Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea

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Drager LF, Polotsky VY, O’Donnell CP, Cravo SL, Lorenzi-Filho G, Machado BH. Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea. Am J Physiol Heart Circ Physiol 309: H1101–H1111, 2015. First published July 31, 2015; doi:10.1152/ajpheart.00094.2015.—Obstructive sleep apnea (OSA) is known to be independently associated with several cardiovascular diseases including hypertension, myocardial infarction, and stroke. To determine how OSA can increase cardiovascular risk, animal models have been developed to explore the underlying mechanisms and the cellular and end-organ targets of the predominant pathophysiological disturbance in OSA—intermittent hypoxia. Despite several limitations in translating data from animal models to the clinical arena, significant progress has been made in our understanding of how OSA confers increased cardiovascular risk. It is clear now that the hypoxic stress associated with OSA can elicit a broad spectrum of pathological systemic events including sympathetic activation, systemic inflammation, impaired glucose and lipid metabolism, and endothelial dysfunction, among others. This review provides an update of the basic, clinical, and translational advances in our understanding of the metabolic dysfunction and cardiovascular consequences of OSA and highlights the most recent findings and perspectives in the field.

intermittent hypoxia; sleep apnea; translational medicine; cardiovascular disease

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Obstructive sleep apnea (OSA) is characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep, resulting in apneas or hypopneas, respectively. The futile efforts to breathe during obstructed events result in increased negative intrathoracic pressure, intermittent hypoxia (IH), and sleep fragmentation (19). OSA is a growing medical problem around the world, which is closely associated with the burden of obesity. Recent evidence from the well-established Wisconsin Cohort showed that among adults from 30 to 70 yr of age, ~13% of men and 6% of women have moderate to severe forms of OSA [apnea-hypopnea index (AHI), ≥15 events/h of sleep] (103). The prevalence of OSA frequently surpasses 50% in patients with cardiovascular diseases, including hypertension (25, 96), metabolic syndrome (26), atrial fibrillation (42), and coronary artery disease (16, 45). More than a common comorbidity or just an epiphenomenon of overweight and obesity, increasing evidence suggests that OSA triggers several mechanisms that ultimately impact cardiovascular risk (29). Much of our knowledge about the pathophysiology of OSA is the result of translational studies conducted in humans and animals. In this review, we first briefly discuss the role of OSA as a cardiovascular risk factor followed by a critical analysis of the several animal models that have been developed to study the cardiovascular consequences of OSA. The translational evidence for mechanistic pathways contributing to the cardiovascular consequences of OSA is also examined. Finally, we assess the need for the development of new experimental models and address potential future directions for translational research on the impact of OSA on cardiovascular morbidity and mortality.

OSA as a Cardiovascular Risk Factor

The cardiovascular implications of OSA have gained growing prominence in the last three decades. Despite a limited
awareness of the medical community (15), there is consistent evidence that severe OSA is independently associated with increased risk of poor cardiovascular outcome mainly because of myocardial infarction and stroke (77, 83, 141, 142). The vast majority of the studies showed a causal relationship between OSA severity (evaluated by AHI) and risk of cardiovascular events. However, most studies also showed that only severe OSA was significantly associated with increased mortality (44). Several randomized studies reported positive effects of OSA treatment with continuous positive airway pressure (CPAP) on intermediate outcomes such as blood pressure, endothelial dysfunction, arterial stiffness, or inflammation [reviewed in Drager et al (29)]. The impact of OSA treatment on hard outcomes such as fatal and nonfatal cardiovascular events in humans is limited so far to observational studies. However, observational studies consistently showed that the treatment of OSA with CPAP was associated with a significant decrease on the risk of cardiovascular events and mortality rates in severe OSA (9, 10, 43, 77, 79, 80). Current ongoing large multicenter randomized studies such as the Sleep Apnea Cardiovascular Endpoints (SAVE) trial (81) will be useful to elucidate whether the treatment of OSA with CPAP is really effective in reducing cardiovascular mortality.

Animal Models of OSA

Animal models have been used extensively to investigate both the pathogenesis and downstream organ- and tissue-specific outcomes of sleep apnea and IH. The current review focuses on animal models of natural or experimentally induced sleep apnea and IH, as well as briefly highlight the role of these models in shaping our understanding of the development of neurogenic hypertension, as one example of cardiovascular risk in patients with OSA.

