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Title

New frontiers in obstructive sleep apnoea.

Permalink

<https://escholarship.org/uc/item/11h106n6>

Journal

Clinical Science, 127(4)

ISSN

0143-5221

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et al.

Publication Date

2014-07-01

DOI

10.1042/cs20140070

Peer reviewed

New frontiers in obstructive sleep apnoea

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Abstract

OSA (obstructive sleep apnoea), the most common respiratory disorder of sleep, is caused by the loss of upper airway dilating muscle activity during sleep superimposed on a narrow upper airway. This results in recurrent nocturnal asphyxia. Termination of these events usually requires arousal from sleep and results in sleep fragmentation and hypoxaemia, which leads to poor quality sleep, excessive daytime sleepiness, reduced quality of life and numerous other serious health consequences. Furthermore, patients with untreated sleep apnoea are at an increased risk of hypertension, stroke, heart failure and atrial fibrillation. Although there are many predisposing risk factors for OSA, including male gender, endocrine disorders, use of muscle relaxants, smoking, fluid retention and increased age, the strongest risk factor is obesity. The aim of the present review is to focus on three cutting-edge topics with respect to OSA. The section on animal models covers various strategies used to simulate the physiology or the effects of OSA in animals, and how these have helped to understand some of the underlying mechanisms of OSA. The section on diabetes discusses current evidence in both humans and animal models demonstrating that intermittent hypoxia and sleep fragmentation has a negative impact on glucose tolerance. Finally, the section on cardiovascular biomarkers reviews the evidence supporting the use of these biomarkers to both measure some of the negative consequences of OSA, as well as the potential benefits of OSA therapies.

Key words: animal model, biomarker, cardiovascular disease, diabetes, obesity, obstructive sleep apnoea (OSA)

INTRODUCTION

OSA (obstructive sleep apnoea) is by far the most common respiratory disorder of sleep. OSA is caused by the loss of upper airway dilating muscle activity during sleep that is superimposed on a narrow upper airway, resulting in recurrent nocturnal asphyxia [1]. Termination of these events usually requires arousal from sleep to re-establish upper airway tone, eliminate obstruction and allow ventilation to resume. This sleep fragmentation and hypoxaemia lead to poor quality sleep, excessive daytime sleepiness, reduced vigilance, accidents, neurocognitive dysfunction, decreased work productivity, and reduced quality of life [2]. Furthermore, patients with untreated sleep apnoea are at increased risks of hypertension, stroke, heart failure and atrial fibrillation (Figure 1) [3].

There are many predisposing risk factors for OSA, including male gender, endocrine disorders (e.g. hypothyroidism and acro-

megaly), use of muscle relaxants, smoking, fluid retention and increased age [4]. However, the strongest risk factor is obesity, particularly central obesity. Fat deposition around the upper airway narrows it and predisposes it to collapse. Furthermore, obesity reduces lung volumes, which also destabilizes the upper airway by reducing the tethering effect of higher lung volume. The links between obesity and OSA are of particular concern given the increasing rates of obesity in the developed world. The prevalence of OSA in obese adults (aged 30 to 69 years) ranges from 11 to 46% in women and 33 to 77% in men [5,6]. Weight gain is also a strong predictor of incident OSA [7].

OSA is diagnosed by sleep testing, which usually consists of an attended overnight sleep study (polysomnogram) in a sleep laboratory or unattended overnight cardiopulmonary monitoring in the patient's home. Disease severity is classified according to the AHI (apnoea/hypopnoea index: the number of times the patient stops or decreases breathing per h of sleep). It is agreed

Abbreviations: AHI, apnoea/hypopnoea index; BP, blood pressure; CIMT, carotid intima media thickness; CMR, cardiac magnetic resonance; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin; HIF, hypoxia-inducible factor; NZO, New Zealand obese; OSA, obstructive sleep apnoea.

