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REVIEW

OBSTRUCTIVE SLEEP APNEA AND INSULIN RESISTANCE: A ROLE FOR MICROCIRCULATION?

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Obstructive sleep apnea is an increasingly recognized medical problem. The recent attention to its frequency in the general population and its important role in metabolic, vascular, and behavioral aspects have sharply increased the number and nature of investigations, thereby revealing new aspects that open new approaches in research. Whereas obstructive sleep apnea is a well-known phenomenon accompanying obesity and diabetes, new findings strongly suggest that this close relationship may also operate in the opposite direction. Indeed obstructive sleep apnea may be a primary feature inducing or aggravating a series of vascular and metabolic disturbances closely resembling the metabolic syndrome. This review will discuss established and potential mechanisms responsible for these changes. Obstructive sleep apnea indeed appears to gather all the elements necessary to induce insulin resistance, hypertension, and possibly heart failure. After careful analysis of these modifications and considering how they are intertwined, we propose that microcirculation could represent the common denominator mediating the progression of this pathology, as it is eventually the case in the metabolic syndrome and diabetes domain. This plausible hypothesis is discussed in detail and should be verified by appropriate preclinical and clinical protocols, which are now achievable by using noninvasive techniques in humans.

KEYWORDS: Obstructive sleep apnea. Insulin resistance. Hypoxia. Metabolic syndrome. Microcirculation.

INTRODUCTION

Few domains of medicine have experienced so much interest as obstructive sleep apnea (OSA) over the last 10 years. The sharp rising interest in this phenomenon started when it was first suggested that OSA may not just be an accompanying symptom but might cause or aggravate metabolic and vascular diseases.

Sleep disordered breathing comprises several processes that provoke repetitive interruptions in sleep, mainly due to snoring and hypopneas/apneas of either central or OSA origin. Epidemiologically, the OSA syndrome affects probably about 5% of the general population. The prevalence of OSA is much higher in diseases as common as hypertension (22-48%)[1] or heart failure (11-37%). In this latter group, central apneas are seen in 45% of subjects[2] and are inversely related to cardiac ejection fraction. Half of the patients with diastolic heart failure have an increase in the number of apneas.

The present review will describe the most recent knowledge about links between obstructive sleep apnea and cardiometabolic disorders. In particular, the possibility that this relationship operates in both directions is a recent view that strongly stimulates interest in new preclinical and clinical research. We will also discuss the plausible hypothesis that the microcirculation may be the common denominator of these intertwined disturbances.

OSA IS A SERIOUS CLINICAL CONDITION

Apneas are either complete or incomplete (hypopneas), which has led to the creation of a so-called apnea/hypopnea index (AHI) that permits the evaluation of frequency of

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apneas in patients. Obstructive sleep apneas are of mechanical origin, due to the failure of upper airways to maintain their muscle tone. Not surprisingly OSAs are most frequent in obese individuals, as a consequence of fat deposition in the muscles of the upper airways. Almost all OSA subjects exhibit intense snoring, but snoring is not necessarily accompanied by OSA. This is important in clinical trials, which partly were based on this indirect parameter. The link between OSAs and obesity is strong, such as to bias many protocols and interpretations of older clinical studies. A 10% increase in body weight over 4 years increases the risk for OSA 6-fold.[3] Recent findings revealed that half of the genetic variance in OSA is shared with obesity phenotypes,[4] which may have important consequences, as will be discussed later. Obstructive sleep apneas are more frequent during REM sleep,[5] and their number, usually of short duration (around 20 s) can reach several hundred per night. Sleep apneas up to 1 min can be found, a situation that may be life-threatening. Each sleep apnea is characterized by hypoxia during breathlessness, with blood oxygen saturation (SaO_2) down to 50% in extreme cases. The degree of desaturation is at least as important as the total number of episodes for complications linked with OSA. Each episode is followed by an arousal reaction restoring breath, thereby inducing abrupt reoxygenation. Patients with OSA suffer daytime sleepiness, a situation closely linked to car accidents, especially in the late afternoon.

