

Obstructive sleep apnoea and cardiovascular disease – time to act!

Robert Thurnbeier

Pulmonary Division, Kantonsspital Münsterlingen, Switzerland

Summary

Sleep related breathing disorders are common and their potential to disrupt sleep leading to daytime fatigue and hypersomnolence is widely acknowledged. In the future, obstructive sleep apnoea (OSA) may become even more important because obesity as a main risk factor is increasingly prevalent. Apart from disturbing sleep, OSA has also been recognised as a risk factor for hypertension, acute cardiovascular events and metabolic disturbance such as insulin resistance. Several randomised controlled trials demonstrated a positive effect of nasal continuous positive airway pressure (CPAP) treatment on arterial blood pressure, leading the “Joint National Council on High Blood Pressure” to list obstructive sleep apnoea as the first identifiable cause of arterial hypertension. Recently, a growing body of evidence demonstrated also a risk reduction of fatal and non-fatal cardio-

vascular events by treatment of obstructive sleep apnoea. A beneficial effect of treatment of OSA was also shown for patients with heart failure, or heart rhythm disturbance. Obstructive sleep apnoea may no longer be seen as a cause for daytime sleepiness and impaired quality of life only, but also as an independent risk factor, at least for the occurrence of hypertension but probably for any cardiovascular and cerebrovascular disease. While prospective controlled trials to document a reduction of cardiovascular morbidity and mortality are awaited, therapeutic nihilism seems no longer appropriate. With effective treatment available, subgroups that may profit best remain to be identified.

Key words: obstructive sleep apnoea (OSA); continuous positive airway pressure (CPAP); cardiovascular disease (CVD); hypertension

Introduction

Obstructive sleep apnoea (OSA) is characterised by repetitive upper airway collapse resulting in drops of oxygen saturation and sleep fragmentation with cortical arousals and activation of the autonomic nervous system. For a long time, OSA was recognised as a potential cardiovascular risk factor.

In a recent prospective controlled study, obstructive sleep apnoea was identified as an independent risk factor for the onset of arterial hypertension. A clear dose-effect was demonstrated: the more apnoeas per hour of sleep – the higher the chance for becoming hypertensive [1]. Different mechanisms may explain the relationship between OSA and cardiovascular disease such as increased sympathetic activity, oxidative stress, inflammation, metabolic disturbance and endothelial dysfunction [2, 3]. OSA has been associated with an increased prevalence of coronary artery disease, heart failure and rhythm disturbance. Sudden car-

diac death and stroke occur preferentially at night in patients with OSA, whereas in patients without the condition, sudden death is more likely to occur in the morning hours [4, 5]. However, with the exception of hypertension, confounding factors have made it difficult to establish causal relationships between OSA and cardiovascular risk. In a recent landmark observational study, CPAP treatment has been shown to reduce the risk of fatal and non-fatal cardiovascular disease [6]. Bearing this new evidence in mind, the importance of OSA as a treatable cardiovascular risk factor may no longer be ignored.

The association of OSA and cardiovascular consequences can be addressed by three key questions. *First:* Is OSA an independent cardiovascular risk factor? *Second:* If so, does treatment of OSA reduce cardiovascular risk, morbidity and mortality? *Third:* Is screening for OSA indicated for patients at risk for cardiovascular disease?

Is obstructive sleep apnoea a cardiovascular risk factor?

In a canine model of artificial OSA, systemic blood pressure rose by approximately 15 mm Hg upon airway occlusion but returned to normal, when the airways were no longer repeatedly occluded [7]. Patients with obstructive sleep apnoea have high sympathetic activity when awake, with further increases in blood pressure and sympathetic activity during sleep. They also have higher catecholamine excretion due to elevated sympathoadrenal activity [8]. Heart rate acceleration following apnoeas and hypopnoeas is regularly seen in sleep studies (figure 1). A blunting of the physiological nocturnal fall in arterial blood pressure (“nondipping”) is often found in patients with sleep-disordered breathing [9]. The relative contribution of oxygen desaturation, hypoxia and sleep fragmentation to increased sympathetic activity remains to be determined.

Increased pleural pressure swings due to inspiratory effort against occluded upper airways may cause transient blood pressure fall and bradycardia followed by an overshooting reaction when breathing continues. High intrathoracic pressure swings increase cardiac transmural pressure and therefore left-ventricular afterload. Increased venous return impedes left ventricular filling by a right-to-leftward shift of the septum [10]. Cardiac contractility is reduced with hypoxia. Tachycardia and hypertension increase myocardial oxygen consumption.

Abnormalities evident in patients with OSA that were identified by a systematic review included increased sympathetic activation, vascular endothelial dysfunction, increased oxidative stress, inflammation, increased platelet aggregation, and metabolic dysregulation [2]. Recent data have shown that intermittent hypoxia as typically seen in OSA activates inflammatory pathways which differs from a sustained hypoxemia response. Sustained hypoxemia results in up-regulation of erythropoietin and vascular endothelial growth factor, whereas intermittent hypoxemia rather affects products of inflammatory

genes such as NF κ B and TNF α [11]. All of these mechanisms may increase the risk for arteriosclerosis and cardiovascular disease such as stroke and myocardial infarction but also heart failure and heart rhythm disturbances.