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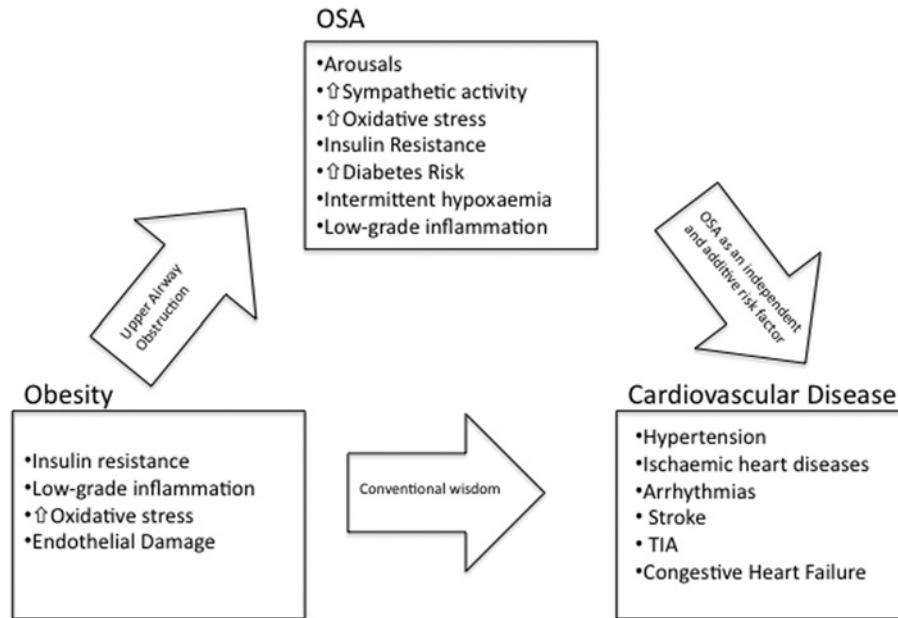


Figure 1 OSA as an important risk factor for cardiometabolic disease
TIA, transient ischaemic attack.

by consensus that an AHI of <5 events/h of sleep is considered normal, between 5 and 15 is considered mild, between 15 and 30 is considered moderate and >30 is considered severe disease [8].

Although common, OSA is under-diagnosed. In a random population based sample of 602 individuals aged 30 to 60 years, an AHI of ≥ 5 was found in 24% of men and 9% of women [9]. Moderate-to-severe disease (AHI ≥ 15) occurred in 9% of males and 4% of females. It is estimated that approximately 90% of women and 80% of men with moderate-to-severe OSA have not been clinically diagnosed [10].

Nasal CPAP (continuous positive airway pressure) therapy is considered first-line treatment for moderate-to-severe OSA [11]. By establishing a positive transmural pressure in the pharynx during sleep, CPAP prevents the upper airway from collapsing. CPAP reduces the severity of sleep fragmentation and improves nocturnal oxygenation, thereby improving daytime sleepiness, quality of life and neurocognitive function [12]. One of the major impediments to CPAP effectiveness is adherence (ranging from 50 to 75%) [13]. It is well established that CPAP improves vigilance, and accumulating data suggest that CPAP improves a variety of other outcomes such as motor vehicle crashes and cardiovascular events. Other therapies for sleep apnoea include dental appliances, weight loss, upper airway surgery, nasal valves and upper airway electrical stimulation.

In the present review, we will focus on three cutting edge topics with respect to OSA: animal models of OSA, diabetes and OSA, and cardiovascular biomarkers and OSA.

ANIMAL MODELS OF OSA

In this section, we review the various strategies investigators have used to simulate the physiology or the effects of OSA in animals,

and how these have helped to understand some of the underlying mechanisms of OSA.

Animals with spontaneous OSA

One naturally occurring animal model of spontaneous OSA is the English bulldog, a canine breed with an enlarged soft palate and narrow oropharynx. These animals can have central and obstructive apnoea with oxyhaemoglobin desaturation to levels below 90% during REM (rapid-eye-movement) sleep [14,15]. This model has been used predominantly to study upper airway anatomy and physiology [15–17], including testing of the impact of pharmacological treatments such as serotonergic medication [19,20].