OSA and Insulin Resistance / Glucose Tolerance / Diabetes

There is a very close link between insulin resistance (IR) and OSA, but causative mechanisms are disputed.[6,7] It was well-known that snoring and OSA are essentially seen in overweight/obese patients characterized by IR or the metabolic syndrome; more recent investigations support this link by showing that other diseases characterized by IR are also linked with OSA: in patients with polycystic ovary syndrome, elevated insulin levels and impaired glucose tolerance correlated with a higher frequency of OSAs, and this correlation was even independent of BMI in glucose normotolerant women.[8,9] Similarly, OSA affects about two thirds of acromegalic patients.[10,11] Nonalcoholic steatohepatitis (NASH), a situation found in most IR-patients, is also linked to severe OSA, with patients having high AHI values being more insulin-resistant and exhibiting more steatosis as well as elevated liver enzymes.[12] Illustrating the close relationship between IR and obstructive sleep apnea, it was proposed that OSA should be added to syndrome X (metabolic syndrome) and the new entity be called syndrome Z.[13] A main question is still whether this correlation is simply due to—or is independent of—excess fat (BMI or visceral fat). Table 1 shows how OSA superimposed on obesity worsens various metabolic and vascular parameters.

Table 1 - Additional effects of obstructive sleep apnea (OSA) on metabolic and vascular parameters in obesity. Data on control (healthy) subjects and obese patients without OSA are also shown (adapted from ref. 6)

	C	Ob	Ob + OSA
BMI	26	36	38
MABP	92	102	107
Visceral fat area		220	337*
Total wake time	66	59	113
REM latency	74	82	93
Minimum O_2 saturation	94	91	74

Indeed, several studies have claimed the correlation to be strictly due to the presence or absence of concomitant obesity in children[14] and adults.[15] In contrast, more recent studies suggest that whereas obesity plays a role, elevated AHI and minimum SaO_2 values are important determinants of impaired glucose tolerance.[16] In these patients, each additional apneic episode increased plasma insulin and the HOMA-index by 0.5%. In another study, the degree of glucose intolerance was related to the severity of desaturation. It was estimated that each 4% drop in SaO_2 represented an odds ratio of 1.99 for glucose intolerance.[17] Independently of BMI, fasting insulin—an indirect indicator of IR—correlated with OSA severity.[18]

However, here again, a bias in interpreting such data lies in the fact that a sleep debt per se, such as frequently interrupted sleep or shortened sleep duration without breathing abnormalities, also leads to IR.[19] Indeed, patients submitted to sleep debt exhibit a higher HOMA index, abnormal glucose tolerance, and a reduction in first-phase insulin secretion.[20] Therefore, some of the mechanisms involved might also be due to sleep deprivation rather than strictly hypoxia/reoxygenation. In the recent Sleep Heart Health Study, the odds ratio for fasting glucose intolerance was 1.7 for mild and 1.46 for severe OSA, and this correlated with SaO_2. In this large-scale clinical investigation, OSA was independently associated with glucose intolerance, IR, and noninsulin-dependent diabetes mellitus.[21] In another trial, fasting and postload glycemia increased with OSA severity, with a concomitant decrease in insulin sensitivity.[22] Recently, it was shown that a high fat diet in normal rats was followed by sleep apneas.[23]

In diabetic patients, the elevated number of sleep apneas appears to be predominantly of central rather than obstructive origin, likely because of the frequent presence of au-

tonomic neuropathy in this disease. Poor sleep quality in diabetic patients is related to higher HbA_{1C} values.[24]

OSA and Cardiovascular Diseases

Mortality is greater in patients having AHI values greater than 20.[25,26] Obstructive sleep apnea severely affects cardiac function in compromised hearts. The Sleep Heart Health Study showed that cardiovascular diseases (CVD) were more frequent in OSA patients, even in those with moderate AHI values.[27] In this cross-sectional study performed on more than 6000 subjects, a strong correlation was established between AHI and the prevalence of CVD (coronary heart diseases, heart failure, and stroke).[27] Obstructive sleep apnea at baseline is a significant predictor of CVD, and a recent study showed that the CVD incidence was 57% in untreated vs 7% in efficiently treated OSA patients.[28] In addition to hypertension, OSA patients have a 58% prevalence of cardiac arrhythmias.[1] Acute experimental OSA leads to arterial stiffness.[29] Chronic OSA patients accordingly show diminished aortic distensibility and have an increased stiffness index.[30] Patients with OSA spending 9% of the night time with SaO_2 below 90% exhibit carotid wall hypertrophy.[31]

OSA, METABOLIC DERANGEMENTS, AND CVD: A BIDIRECTIONAL PROCESS?