Natural models of OSA. One of the major limitations in the field of OSA is the lack of clinically relevant models of sleep apnea, particularly OSA. Early reports of spontaneous apnea in English bulldogs have not led to significant insights into the pathology of OSA, in part because apneas were largely limited to periods of rapid eye movement (REM) sleep (57). Similarly, the presence of central and obstructive apneas was not pursued in the initial studies of obese Yucatan (76) and Vietnamese pot-bellied (140) pigs that presented inspiratory airflow limitation. However, large animal models are complex, expensive, and genetically heterogeneous. In contrast, rodent models have advantages of the well-characterized genotypes and availability of inbred and transgenic animals.

Rodents exhibit periodic cessations in breathing that occur almost exclusively in the absence of diaphragmatic electromyography activity (122) and defined as spontaneous or more commonly post-sigh if preceded by a larger breath (14). The rates of these central apneas in rodents depend on the strain (41, 47) and expression of particular genes, including the monoamine serotonin (55) and orexin (87). Serotonin pathways have been implicated in central apnea generation using receptor subtype-specific pharmacological blockade (115). Interestingly, from a cardiovascular perspective, experimentally inducing hypotension reduces central apnea rates in rats (114), whereas spontaneously hypertensive rats exhibit an increase in spontaneous apneas during both non-REM and REM sleep (11).

Although obesity is a major risk factor for sleep apnea in humans, genetically obese mice do not exhibit higher central apnea rates than control lean mice (17). With respect to the upper airway, obese New Zealand mice have MRI-assessed increases in fat mass of tongue, soft palate, and lateral pharyngeal walls (5), and obese ob/ob mice have defects in upper airway neuro-mechanical control that can be reversed with leptin administration (105). Hernandez et al. (49) reported inspiratory flow limitation in the obese New Zealand mouse, but in contrast to mice, obese rats maintain a stable upper airway, even during REM sleep (133). In summary, rodents remain the animal model of choice to study the genesis of central sleep apnea and the cardiovascular consequences of the IH, but an ideal experimental model for the pathogenesis of OSA remains to be developed.

Experimentally induced models of sleep apnea. In the absence of compelling natural models of upper airway obstruction, studies focusing on the pathophysiological consequences of OSA have either directly obstructed the upper airway or modeled the downstream physioconsequences of airway obstruction, including the most commonly employed intervention of IH. In the 1990s, two laboratories developed chronic dog models of experimentally induced airway obstruction to assess cardiovascular outcomes of OSA (63, 92). More recently, upper airway obstruction models have been extended to rats using either isolated head and body chambers in restrained rats (33) or a balloon inflation mechanism in the trachea of unrestrained rats (Fig. 1) (127). Depending of the OSA model, balloons last for a long time, cause few complications, allow induction of apnea during sleep, allow induction of apneas that start at a fixed point in the respiratory cycle, and elicit cardiorespiratory responses similar to those observed in humans (Fig. 1).

The classic model to study the consequences of OSA involves administration of IH to simulate the repetitive brief periods of hypoxia and reoxygenation that result from airway obstruction. The first experimental study of IH was performed by Fletcher et al. (35) in the early 1990s in an effort to understand the impact of the hypoxic component of OSA on the development of high blood pressure. In the ensuing years there have been over 1,000 studies of various forms of IH in rats and mice. The periods of IH, which are usually repetitively administered for 8–12 hr during the light or sleeping phase can also induce arousal responses in rodents (106) and induce a sleepy phenotype (143), mimicking other important characteristics of OSA; however, arousals are limited to periods where the IH occurs during sleep, and a significant proportion of IH occurs with the animal awake. Two laboratories have developed computer-controlled feedback systems to deliver hypoxia only during periods of sleep in mice (120, 135) and rats (46). Other limitations of the IH model include the absence of intermittent hypercapnia, although some studies have incorporated both stimuli (36, 91) and the absence of intrathoracic swings that occur with upper airway obstruction. Finally, there is a large variability among experimental models, which is also observed among clinical studies of patients with OSA, that make it difficult to standardize an ideal model of OSA. With this limitation in mind, it seems that the duration of exposure
more likely to influence outcomes than the hypoxic nadir or the rate of hypoxic cycling (38).