Several rodent models of upper airway obstruction during sleep have been identified recently [21]. The NZO (New Zealand obese) mouse is a model of polygenic obesity and the metabolic syndrome exhibiting leptin resistance [22]. Similar to OSA patients, NZO mice have an increased volume of pharyngeal soft tissue structures and fat deposition in the tongue [16,23–25]. These mice also suffer from inspiratory flow limitation and apnoeas. In addition, Polotsky et al. [26] measured upper airway collapsibility in genetically obese leptin-deficient (*ob/ob*) dietary obese and lean mice. Increased upper airway collapsibility occurred in both genetic and dietary obese mice [20]. These novel rodent models of sleep apnoea will provide new insights into the pathogenesis and pharmacotherapy of OSA.

Airway occlusion

Researchers have also simulated OSA with induced airway obstruction in animals. Examples include sedated and intubated pigs, where obstructive apnoeas were induced by recurrent endotracheal occlusions that allowed for the assessment of acute haemodynamic and autonomic nervous system responses [27],

and a rodent model of upper airway occlusion that has also been developed [28]. Changes in neck flexion and body position of cats to cause airway obstruction during sleep have been reported [29].

In a sophisticated model using tracheostomized dogs, sleep state was continuously monitored using electroencephalography. A computer would generate periods of sleep-induced airway obstruction using a remote control signal closing a valve in the tracheostomy [30]. Upon arousal from sleep, the valve would be opened and the airway obstruction released. This model was used to study sleep architecture, blood pressure and cardiac responses to apnoea [24,25,31]; however, the model is labour intensive with a low throughput making them challenging to use in studying OSA complications. Nevertheless, it is the animal model that most closely mimics the effects of human OSA yet developed because it not only induces apnoea, intermittent hypoxia and arousals from sleep, but it also induces marked negative intrathoracic pressure swings during obstructive apnoeas similar in magnitude to those that occur in humans. Using this model, it was shown that exposure of these dogs to OSA for several weeks caused daytime hypertension [26] and left ventricular systolic dysfunction [28].

Intermittent hypoxia

Today, the most commonly used rodent model of OSA is induction of intermittent hypoxia/re-oxygenation by rapid delivery of a hypoxic gas mixture to an airtight chamber, followed by flushing of the chamber with room air (e.g. 30 s of hypoxia alternating with 30 s of normoxia). Some models have tried to coincide delivery of hypoxic gases with the onset of sleep and removal when arousal occurs [32]; this approach is complex and labour intensive. Therefore the majority of studies have utilized models that are not strictly dependent on the timing of sleep and arousal. That is, rodents are exposed to periods of hypoxia of a fixed duration throughout the light phase (when they are usually asleep) and maintain normoxia during the dark phase when they are usually awake. Of note, studies using electroencephalography show that rodents exposed to this schedule of intermittent hypoxia also suffer from sleep fragmentation, abnormal sleep architecture, cognitive dysfunction and hypersomnolence [33,34].

It must be kept in mind that intermittent hypoxia does not reproduce all the physiological effects of OSA. That is, OSA is usually characterized by extreme swings in intrathoracic pressure due to effort against a closed airway and hypercapnia due to a reduction in ventilation; these would not be present in this model. Indeed, rodents are hypocapnic under conditions of hypoxia [35]. Furthermore, the degree of hypoxaemia is quite severe, to an extent not experienced by the vast majority of human patients with OSA [36]. Nevertheless, given that hypoxia/re-oxygenation is a key physiological feature of OSA and rodents exposed to intermittent hypoxia appear to suffer from many of the cardiovascular sequelae observed in patients with OSA (including hypertension, endothelial dysfunction, metabolic disorders and atherosclerosis) [37–40], this model is useful in potentially elucidating mechanisms of metabolic and cardiovascular effects of OSA.

Fletcher et al. [41] showed that rats exposed to intermittent hypoxia for 3 weeks developed hypertension. Furthermore,

carotid body denervation attenuated the hypertensive response, demonstrating that carotid body stimulation and increased sympathetic output [42] were mechanisms of this effect. It was later established that intermittent hypoxia activates the carotid body via oxidative stress mechanisms, and that induction of HIF (hypoxia-inducible factor)-1 α and inhibition of HIF-2 α were involved [43].

Intermittent hypoxia induces metabolic complications, including dyslipidaemia, insulin resistance and glucose intolerance, and this effect is augmented by obesity [44]. Although the molecular mechanisms of this interaction are not entirely clear, hypoxia of liver and adipose tissue probably play major roles [45,46].