As briefly stated above, the increase in OSA in patients suffering from IR/diabetes or severe cardiac pathologies is a well-known clinical observation. Additionally, OSA is likely to aggravate preexisting diseases. The first clinical studies were biased by confounding factors, mainly the presence of obesity, but also by subjective self-answered questionnaires or self-reporting of snoring. Later studies using more careful patient observations (eg, polysomnography and blood sampling during apneas) and improved matching of patients control groups, as well as experimental investigations, suggested that OSA might induce by itself—or intensify—the switch towards diabetes and lead to macrovascular complications.[32]

Do OSAs Induce Insulin Resistance?

A main question is whether OSA can be causal to the metabolic- and vascular-related disturbances (Fig.1). In snoring children[19] and adults,[33] higher insulin levels are present, usually revealing IR. Fasting insulin levels correlate with OSA.[34] Nonobese patients suffering from OSA have more visceral fat[35] and diminished adiponectin,[36] both major situations favoring IR and vascular disturbances. Pioneering studies have recently suggested that the presence of the ApoEe4 allele might predispose to OSA, and the presence of this genetic variation also in Alzheimer's disease raises the possibility that OSA might, via recurrent hypoxic episodes, be involved in the cognitive deterioration affecting these patients.[37] Humans exposed to high altitude hypoxia exhibit decreased insulin sensitivity, indicating that hypoxia per se is able to generate IR.[38] Even acute hypoxia for 30 min at a $SaO_2 < 75\%$ leads to a decrease in glucose disposal rate.[39] Interestingly, such data are similar to what is observed in hypoglycemia, despite major differences in stress hormone profiles, thus pointing again towards a specific role for hypoxia. Here also, sleep deprivation per se may play a role, since short sleepers have an odds ratio of 2 for developing IR.[40]

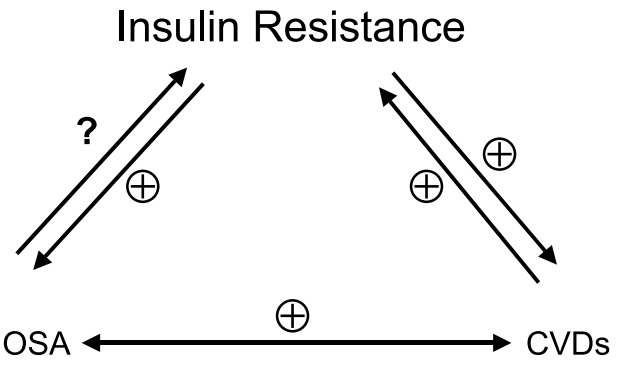

Figure 1 - Scheme illustrating the actual hypothesis of possible bidirectional relationships between obstructive sleep apneas (OSA), insulin resistance, and cardiovascular (CVD) disorders

In preclinical experiments, the main features of OSA can be simulated by sophisticated technical devices allowing repetitive and abrupt adjustable changes in respiratory gas in chambers. This procedure is called intermittent hypoxia (IH). In vitro, cultured cells can be exposed to selected levels of oxygenation. For example, IH or fructose feeding (another way to induce IR) both reduce the ventilatory response to hypoxia and hypercapnia and lead to elevated insulin concentrations[41] and reduced insulin sensitivity.[38,42] Interestingly, IH worsens—while continuous hypoxia improves—glucose tolerance, suggesting that repetitive cycles of low and high oxygen play a determining role.[38]

Do OSAs Favor Diabetes?

Occasional and regular snoring increases the risk of diabetes by 1.5 and 2.25 respectively.[43] The incidence of diabetes was doubled over 10 years in middle-aged, habitual snorers.[44] In a paper that just appeared, a prospective study, the Wisconsin Sleep Cohort, comprising 1387

patients, evaluated the prevalence and the incidence of type 2 diabetes in subjects with OSA. It appeared that the odds ratio for developing diabetes within 4 years was 1.62 with an AHI > 15, compared with subjects with AHI < 5 after adjustments for age, sex, and body habitus.[45] The prevalence of diabetes in subjects with AHI > 15 was 14.7%, as compared with 2.8% in those with AHI < 5. Although this study does not constitute a definitive proof, such data strongly argue for a causal role of OSA in diabetes development.

