figure 1.

underwent polysomnography. Proteins that regulate basal NO production and inflammation and markers of oxidative stress were quantified in venous endothelial cells. The investigators reported that expression of endothelial NO synthase (eNOS), phosphorylated eNOS, and flow-mediated dilation were significantly lower (Fig. 4),

whereas expression of nitrotyrosine (a marker of oxidative stress) was significantly greater in patients with OSA than in OSA-free subjects regardless of central adiposity. Expression of nuclear factor κ B, a marker of inflammation, was greater in obese patients with OSA than in obese OSA-free subjects. Effective treatment of OSA with CPAP

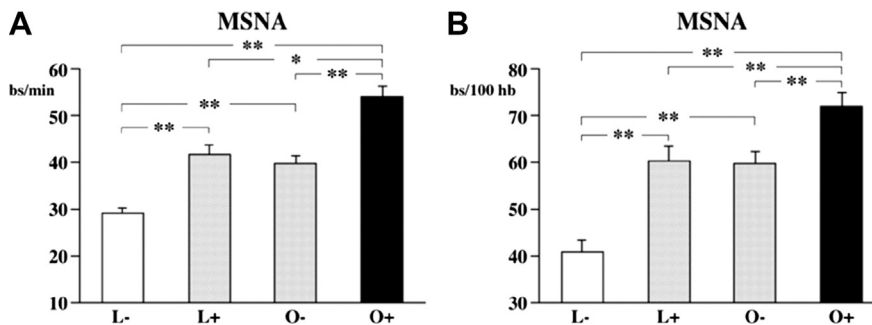
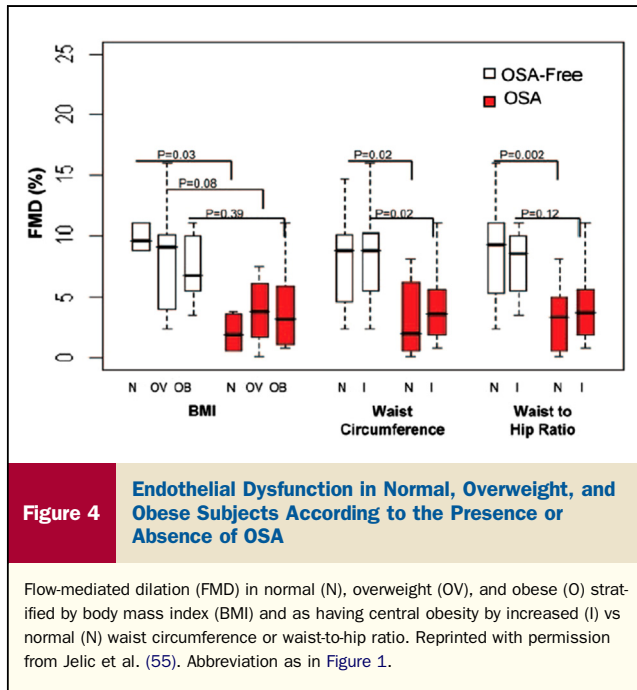


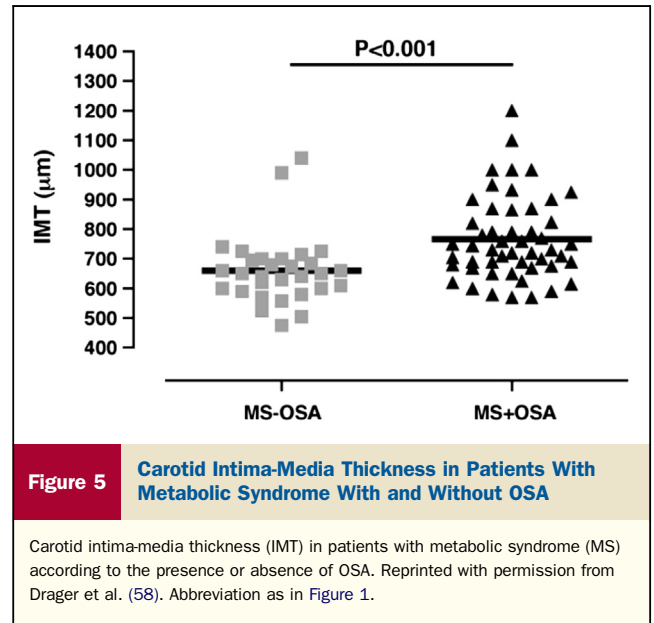
Figure 3 Sympathetic Activity in Lean and Obese Subjects According to the Presence or Absence of OSA