One of the functions of the vascular endothelium is to regulate smooth muscle tone in arteries and arterioles. Endothelial function is assessed by measuring the degree of vasodilation in response to various stimuli (e.g. acetylcholine and transient forearm occlusion) and dysfunction is a precursor of atherosclerotic and other vascular diseases. Rats and mice exposed to intermittent hypoxia develop endothelial dysfunction [47,48]. Interestingly, treatment with allopurinol (a xanthine oxidase inhibitor) improved cardiac function in the setting of intermittent hypoxia, suggesting that free radical generation probably plays a role in mediating the vascular effects of intermittent hypoxia [49]. Furthermore, Savransky et al. [40] reported that 12 weeks of intermittent hypoxia in mice fed on a high-cholesterol diet resulted in atherosclerotic lesions of the aorta, which were absent in mice not exposed to intermittent hypoxia. In mice fed on a normal diet, there was no significant atherosclerosis, suggesting a potential modulating effect of diet on the vascular impacts of OSA [38].

In summary, rodent models of intermittent hypoxia mimicking oxyhaemoglobin desaturations in human OSA have been developed and used to study the mechanisms of cardiovascular and metabolic dysfunction.

OSA AND DIABETES

Diabetes is a chronic illness that is increasing in prevalence. Mechanistic studies in humans and animal models have demonstrated that intermittent hypoxia and sleep fragmentation can have a negative impact on glucose tolerance [50–52]. There is substantial evidence from population-based and clinical studies that associates OSA with metabolic derangements [53,54].

Multiple studies have assessed the prevalence and incidence of diabetes in patients with OSA [55–60]. Cross-sectional analyses indicate a significantly higher prevalence of diabetes in patients with OSA compared with those without OSA, with rates ranging from 15 to 30% depending on the study population, the definition of OSA severity and the methods used to diagnose diabetes [55–57]. Several studies have also reported a significant association between increasing severity of OSA and the prevalence of diabetes [56,58].

A number of prospective studies have also examined the incidence of diabetes in patients with OSA. Overall, the results are somewhat mixed in terms of demonstrating an independent effect of OSA on incident diabetes. In the Wisconsin Sleep Cohort [56], OSA was associated with a higher risk for incident diabetes over a 4-year period, but this association was no longer significant after

Table 1 Randomized controlled studies examining the effects of CPAP treatment of OSA on glucose metabolism
HOMA, homeostatic model assessment.

Author (year)	Number of patients	Duration of study	Main findings
Coughlin et al. (2007) [69]	17 (CPAP/sham) 17 (sham/CPAP)	6 weeks	No difference in insulin sensitivity or fasting glucose and insulin
West et al. (2007) [70]	20 Type 2 diabetics (CPAP/sham) 22 Type 2 diabetics (sham/CPAP)	3 months	No difference in insulin sensitivity or HbA _{1c}
Lam et al. (2010) [68]	31 (CPAP) 30 (sham)	1 week	Improvement in insulin sensitivity at 1 week
Nguyen et al. (2010) [73]	10 (CPAP) 10 (sham CPAP)	3 months	No difference in fasting glucose
Kohler et al. (2009) [109]	20 (CPAP) 20 (CPAP withdrawal)	2 weeks	No difference in insulin sensitivity
Hoyos et al. (2012) [72]	34 (CPAP) 31 (sham)	12 weeks	No difference in insulin sensitivity at 12 weeks
Sivam et al. (2012) [74]	27 (CPAP/sham or sham/CPAP)	8 weeks	No difference in fasting glucose
Weinstock et al. (2012) [71]	25 Pre-diabetics (CPAP/sham) 25 Pre-diabetics (sham/CPAP)	8 weeks	No difference in HOMA or 2 h glucose; improvement in insulin sensitivity and 2 h insulin only in severe OSA

adjusting for confounders such as age, sex and body habitus. In the Busselton Health Study [58], there was a significant independent association between moderate-to-severe OSA and incident diabetes over a 4-year follow-up period, but the sample size was small. In another study [59], OSA was independently associated with diabetes after adjusting for confounders [including BMI (body mass index)] over a mean follow-up period of 2.7 years. Interestingly, one clinic-based study of 168 middle-aged patients [60], reported a significantly higher incidence of diabetes in women with OSA, but not in men with OSA, after a follow-up period of 16 years. In a prospective study of 4000 middle-aged adults, intermittent hypoxia was associated with an increased risk of developing diabetes after a 3-year median follow-up [61]. There is evidence from clinical studies to suggest that the presence and severity of OSA is associated with poor glucose control in diabetic patients [62].