Do OSAs favor Cardiovascular Diseases?

One of the most striking cardiovascular complications of OSA is hypertension. The sympathetic discharge accompanying hypoxia/reoxygenation induces vascular resistance which does not resume during daytime.[1,40] Therefore, there is a state of persistent chemoreceptor activation.[32] The hypertension induced by OSA has a particular profile: diastolic pressure increases early, and patients experience no diurnal variation of systemic blood pressure. Importantly, there is also no nocturnal dipping of blood pressure. This type of hypertension severely affects the brain and heart, with little effect on the kidneys.[46] Otherwise healthy patients suffering from OSA show increased body weight and sympathetic muscle activity.[47] Stroke and cardiac arrest in the early morning hours are other typical features of OSA: a lack of normal reaction of brain vessels to isocapnic hypoxia during non-REM sleep could explain the vulnerability of these subjects towards stroke.[48]

In mice, chronic IH increases blood pressure and hematocrit as well as the weights of the left and right ventricle and septum, signs of right heart loading and pulmonary vasoconstriction.[49,50] The same profile is found in humans: 25% of OSA patients have mild pulmonary hypertension; 18% suffer right ventricular dysfunction, and they have a 3-fold increase in risk for CVD.[51] The susceptibility of hearts to infarction was increased in rats subjected to 35 days of IH.[52] Here again, IH is more detrimental than sustained hypoxia for increasing blood pressure and sympathetic activation.[53] Obstructive sleep apnea also leads to elevated levels of NPY, another factor of vasoconstriction.[54] In a study in rats, the IH-induced hypertension was found to last several weeks after cessation of the procedure.[55] Each additional incident of apnea increased the odds ratio for hypertension by 1%.[56] This striking link between OSA and hypertension[57], as well as that between OSA, congestive heart failure and respiratory alterations[58] have been widely reviewed recently.

Figure 2 summarizes the main potential consequences of OSAs on metabolic and vascular parameters.

MECHANISMS OF OSA-INDUCED METABOLIC AND VASCULAR DISORDERS

The similarity of OSA-related pathologies with metabolic syndrome is striking: in addition to hypertension, risk factors for atherosclerosis, inflammation (cytokines), hemostatic disorders, oxidative stress, and defects in vascular reactivity are among the major common features. The following chapter will document the major recent findings in biochemical and cellular mechanisms underlying these complications.

Inflammation / Adhesion Molecules

As in metabolic syndrome, a mild inflammatory state characterizes OSA.[1] Indeed, several studies have reported an increase in CRP, IL-6, IL-8, or TNFα in patients with OSA.[59–61] In adolescents free of CVD but with an AHI > 5, CRP levels were increased even after adjustment for the confounding obesity factor.[62] Interestingly, partial sleep deprivation also increases CRP levels.[63] TNFα levels are also elevated in serum and monocytes.[60,61,64,65] Post apnea,

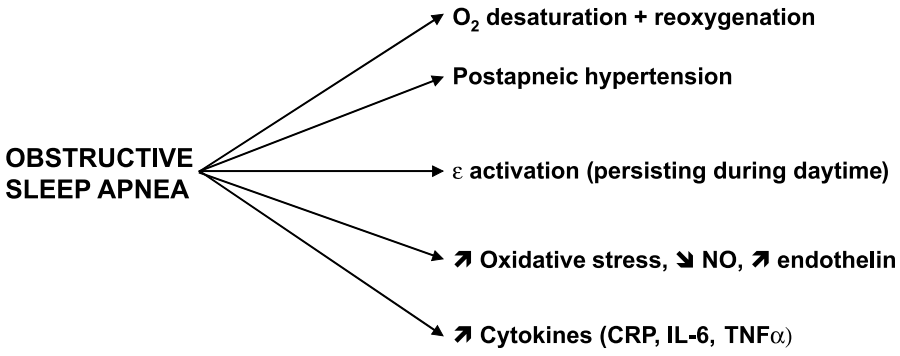

Figure 2 - Main cardiometabolic consequences of obstructive sleep apneas

TNFα increases immediately after SaO_2 reaches a threshold of 85%.[66] Moreover, the TNFα circadian rhythm is disturbed (less during night, more during day).[67] These molecules are known to be closely linked with IR and predictive of type 2 diabetes.[68] Adhesion molecules such as ICAM-1, VCAM-1, or E-selectin are also increased in patients suffering from OSA.[1,69] A particular role for CD11c and CD15 has been recently proposed.[70]