Muscle sympathetic nerve activity (MSNA) in lean (L) and obese (O) subjects according to the presence (+) or absence (-) of OSA. * $p < 0.05$; ** $p < 0.01$. Reprinted with permission from Grassi et al. (46). Abbreviation as in Figure 1.



significantly increased flow-mediated dilation and expression of eNOS and phosphorylated eNOS, whereas expression of nitrotyrosine and nuclear factor κ B significantly decreased (55). More recently, Namtvedt et al. also reported a positive association between severity of OSA and impaired endothelial function independently of obesity and other cardiovascular risk factors (56). In the metabolic syndrome scenario, Akishita et al. (57) found that patients with both the metabolic syndrome and OSA had lower flow-mediated dilation than patients with the metabolic syndrome alone or controls. Regarding surrogate markers of atherosclerosis and arterial stiffness, a previous investigation found that patients with both the metabolic syndrome and OSA had higher values of carotid intima-media thickness (Fig. 5), pulse wave velocity, and carotid diameter. The apnea-hypopnea index was independently associated with impairments in these 3 vascular parameters (58). Finally, in a preliminary single-arm study, Oyama et al. (59) reported that CPAP therapy improved endothelial dysfunction and decreased markers of oxidative stress in patients with the metabolic syndrome and OSA. Taken together, these findings suggest that OSA has an independent effect on endothelial dysfunction, surrogate markers of atherosclerosis, and arterial stiffness in obesity and the metabolic syndrome.

High blood pressure. The relationship between OSA and high blood pressure is supported by a large body of evidence and has been extensively discussed in previous reviews (60,61). Increased blood pressure in patients with OSA is multifactorial in origin and may depend on sympathetic overactivity, systemic inflammation, oxidative stress, endogenous vasoactive factors, and endothelial dysfunction (60,61).



Regarding the impact of OSA treatment on blood pressure, a previous meta-analysis not involving drug-resistant hypertension suggested a very modest impact of CPAP on blood pressure (approximately 2.5 mm Hg for systolic blood pressure and 2 mm Hg for diastolic blood pressure) (62) but very heterogeneous populations (including normotensive patients) were combined, which potentially may mitigate the effects. The results of recent randomized studies suggest that the effect of CPAP is more significant in the subgroup of patients with uncontrolled and drug-resistant hypertension (63,64). More recently, Drager et al. (65) showed that 3 months of CPAP therapy normalized blood pressure in patients with OSA who had pre-hypertension and masked hypertension. This result suggests that treatment of OSA may prevent the development of sustained hypertension.

Despite the aforementioned evidence, there is a paucity of data that specifically address high blood pressure in patients with OSA according to the presence or absence of obesity and the metabolic syndrome. Previous investigations showed inconsistent results. For instance, studies of the adrenergic overdrive in obesity and the metabolic syndrome did not show further increases in blood pressure in patients with OSA (46,47). In contrast, Trombetta et al. (48) found that patients with the metabolic syndrome and OSA had higher blood pressure than patients with the metabolic syndrome alone. Further studies with a higher sample size and analysis of 24-h ambulatory blood pressure monitoring should clarify this issue.

Heart remodeling and arrhythmias. Recent evidence indicates that OSA is independently associated with incident heart failure (66). There are multiple mechanisms by which OSA could lead to heart remodeling, including exacerbation of nighttime and daytime hypertension, increased sympathetic tone, increased left ventricular afterload due to increased arterial stiffness, and exaggerated swings in intrathoracic pressure during obstructive episodes, among others (67–69).