One key question is whether CPAP therapy in patients with OSA improves glucose control in patients with diabetes. Five uncontrolled studies have examined the effects of CPAP on glycaemic control [63–67]. Two studies reported improvements in night-time glucose levels after 1 night [67] and 5 weeks [66] of CPAP use. Two other studies showed improved insulin sensitivity without a change in HbA_{1c} levels after 3–4 months of CPAP use [63,64]. In one study involving 25 obese patients with diabetes [65], there was a significant improvement in HbA_{1c} and post-prandial glucose levels after 3 months of CPAP therapy. One observational study found that patients with moderate-to-severe OSA who used CPAP regularly had a significant reduction in the rate of diabetes, even after adjusting for weight changes [59].

A total of eight studies using either parallel or cross-over randomized controlled designs have investigated the effects of CPAP therapy on measures of glucose metabolism; characteristics and main findings of these studies are shown in Table 1. Overall, only two of the eight studies [68,71] reported positive findings during the randomized treatment period, and another [72] had positive

findings only in the open non-randomized extended portion of CPAP therapy. In the only randomized controlled study conducted in diabetic patients [70], 3 months of CPAP use had no effect on insulin sensitivity or HbA_{1c} (glycated haemoglobin) levels. Notably, use of CPAP was low, averaging about 3.3 h per night. Overall, the nightly treatment use (CPAP or sham-CPAP) was 5 h or less in most studies [70–74], which represents an important limitation of these randomized trials.

In summary, current evidence strongly supports an association between OSA and diabetes with a substantial proportion of patients with diabetes suffering from unrecognized OSA. Whether OSA represents an independent risk for the development of diabetes needs to be investigated further in large prospective studies. The role of OSA in the management of diabetes is in urgent need of further assessment, and there remains debate about whether CPAP treatment of OSA leads to improved glucose metabolism. Large scale randomized controlled trials of CPAP treatment of OSA with robust assessments of insulin sensitivity and glucose tolerance are needed.

CARDIOVASCULAR BIOMARKERS IN OSA

As described above, animals exposed to intermittent hypoxia suffer adverse cardiometabolic effects, including hypertension, dyslipidaemia, endothelial dysfunction and atherosclerosis. In observational studies, patients with OSA have a 3-fold increased risk of incident CVD (cardiovascular disease), including stroke and myocardial infarction [75]. However, there is currently a lack of definitive data regarding the benefits of CPAP for measurable cardiovascular outcomes such as stroke and myocardial infarction [76]. Long-term randomized controlled trials using such end points are challenging to perform in patients with OSA for many reasons [77]. One issue is that it is both difficult and unethical to enrol sleepy patients into a prolonged study in which no therapy is provided to one of the groups, since patients would

be denied symptomatic benefit as a result of the study design. In addition, the enrolment of asymptomatic patients may be problematic, since such patients may be poorly adherent with CPAP therapy due to lack of perceived benefits [78]. To complicate matters further, some data suggest that sleepy patients with OSA may be the ones more likely to experience cardiovascular benefits with CPAP treatment [79].

Consequently, many investigators have suggested that biomarkers could potentially be used as surrogate outcome measures to test the impact of sleep apnoea therapies [76,80,81]. A useful biomarker should be easy to measure, be consistently and strongly associated with future cardiovascular risk (preferably on the causal pathway), plausible and potentially show signs of improvement with treatment within a reasonably short time period [82].

One potentially useful biomarker would be BP (blood pressure) [83]. OSA is linked to the development of systemic hypertension based on animal studies of intermittent hypoxia for 24 h and also prospective epidemiological studies [2,84–86]. In addition, BP is easy to measure, and a consistent and well-recognized strong risk factor for the development of CVD [87].