Adipokines

Several studies have demonstrated an increase in circulating leptin levels in OSA patients, which correlates with SaO_2.[71] Indeed, it has been shown that leptin rises in order to compensate for IH.[38] The leptin increase is seen even in otherwise healthy subjects suffering from OSA.[47] High plasma soluble leptin receptor concentrations and reduced glucose uptake are correlated with OSA, and globally there seems to exist an inverse correlation between insulin sensitivity and leptin receptor concentration.[33,72] Another substance liberated by fat cells is adiponectin, the role of which is increasingly considered to be protective against IR and vascular disturbances. In OSA patients, in addition to increases in hsCRP and IL-6, adiponectin levels were reduced[36]; however, another study reported the opposite.[73] This should be taken into account, since leptin is considered important in IR and promotes oxidative stress, another potential factor involved in prediabetes and diabetes (see below).[74,75]

HIF-1 Alpha

Intermittent hypoxia, even in vitro, increases levels of hypoxia-inducible factor 1 alpha (HIF-1 alpha).[76] While HIF-1 might first increase as a protective, compensatory mechanism,[77] its sustained liberation may have deleterious effects[77]: indeed, HIF-1 is able to reduce eNOS (the endothelial isoform of nitric oxide synthase) and increase iNOS (inducible nitric oxide synthase) and VEGF (vascular endothelial growth factor), with possible consequences to vascular reactivity and permeability.[77-80]

Hemostasis

Blood platelets are activated and aggregate in OSA.[1] The blood coagulation system is activated by acute hypoxia.[81] Type III procollagen, as seen in NASH, correlates with SaO_2.[71] Patients with reduced SaO_2 have elevated D-dimer concentrations, indicating defects in the fibrinolytic system.[82]

Lipid Metabolism

Intermittent hypoxia leads to increased levels of total cholesterol, phospholipids, and triglycerides in normal animals. However, no further aggravation was seen if animals were already hyperlipidemic.[83] In vitro, IH also leads to lipid loading of macrophages, a process critical for the development of atherosclerosis.[84]

Vascular Reactivity, Endothelin, Nitric Oxide

Patients with moderate to severe AHI values show reduced endothelial function and a strong correlation between both parameters.[85] The endothelium-dependent vasodilatation in response to acetylcholine or bradykinin is reduced, while endothelium-independent vasodilatation is unaffected.[86,87] Another study found this defect only in small resistance vessels but not in conduit vessels.[88] Impaired endothelium-dependent vasodilatation may be due to a defect in nitric oxide (NO) production and/or an excess of vasoconstrictor molecules. In fact, both are seen in OSA: NO production is reduced[88,90] (Fig. 3), and endothelin 1 (and possibly 2) is increased. In vitro, hypoxia reduces eNOS activity,[91] and in vivo, basal NO release is decreased in arterioles of rats chronically submitted to IH.[92] In addition, plasma levels of ADMA (plasma asymmetric dimethylarginine), an arginine metabolite that interferes with normal arginine uptake, are increased.[93]

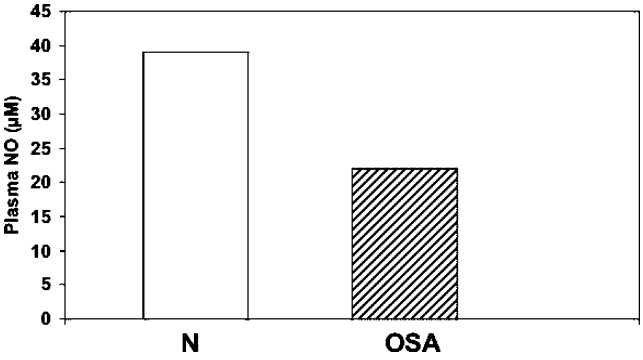

Figure 3 - Reduction in nitric oxide (NO) production in persons with obstructive sleep apnea (OSA) as compared to normal (N) controls (adapted from ref. 89)