Animal models of OSA and the development of hypertension. The general acceptance of hypertension as an established outcome of OSA has, in part, been dependent on animal models demonstrating causality and uncovering mechanistic pathways impacting blood pressure. The landmark study from Toronto showed that 5 wk of experimentally induced airway obstruction during sleep in dogs elevated mean arterial blood pressure (MABP) by more than 10 mmHg within 5 wk and that MABP returned to a normotensive state within 3 wk of normal, unobstructed sleep (6). Multiple studies in mice and rats have also shown MABP increases of ~10 mmHg within 7–10 days of IH exposure and that the hypertension can be sustained for several weeks (8, 68, 100, 101, 136). Although a diverse array of mechanisms have been implicated in the development of hypertension in rodents exposed to IH, hyperactivation of the carotid body-sympathetic-renal axis has both strong experimental support (2, 70, 101) and relevance to clinical OSA where patients are known to exhibit increased sympathetic nerve activity (SNA) (131). There is a consensus that experimental models of IH are characterized as a neurogenic model of hypertension. Animal models continue to make significant contributions to our understanding of tissue and organ pathology that result from OSA/IH. The ability to directly interrogate causality and either to exclude or to add comorbid features of OSA/IH in a controlled fashion will ensure that animal models continue to have long-term translational relevance to the field of sleep and breathing.

Autonomic Dysfunction and Elevated Blood Pressure in Sleep Apnea

Corroborating evidence from rodent models and clinical studies strongly suggest that IH and OSA, respectively, increase blood pressure. The Wisconsin Sleep Cohort showed an increased incidence of hypertension associated with OSA, even for mild/moderate levels of OSA (102). In a landmark paper from Somers et al. (131), patients with OSA were found to have higher levels of SNA during wakefulness, with further increases in blood pressure and sympathetic activity during sleep. The ability of CPAP therapy to reverse the elevations in SNA and blood pressure in patients with OSA, combined with data from animal models (147, 151), defines OSA/IH as a neurogenic model of hypertension.

In rodents, repetitive, rapid, and intermittent reduction of inspired O2 fraction in the IH model induces cyclical falls in the arterial PO2 with subsequent activation of the arterial chemoreceptors (18, 99, 100, 118). Because in IH models there is no upper airway obstruction and negative intrathoracic pressure swings, it is conceivable that the subsequent blood pressure elevations are due to the repeated episodes of activation of peripheral chemoreceptors and/or enhancement of the downstream chemoreflex responses.

Several studies have demonstrated that IH induces structural and functional alterations in the glomus chemosensitive cells located in the carotid body. Potentially, disturbances in glomus cell function could cause increased sensitivity and reactivity of the peripheral chemoreceptors, contributing to an enhancement of cardiorespiratory responses to hypoxia (66).

One mechanism by which IH may induce neurogenic hypertension is enhancement of central pathways activated by peripheral chemoreceptor stimulation. Particularly interesting are recent findings indicating changes in the sympathetic respiratory coupling in animals chronically exposed to IH (85, 151). The sympathetic and respiratory coupling is observed during inspiration, and this phenomenon is characterized by the sinus arrhythmia. In animals exposed to IH for 10 days, a large increase in the sympathetic activity during the late expiratory phase of the respiratory cycle is observed, indicating a significant change in sympathetic and respiratory coupling (84, 85, 148, 149, 150). Alterations in neurons of the respiratory network contribute to an increase in the frequency discharge of the rostral ventrolateral medulla presympathetic neurons and changes in the respiratory-sympathetic coupling (1, 84). Thus...
the primary changes in the IH model occur in the respiration pattern and then secondarily impact the frequency discharge of the presym pathetic neurons, the sympathetic outflow, and ultimately arterial pressure. Similar changes in the respiratory pattern and the sympathetic-respiratory coupling were recently described in patients with OSA (34).

Metabolic Intermediates of the Cardiovascular Risk in Sleep Apnea

OSA, insulin resistance, and type 2 diabetes. An independent association between OSA and insulin resistance was first described in observational studies by Brooks et al. (7) and Vgontzas et al. (144). In 2002, two groups of investigators published cross-sectional data in larger patient cohorts (52, 112). An independent relationship between insulin resistance and OSA was demonstrated in the Sleep Heart Health Study (113). The cross-sectional data from the Wisconsin Sleep cohort of patients with sleep apnea showed a significant increase in the prevalence of type 2 diabetes in patients with OSA. The odds ratio for having type 2 diabetes mellitus with an AHI of $\geq 15$ versus $< 5$ was $2.30$ after adjustments for age, sex, and body habitus (116). A recent historical cohort study involving 8,678 patients showed that OSA and nocturnal desaturations are associated with incidence of type 2 diabetes (62), which was in line with several previous prospective studies (4, 78). OSA is highly prevalent in patients with type 2 diabetes (94). The prevalence of OSA (diagnosed by the AHI $> 5$/h) in patients who are obese with type 2 diabetes exceeds 80%, and the prevalence of moderate and severe OSA exceeds 50% (39). The severity of nocturnal intermittent hypoxemia has been associated with the impairment of insulin sensitivity and insulin secretion by pancreatic $\beta$-cells (110).