However, the degree to which daytime BP is reduced after CPAP therapy is very modest (i.e. 2–3 mmHg) [88] and far less than that of antihypertensive medical therapy [89]. Before BP is dismissed as being unhelpful in the OSA biomarker arena, several points are worth considering. It is clear that OSA causes marked nocturnal surges in BP, which could be an important risk factor in plaque rupture [90]. These nocturnal BP surges are typically not captured by studies of daytime BP and thus the magnitude of the therapeutic benefits may be underestimated. In addition, some patients, such as those of younger age, sleepiness and increased CPAP adherence, may experience substantial BP reductions with OSA therapy [91–93]. Autoregulatory mechanisms maintain BP within a relatively narrow range [94]. Although speculative, reductions in catecholamines due to OSA treatment might thus have only a modest effect on BP due to these counter-regulatory mechanisms (e.g. baroreflexes and autoregulation), but the cardiovascular effects might be more substantial. Thus, although BP might be useful, other markers should also be looked at.

Inflammatory markers may also be useful biomarkers to consider. Many investigators accept CRP (C-reactive protein) as a marker of systemic inflammation and its regulation is thought to be IL (interleukin)-6-dependent. The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study showed robust improvements in cardiovascular outcomes in patients with elevated CRP treated with rosuvastatin [95,96]. Hypoxaemia in sleep apnoea is thought to increase CRP levels. Several OSA studies have shown associations between OSA and CRP; however, these data are controversial since obesity is a dominant predictor of CRP in some studies. Interventional studies have also shown improvements in CRP with apnoea therapy [97], although these findings are not consistent across studies. However, the marked variability in the results with CPAP intervention suggests that CRP may be relatively insensitive to the burden of OSA. In addition, CRP may be predominantly a marker of CVD, rather than causally linked [98].

CMR (cardiac magnetic resonance) imaging is being increasingly used to assess cardiac structure and function [99]. Prelimin-

ary data support the use of CMR markers in studying the impact of OSA severity and treatment [100,101]. CMR imaging may thus provide a useful surrogate outcome measure which could be used in OSA clinical trials. A major issue is that testing is expensive, which may preclude use in large multi-centre trials.

CIMT (carotid intima media thickness), as assessed with carotid ultrasonography, may also be a marker to consider. CIMT is a marker of future atherosclerosis (atherosclerosis precursor) [102], and patients with increased CIMT (or changes in CIMT) are at increased risk of future cardiovascular events [103–105]. OSA appears to be associated with increased CIMT in a number of studies and is related to disease severity even after controlling for confounders [106,107]. A small randomized trial reported that CPAP treatment of OSA reduced CIMT [108].

Clinical trials in OSA are limited by the lack of adequate biomarkers to use as surrogate outcome measures. Defining important markers, which can change in the shorter term, is a priority. Changes in biomarkers that provide compelling evidence for improved cardiovascular risk can be assessed in future controlled clinical trials using more robust clinical end points.

CONCLUSIONS

OSA is a common under-recognized disease. Accumulating data from both animals and humans implicate OSA as an important risk factor for cardiometabolic disease (see Figure 1). Future mechanistic studies using animal models, and human observational and intervention studies using biomarkers and robust clinical end points should provide more insights into the link between cardiometabolic health and sleep apnoea.

FUNDING

Our own work was supported by the National Institutes of Health [grant numbers R01-HL-075079 (to E.T.), program project grant P01-AG11412 (to E.T., project leader), CTSA-UL1 TR000430 (awarded to the University of Chicago), and R01 HL080105 (to V.Y.P)], the Canadian Institutes for Health Research [Sleep Team grant (to N.T.A., A.A.J.H. and I.L.)], a Vancouver Coastal Health Research Institute Clinician Scientist award (to N.T.), a Canadian Institutes of Health Research Operating Grant [grant number MOP-82731] and the Clifford Nordal Chair in Sleep Apnea and Rehabilitation Research (to T.D.B.)

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Received 27 January 2014/27 February 2014; accepted 28 February 2014

Published on the Internet 10 April 2014, doi: 10.1042/CS20140070