The impact of OSA on heart remodeling has recently been explored in obese patients. Avelar et al. (70) performed echocardiography and laboratory testing in 455 severely obese subjects and 59 nonobese reference subjects and showed that more severe nocturnal hypoxemia, increased systolic blood pressure, and BMI are independently associated with increased left ventricular mass. Otto et al. compared the cardiac structural and functional changes in obese and otherwise healthy adults with and without OSA (71). Obese patients with OSA had an increased left atrial volume index and altered diastolic function compared with similarly obese patients without OSA, which implicates OSA in early subclinical impairment of cardiac function (71). Taken together, the early cardiac changes induced by OSA may contribute to heart remodeling, heart failure, and arrhythmias reported in obese patients. Indeed, in a retrospective cohort study of 3,542 adults in Olmsted County, Minnesota, obesity and the magnitude of nocturnal oxygen desaturation were independent risk factors for incident atrial fibrillation in individuals <65 years of age (72). It is conceivable that structural changes in the left atrium may contribute to an increased risk of atrial fibrillation in patients with OSA (68). Recent detailed electrophysiological and electroanatomic mapping found an abnormal atrial substrate in patients with OSA compared to age- and BMI-matched controls without OSA (73). The patients with OSA showed both structural changes, including increased atrial size and extensive areas of low voltage, and regions of electrical silence and conduction abnormalities (73). Regarding the impact of treatment of OSA on atrial fibrillation, appropriate treatment with CPAP in patients with OSA is associated with lower recurrence of atrial fibrillation at 12 months compared with untreated patients (74).

Reversing metabolic syndrome components in the treatment of patients with OSA. Recent studies were designed to explore the impact of OSA on the metabolic syndrome and its components (75–78). In a nonrandomized study, Dorkova et al. showed that CPAP therapy reduced several components of the metabolic syndrome in patients who used CPAP for ≥ 4 h/night for 8 weeks, including blood pressure, triglyceride levels, and glucose levels, compared with patients with low adherence to CPAP (<4 h/night) (75). More recently, Sharma et al. performed a crossover, double-blind, randomized study exploring the impact of treatment with CPAP for 3 months on components of the metabolic syndrome (76). In this study, treatment with CPAP (vs. sham CPAP [i.e., a placebo]) was associated with significant mean decreases in systolic blood pressure, diastolic blood pressure, serum total cholesterol levels, low-density lipoprotein cholesterol levels, triglyceride levels, and glycated hemoglobin. The prevalence of the metabolic syndrome was significantly reduced after CPAP therapy (reversal found in 11 of 86 patients [13%] undergoing CPAP therapy vs. 1 of 86 [1%] undergoing sham CPAP) (76). Surprisingly, treatment with CPAP also reduced BMI and visceral adiposity, which may partially explain the metabolic improvement (76). The reduction in BMI and visceral adiposity after the use of CPAP for the treatment of

patients with OSA is in contrast to other reports (77,78). However, an important caveat is that none of the studies discussed in the preceding text fully controlled for physical activity and diet pre-intervention and post-intervention. Further studies are necessary to clarify these important issues.

Perspectives

The current literature clearly shows that OSA is an emerging risk factor for modulating the cardiometabolic consequences of obesity. There is consistent evidence from animal models and clinical studies suggesting that OSA augments metabolic, inflammatory, autonomic, vascular, and cardiac dysfunction of obesity and exacerbates the metabolic syndrome. However, OSA is commonly underdiagnosed. Several challenges and research priorities should be mentioned. First, we need to call attention to the need for more screening for OSA in patients with obesity and the metabolic syndrome. We should keep in mind that traditional risk factors for OSA such as excessive daytime somnolence may not be present in a significant proportion of patients (4). It would be important to actively pursue other symptoms and clinical characteristics such as frequent snoring and difficult-to-control hypertension, nocturnal blood pressure abnormalities, atrial fibrillation, or left ventricular hypertrophy. Second, there is an urgent need to provide a cost-effective way to appropriately screen for and diagnose OSA in millions of patients with obesity and/or the metabolic syndrome. Portable monitoring (79) and new technologies for diagnosing OSA (80) are promising options in high-risk groups, given that full polysomnography may not be readily available. Third, despite the tight link between obesity and OSA, it is not clear why a significant proportion of obese patients, including those with severe forms of obesity, do not develop OSA. Comprehensive genetic studies with anatomic and functional upper airway assessment should be undertaken to elucidate protective mechanisms (81). Fourth, there is a clear reciprocal interaction between obesity and OSA, but there are several gaps in knowledge (82). Therefore, there is a clear demand for additional research at both the basic science and clinical levels to understand the mechanisms by which OSA and its components exacerbate metabolic dysfunction and vascular impairment in obesity and the metabolic syndrome. Finally, large randomized clinical studies will be necessary to define the impact of treatment of OSA on metabolic and cardiovascular outcomes.

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