Numerous uncontrolled studies examined the effect of CPAP on glucose tolerance, insulin sensitivity in subjects with prediabetes, and glycemic control in patients with type 2 diabetes. The studies in prediabetes yielded contradictory results, whereas glycemic control in diabetics largely improved [reviewed in Pamidi and Tasali (94)]. However, a recent randomized clinical trial of 8 h of nightly CPAP showed significant improvement of insulin sensitivity in prediabetics after 2 wk of treatment, which emphasizes importance of CPAP adherence for metabolic outcomes (95).

Exposure mice to IH have been employed to determine the impact on glucose metabolism (117). In lean mice, short-term IH for $9–24$ h increased fasting blood glucose levels, insulin resistance, glucose intolerance, and suppressed insulin secretion by the pancreatic $\beta$-cells (61, 69). After 4–6 wk of IH, suppression of insulin secretion persisted but glucose intolerance and insulin resistance subsided (69, 130, 145). In contrast, in mice with diet-induced and genetic obesity, IH induced severe glucose intolerance, and insulin resistance persisted even after chronic exposure (27, 107). Animal studies demonstrated that effects of IH on glucose metabolism are mediated by the sympathetic nervous system (SNS) (128, 129). As noted above, IH stimulates the carotid bodies, which in turn activates the central sympathetic outflow to the liver and increase the catecholamine efflux by the adrenal medulla, resulting in suppression of insulin secretion, stimulation of hepatic gluconeogenesis and glucose output (130). These changes are abolished by carotid body denervation and adrenal medullectomy (129, 130) (Fig. 2). Thus there is evidence in the literature suggesting that the hypoxic stress of OSA contributes to the development of insulin resistance and type 2 diabetes via SNS activation, but this causal link was not yet confirmed in humans.

OSA, dyslipidemia, and nonalcoholic fatty liver disease. Relationships between OSA and dyslipidemia have not yet been fully characterized. The largest cross-sectional data set...
from the Sleep Heart Health Study showed that fasting levels of total serum cholesterol and triglycerides directly correlated and HDL cholesterol levels inversely correlated with the severity of OSA in men under 65 (88). More recently, Trzepizur et al. (139) reported independent associations between higher triglyceride and lower HDL cholesterol levels and the severity of nocturnal IH measured by the oxygen desaturation index in 2,081 patients. Sleep apnea has been associated with increased plasma free fatty acids (s) levels (3, 58), which were decreased by supplemental oxygen (58). The largest randomized clinical study of CPAP examining serum lipids was performed in 220 adults for 1 mo and showed a decrease in plasma total cholesterol by 10.8 mg/dl in the treated group, whereas triglyceride levels were unchanged (119). Studies by Chirinos et al. (13) showed that CPAP decreased serum triglycerides only when it was combined with weight loss. It is important to note that only one study examining the effect of OSA on postprandial lipids by Phillips et al. (104) reported a significant decrease in triglyceride and cholesterol with CPAP treatment. Postprandial lipids circulate in the form of triglyceride-rich chylomicrons. Postprandial hypertriglyceridemia confers risk of myocardial infarction, ischemic heart disease, stroke, and death (40, 90) and may contribute to OSA-related cardiovascular morbidity and mortality. The hypoxic stress of OSA increases levels of s and triglyceride-rich lipoproteins that are markers of insulin resistance (65). In fact, a recent study linked OSA-induced dyslipidemia to insulin resistance (75). Murine studies have also shown a predominant effect of IH on s, triglyceride-rich lipoproteins, fasting VLDL, and post-prandial chylomicrons (28, 123). Data from the rodent studies of IH suggested that 1) an increase in levels is related to SNA-induced excessive adipose tissue lipolysis (59) and 2) VLDL and chylomicron hyperlipidemia is caused by inhibition of lipoprotein lipase, a key enzyme of lipoprotein clearance mediated by hypoxia inducible factor-1α transcriptionally activating an lipoprotein lipase (LPL)-inhibitor angiopoietin-like 4 in adipose tissues (30, 146). Thus the effect of OSA on serum lipids remains poorly characterized, but available data in the literature suggest that OSA may lead to proatherogenic dyslipidemia with selective increases of s and triglyceride rich lipoproteins. Therefore, SNS activation, insulin resistance, and adipose tissue hypoxia may be implicated in the pathogenesis of proatherogenic dyslipidemia in OSA.