As for endothelin, several groups have reported increases in endothelin-1 in sleep deprivation[93] and OSA.[94,95] Others have reported increases in big endothelin-1.[96,97] Interestingly, experimental IH-induced hypertension showed an oversensitivity in vascular constriction that was selective towards endothelin.[98] Endothelin is indeed a powerful vasoconstrictor[98] that may be responsible for IH-induced

hypertension.[99] It may also induce oxidative stress by generating superoxide via NADPH oxidase activation.[100,101] In contrast, one clinical investigation failed to find endothelin-1 modifications in patients with OSA.[102] Thus, despite some remaining controversy, most data points towards an important implication of endothelin in peripheral vascular resistance and hypertension in OSA.

Oxidative Stress

The occurrence of multiple cycles of hypoxia/reoxygenation occurring in OSA patients raises the question of oxidative stress as a logical, main cause of the complications found in this pathology. Indeed, both hypoxia per se and, more expectedly, the reoxygenation phase are prone to produce free radicals[102]; in particular superoxide produced by mitochondria during hypoxia acts as an oxygen sensor for adaptive mechanisms to limit the harmfulness of low oxygen.[103–109] Oxygen species released during hypoxia may act as signalling molecules and have been postulated to resemble a preconditioning stimulus.[110] It is known from the impressive amount of literature on oxidative stress that this phenomenon is linked to all undesirable side effects associated with OSA. For example, provoking oxidative stress in rats leads to vasoconstriction, to an increase in blood pressure, and a reduction in NO production.[111] If animals are already insulin-resistant (Zucker rats), administration of a pro-oxidant for some days switches IR to frank diabetes.[112]

Surprisingly, however, the role of oxidative stress in OSA is controversial. Investigations about the occurrence and extent of oxidative stress in OSA have, paradoxically, generated conflicting results. In animals, sleep deprivation reduced glutathione levels in the thalamus and hypothalamus.[113] Chronic IH led to left ventricular dilatation with increased lipid peroxides and lower superoxide dismutase levels.[114] The so-called " reductive stress" observed during hypoxia is mediated by NADPH oxidase, the gene and protein expression of which is increased in IH.[115] Conversely, in mice with no or suppressed capacity to produce NADPH oxidase, no lipid peroxidation or inflammatory reaction could be observed.[115] However, in humans, data are more controversial; the production of superoxide was increased in neutrophils of OSA patients,[116] and 8-isoprostane was elevated in the breath condensate in a manner correlating with AHI values.[117] In contrast, several studies failed to document oxidative stress; susceptibility of LDL (low-density lipoprotein) to oxidation, which is an indirect way to detect oxidative stress, was not different from controls.[118] Another study could detect neither differences in lipid peroxidation nor diminished superoxide dismutase levels.[119] Very recently, a clinical study dedicated to this topic completely failed to find changes in oxidized LDLs, thiobarbituric acid reactive substances, or isoprostanes, which are different substances that reflect various possible sources/targets of oxidative stress.[120]

Oxidative stress may precede endothelial dysfunction and IR,[121] which makes it an attractive candidate. However, it seems that in humans, against expectations, there is presently no firm evidence for oxidative stress, at least as a chronic pathological defect.[122] Considering on one hand the complexity of this field and its numerous contradictions[121] and, on the other hand, the possibility that local, repetitive, and transient peaks of oxidative stress are not necessarily translated into permanently measurable defects, a definitive conclusion should not be drawn here. Alternative explanations may also exist. For example, early IR primarily occurs in the skeletal muscles, but we ignore whether the insult developing in OSA is sufficient to induce severe abnormalities in this tissue: a recent paper showed that, at least globally, oxygen levels in muscle tissue did not reach critical anaerobic levels during systemic hypoxia close to levels observed in OSA.[123] Finally, because stress reactions are induced at the gene level, it could be that such mechanisms can compensate for the hypoxic stimulus over long periods of time.

OSA, IR, AND CVD: IS MICROCIRCULATION THE CLUE?

The similarities between metabolic syndrome (syndrome X) and OSA are striking. If we do not consider the literature about OSA in IR or diabetes but take it from the point of view of OSA as the primary defect, we observe the same profile of disturbances as described for IR and its associated vascular pathologies.