Emergent evidence suggests that nonalcoholic fatty liver disease (NAFLD) is independently associated with OSA (60, 89). The severity of OSA predicts the presence of liver fibrosis on biopsy (60, 108). According to some studies we have available so far, CPAP had no effect on liver enzymes (64) or expression of hepatic steatosis by MRI or CT scan (50, 138). To our knowledge, no CPAP trial was conducted to evaluate the effect of OSA on biopsy-confirmed NAFLD.

In animal models, IH augments liver triglyceride content by increasing influx of s from adipose tissue and activating lipid biosynthetic pathways, sterol regulatory element binding protein 1 (SREBP-1), and a SREBP-1-regulated enzyme stearoyl CoA desaturase 1 (71, 72). Partial deficiency of hypoxia inducible factor-1α abolished SREBP-1 and stearoyl-CoA desaturase-1 upregulation and prevented triglyceride accumulation in the liver during IH (73). Mouse IH induces oxidative stress in the liver, activating NADPH oxidase (57), and causes inflammation activating a proinflammatory transcription factor NF-κB (124) and NF-κB regulated proinflammatory cytokines TNF-1α, IL-1β, IL-6 and macrophage inflammatory protein-2 (125). In mice on a high-fat diet, IH converted diet-induced hepatic steatosis to steatohepatitis (nonalcoholic steatohepatitis) and liver fibrosis (125). Thus there is experimental evidence of a strong independent association between OSA and NAFLD with nonalcoholic steatohepatitis and liver fibrosis backed by experimental evidence, but causal relationships between OSA and NAFLD have not been established.

Figure 2 shows the putative pathways mediating prodiabetic effects of IH.

Vascular Dysfunction and Atherosclerosis in Sleep Apnea

OSA is associated with endothelial dysfunction and altered repair mechanisms, (54, 61) increased arterial stiffness (22, 97), and premature development of atherosclerosis (20, 23, 24, 67, 82). Interventional studies, including several randomized trials, showed that OSA treatment with CPAP reversed or attenuated parameters of vascular dysfunction and atherosclerosis (21, 53, 54). Interestingly, markers of inflammation were associated with the vascular dysfunction in OSA (54, 82). Moreover, improvements in surrogate markers of atherosclerosis and arterial stiffness were improved by CPAP in parallel to significant decreases in inflammatory markers and sympathetic activation (21). Two main mechanisms underlying vascular dysfunction and atherosclerosis in patients with OSA—impaired lipid metabolism and inflammation—were elucidated mainly through application of rodent models of IH.

Lipid metabolism impairment and atherosclerosis. The impact of IH on dyslipidemia and lipid metabolism was discussed in the previous section. Consistent evidence from animal models suggests the potential role of dyslipidemia on atherosclerosis in OSA. In a pivotal study, Savransky et al. (123) showed that IH promoted formation of fatty streaks and small mature plaques in the aortic arch and descending aorta of wild-type male C57BL/6J mice on a high-cholesterol diet. Combined exposure to IH and a high-cholesterol diet resulted in marked progression of dyslipidemia with further increases in serum total cholesterol and LDL cholesterol, increase in serum lipid peroxidation, and upregulation of an important hepatic enzyme of lipoprotein secretion, stearoyl-CoA desaturase-1 (123). Consistently, dyslipidemia and atherosclerosis induced by IH were attenuated by deficiency of stearoyl CoA desaturase-1 (126). In a prone model of atherosclerosis [apolipoprotein E (ApoE) knockout (KO) mice under high-cholesterol diet], Jun et al. (56) showed that IH accelerated atheroerotic plaque growth without affecting plaque composition. These observations in the animal model suggest that the harmful effects of IH on the vascular bed are potentiated when other risk factors for atherosclerosis are also present. Data from recent studies suggested that decreased lipoprotein clearance is a complementary mechanism of atherosclerosis induced by IH. As previously discussed, IH inhibits adipose tissue LPL because of the activation of angiopoietin-like 4 (Angptl4) (28).

Using Angptl4-neutralizing antibody, Drager et al. (30) demonstrated the important role of lipoprotein clearance on atherogenesis in a model of sleep apnea. In vehicle-treated mice, IH increased adipose Angptl4 levels, inhibited adipose LPL, increased fasting levels of plasma triglycerides and very LDL cholesterol, and increased the size of athero-
sclerotic plaques. The effects of IH were abolished by the Angptl4-neutralizing antibody (Fig. 3).

Thus there is consistent evidence from animal models that IH is an important trigger to induce atherosclerosis through dyslipidemia and lipid metabolism impairment, but we still need more data from clinical studies to confirm these findings in humans.

**Inflammation and atherosclerosis.** Several studies have shown that patients with OSA have elevated markers of pro-inflammatory mediators and inflammatory markers with proatherogenic properties such as TNF-α, IL-6, IL-8, C-reactive protein, leukotriene B4 (LTB4), and adhesion molecules (ICAM-1, VCAM-1, L-selectin, SE-selectin, P-selectin) (26, 31, 93, 128, 134). Interestingly, Ryan et al. (121) showed the crucial role of NF-κB activation with the downstream consequences of production of inflammatory genes in response to IH in a translational study. Of note, patients with OSA have an increased NF-κB activity, a key transcription factor that elicits inflammatory pathways (51).

Recent experimental studies have pointed to the importance of inflammation in the vascular dysfunction and atherogenesis induced by OSA. Li et al. (74) exposed THP-1 cells (human monocytic cell line derived from acute monocytic leukemia) to IH (74). They found an increased production of LTB4 and the expression of 5-lipoxygenase and leukotriene A4 hydrolase, the key enzymes for producing LTB4. In addition, IH exposures promoted increased cellular cholesterol accumulation and foam cell formation. The LTB4 receptor 1 (BLT1) antagonist U-75302 markedly attenuated IH-induced changes. Furthermore, IH-induced lesion formation was markedly attenuated in BLT1−/−/ApoE−/− mice (74).

Exploring the potential role of NF-κB in the atherogenesis induced by OSA, Song and colleagues (132) studied wild type and mice deficient in the p50 subunit of NF-κB (p50-KO), fed normal chow diet or high-cholesterol diet, and exposed to sham or IH. P50 gene deletion diminished IH high-cholesterol diet-induced NF-κB activation and abolished IH high-cholesterol diet-induced atherosclerosis. P50 gene deletion inhibited vascular wall inflammation, reduced hepatic TNF-α level, attenuated the elevation in serum cholesterol level, and diminished macrophage foam cell formation induced by IH high-cholesterol diet exposure (132). Studying ApoE-KO mice or in both ApoE and p50 genes (ApoE-p50-double KO) exposed to sham or IH, the same group found that IH caused more pronounced atherosclerotic lesions in ApoE-p50-double KO mice than ApoE-KO mice in parallel to a greater elevation in serum cholesterol level, serum levels of TNF-α and IL-6, aortic TNF-α, and inducible nitric oxide synthase expression and aortic infiltration of Mac3-positive macrophages (32). Recently, Poullain and colleagues (109) examined the role of the visceral fat in modulating the inflammation and atherogenesis induced by IH. IH induced morphological (shrunken adipocytes), functional (increased uncoupling protein-1 expression), and inflammatory (increased macrophage recruitment and secretion of IL-6 and TNF-α) remodeling of epididymal adipose tissue. Hypoxic mice presented more severe dysli-
demia and atherosclerosis lesions. Epididymal lipoectomy attenuated both IH-induced dyslipidemia and atherogenesis (109). In summary, animal models of OSA and cell culture provide evidence that OSA promotes vascular dysfunction and premature atherosclerosis via multiple pathways, including impaired metabolism and inflammation.

Perspectives

Nowadays OSA is a major public health concern. Clinical studies in patients and animal IH models indicate that OSA activates multiple intermediate pathways that lead to cardiovascular disease. Despite significant advances in our understanding of pathways promoting cardiovascular disease in patients with OSA, we need to be more innovative and develop new experimental models and strategies for a better understanding of the mechanisms underlying the cardiovascular disease induced by OSA. The potential effects of OSA on circadian variability sleep structure, sleep fragmentation, and deprivation have received little attention and deserve further investigation. We currently have limited understanding of the relative contributions of metabolic intermediates such as insulin resistance, hyperlipidemia, and inflammation on cardiovascular end points of atherosclerosis and hypertension. Although much progress has been made with respect to hypertension, there is a need to systematically explore the impact of OSA treatment on the progression and regression of atherosclerosis. Large prospective randomized studies are necessary to fully establish whether the treatment of OSA can decrease metabolic dysfunction and reduce cardiovascular events. Finally, translational approaches are essential for a better understanding of the causes, and they will be critical in helping the development of new strategies for the prevention and the treatment for OSA.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


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