Sympathetic Activation and Its Consequences

Experimental IH and clinical OSAs lead to elevated sympathetic tone that persists during the daytime.[124,125] Muscle sympathetic nerve activity and its chemoreflex control are also chronically elevated.[126,127] Evidently, sympathetic activation will also translate into elevated heart rate and blood pressure as well as left ventricular thickness, eventually leading to cardiac failure. Activation of the central sympathetic nervous system and activation of the hypothalamic-pituitary-adrenal axis, which is also increased in OSA,[128] are known factors responsible for the development of HT, cortisol elevation, and IR.[129] Furthermore the sympathetic nervous system controls organs such as the liver and the pancreas, which are closely involved in insu-

lin and glycemia regulation.[130,131] In addition, insulin, which increases in OSA, is itself able to stimulate the sympathetic system. Higher levels of heart rate and pulse pressure are responsible for a phenomenon called "hyperdynamic circulation," which is linked to the metabolic syndrome[131,132] and adverse cardiovascular risks.[133,134] Interestingly, hyperdynamic circulation occurring in parents predicts IR in their children.[135]

Left ventricular relative wall thickness is inversely correlated with skeletal muscle glucose uptake, both in the presence and absence of hypertension.[136] Despite normal hormonal signaling in muscles, insulin-stimulated glucose uptake is impaired in patients with chronic heart failure.[137] Chronic OSA can lead to some degree of heart failure, and this complication, in turn, reduces flow to the hindquarters and limits the vascular flow capacity of mainly high oxidative muscle fibers, ie, those most sensitive to insulin.[138] Therefore, heart failure reduces the proportion of capillaries supporting continuous whole blood flow.[139] Interestingly, left ventricular dysfunction without concomitant heart failure may be sufficient to induce disturbances in skeletal muscle arteriolar dimensions and reactivity, suggesting that perturbations in muscle may start very early.[140]

Systemic blood pressure, on the other hand, is accompanied by microvascular rarefaction in skeletal muscle and impaired vasodilatation.[141] This, in addition to a decrease in type I oxidative muscle fibers and an increase in the diameter of fast-twitch fibers, would increase the diffusion distance for insulin to its sites of action, explaining at least in part how hypertension could be linked to peripheral IR.[142–144] Indeed, serum cholesterol and glucose are inversely related to the percent of highly insulin-sensitive type I fibers in hypertensive patients, whereas negative correlations were found between the degree of capillarization and glucose, cholesterol, and uric acid. Under conditions of stimulation, the reactivity of skeletal muscle arterioles is limited in hypertensive rats.[145,146] Impaired endothelium-dependent vasodilatation of small arteries and arterioles is also seen in experimental IH.[47,147]To what extent these limited reactions of the resistance vessels are responsible for IR in HT is still unclear, but they are clearly related.[148,149]

Microcirculation as a Key Player?

A somewhat provocative hypothesis should be discussed here: if we consider the group of nervous, chemical, and vascular factors found in OSA, all ingredients are present that favor malfunctioning of the microcirculation. It is interesting to note that the resistance vessels, and not the larger conduit vessels, are the site of impaired endothelium-dependent vasodilatation in OSA.[88] The question then is if—and how—impaired microcirculation can lead to—and aggravate—the cardiovascular disorders observed in OSA patients.

It has been proposed that microvascular (arterioles, capillaries) defects could precede or act in concert with IR.[150,151] In skeletal muscle, each capillary supplies several muscle fibers; therefore, one might expect capillary rarefaction, as seen in hypertension or heart failure, to be one of these defects. Moreover, because several (10 to 15) capillaries are grouped into functional units and each unit is controlled by one terminal arteriole, the recruitment of capillaries upon demand depends on the reactivity of the feeding arteriole. Therefore, defects in arteriolar reactivity to nervous inputs or local hemodynamic forces, such as shear stress, may impair the recruitment and/or perfusion of capillaries. Among substances involved in capillary recruitment, insulin itself has hemodynamic properties at the microvascular level; low insulin concentrations that do not increase bulk blood flow dilate terminal arterioles and increase capillary flow.[152–154] It has been suggested that small increases in insulin from meals, by opening additional microcirculatory units, "open its own way" for reaching skeletal muscle cells in order to store excess postprandial glucose.[155] Other physiological regulatory processes that are specific for the microcirculation, such as precapillary arteriolar vasomotion, may also be defective and lead to a patchy and inadequate tissue perfusion.[156] Any defect in these processes leads to reduced functional capillary density and thereby to impaired muscle glucose delivery and uptake, which consequently favors the development of IR.

Although this hypothesis still needs to be fully confirmed,[157–159] the profile of OSA fits largely with this theory. Today, OSAs can be reasonably well simulated in animals, new devices allow microcirculation to be measured noninvasively in humans, and clinical awareness of the frequency and importance of this pathology is sharply growing. Therefore, targeted microcirculatory investigations should be implemented to evaluate the importance of this anatomical entity.

CONCLUSION / PERSPECTIVES

The explosion of data within the past 5 years indicates that OSA is a "young" investigated disease, inasmuch as its potential harmfulness is concerned. The classical view of this pathology has largely been modified in recent years by demonstrating that it is a serious medical situation linked with behavioral, anatomical, and physiological disturbances leading to metabolic and cardiovascular complications. Moreover, it appears to be responsible for a non-negligible fraction of car accidents and human deaths as a conse-

quence of daytime sleepiness.

The development of continuous positive airway pressure (CPAP) as a therapy for OSA has generated mixed results, even if one excludes the limited patient compliance due to discomfort. Thus, while surrogate endpoints such as AHI[5], TNFα[65], reactive oxygen species,[87,93] or endothelial function were improved by CPAP, some global clinical outcomes have not necessarily shown the same benefit.[5,160] Moreover, for various reasons, a good portion of the general population has mild OSA and, as such, is at risk for CVD but is not amenable to CPAP therapy. It is therefore important to know much more about this widespread and harmful pathology in order to possibly develop alternative therapeutic strategies.

As for most domains, available data in OSA are partly conflicting. This field of investigation is only beginning and needs more experimental models, confirmations of preliminary findings, and target-directed clinical protocols. In the present review, we have tried to give a broad and updated objective state of our actual knowledge to date. Nevertheless, recent data indicates that OSA may not only be a consequence of IR or obesity but might also be causal, making these relationships bidirectional. If true, this would mean that not only could OSA aggravate existing IR and its related vascular abnormalities, but it could also directly induce an array of perturbations favoring—or directly generating—a state much resembling the well-known metabolic syndrome. We believe that, although the amount of sound data is still limited, the convincing nature of this data supports this latter hypothesis. In view of the list of OSA-modified parameters, we also propose a hypothesis according to which microcirculation might play a key role in this pathology.

RESUMO

Wiernsperger N, Nivoit P, Bouskela E. Apnéia obstrutiva do sono e resistência à insulina: qual o papel da microcirculação? Clinics. 2006;61(3):253-66.

A apnéia obstrutiva do sono é um problema médico cujo reconhecimento tem aumentado. As últimas pesquisas mostrando sua freqüência na população em geral e seu importante papel metabólico, vascular e comportamental aumentou o número e a natureza das investigações revelando, assim, novos aspectos que abrem caminhos para estudos. Embora a apnéia obstrutiva do sono seja um fenômeno bem conhecido acompanhando diabetes e obesidade, novas descobertas sugerem que esta relação causal pode também ser verdadeira no sentido inverso. Na realidade, a apnéia obstrutiva do sono pode ser o marco inicial ou primário que induz ou agrava uma série de distúrbios vasculares e metabólicos que se aproximam da síndrome metabólica. Esta revisão discutirá mecanismos estabelecidos e potenciais responsáveis por estas mudanças. A apnéia obstrutiva do sono parece realmente juntar todos os elementos necessários para induzir resistência à insulina, hipertensão e possivelmente insuficiência cardíaca. Após análise cuidadosa destas modificações, con-

siderando que as mesmas são interligadas, propomos que a microcirculação, como ocorre nos casos de síndrome metabólica e diabetes, poderia representar o denominador comum que mediaria a progressão desta patologia. Esta hipótese é discutida em detalhe e deve ser verificada em estudos pré-clínicos e clínicos apropriados que são atualmente possíveis usando técnicas não-invasivas em humanos.

UNITERMOS: Apnéia obstrutiva do sono. Resistência à insulina. Hypoxia. Síndrome metabólica. Microcirculação.

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