Hypertension

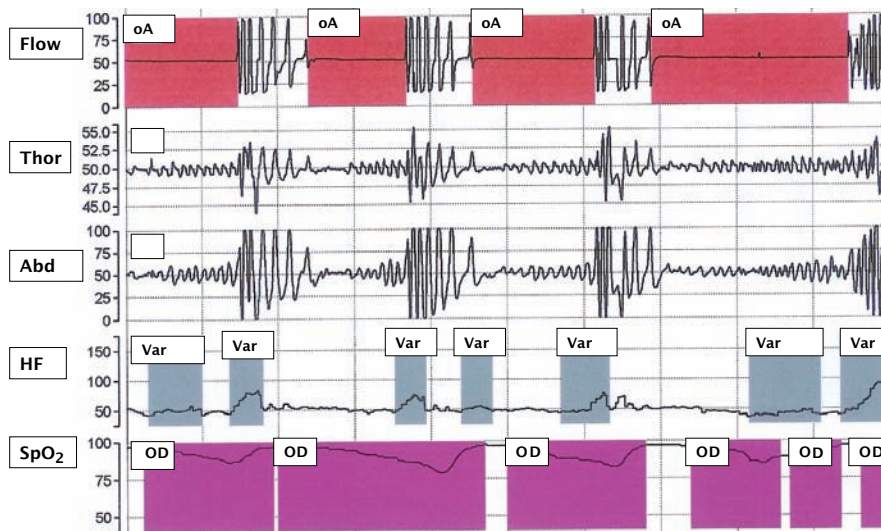
Moderate to severe OSA presenting with an apnoea-hypopnoea index (AHI >15/hr) (apnoeas and hypopnoeas per hour of sleep) affects 4% of women and 9% of men in their middle age [12]. The prevalence of hypertension in OSA patients may be as high as 50% and in hypertensive patients, OSA can be diagnosed in up to 30%. Early studies found increased AHI and decreased oxygen saturation but not snoring to be independent risk factors for hypertension. The association of OSA with hypertension was demonstrated with large population based studies [13]. Onset of hypertension with OSA was demonstrated by the Wisconsin group, showing dose-dependent increase of incident hypertension even with very mildly elevated AHI (ie AHI from 5–15/hr). With moderate to severe OSA, hypertension was 2.89 times more likely to occur in a 5-years period [1]. OSA was listed first among identifiable causes of hypertension by the ‘Joint National Council on High Blood Pressure’ in 2003 [14].

Cardiovascular and cerebrovascular disease (CVD)

In a case-control study, Peker et al. identified OSA as an independent risk factor for coronary artery disease (CAD) after adjusting for important confounding factors [15], also *mortality* from CAD was found to be associated with OSA by the same study group [16]. In the Sleep Heart Health Cohort, the prevalence of CVD was 1.4 times higher in OSA patients than those without OSA [17]. In an observational cohort study, patients with OSA (AHI >5) were compared to those with a negative sleep study.

Figure 1

Five minutes of respiratory polygraphic recording at 03:30 a.m. in a patient with severe OSA. Heart rate always increases at the end of an apnoea. The longest apnoea (duration > one minute) is followed by an increase of the heart rate from around 50 bpm to over 90 bpm.



Abbreviations: oA obstructive apnoea; OD: Oxygen Desaturations; Flow: nasal airflow pressure swings; Thor and Abd: thoracic and abdominal strain gauge signals; Var: Heart rate variability, variability of more than 6 beats per minute is registered and marked by the inbuilt software

The mean AHI in the OSA group was 35. After adjustment for other risk factors, hazard ratio for stroke or death from any cause was 1.97 (95% CI 1.12-3.48) in disfavour of the OSA group [18].

Heart failure

Of patients with stable heart failure 11 up to 37% suffer from obstructive sleep-apnoea [19, 20]. In the Sleep Heart Health Study, the diagnosis of OSA heralded a 2.38-fold increased risk for heart failure [17]. Obstructive sleep apnoea has negative effects on ejection fraction as well as diastolic function. Moreover, mild pulmonary arterial hypertension with right ventricular dilatation has been documented. The normal fall in heart rate at sleep onset is blunted by OSA. Highly negative intrathoracic pressure swings during airway occlusion

sharply increase cardiac afterload. Systemic hypertension and intermittent hypoxia as a consequence of OSA may play a major role in the development of heart failure.

Atrial fibrillation

In a comparative study, consecutive patients undergoing electrocardioversion for atrial fibrillation (AF) and patients without past or current AF referred to a general cardiology practice were followed. The study group found a strong association between OSA and AF, such that OSA was clearly more prevalent in patients with AF than in high-risk patients with multiple other cardiovascular diseases. The coinciding epidemics of obesity and AF underscoring the clinical importance of these data were stressed by the authors [21, 22].

Does treatment of obstructive sleep apnoea reduce cardiovascular risk, morbidity and mortality?

Arterial hypertension

In a parallel group study, mean 24 hr blood pressure was significantly reduced by 3.3 mm Hg with continuous positive airway pressure (CPAP) treatment compared to subtherapeutic CPAP, which corresponds to a risk reduction for coronary artery disease of about 15%, an effect-size comparable to an antihypertensive drug [23]. In another (placebo-controlled) cross-over study, blood pressure was non-significantly reduced by 1 mm Hg only [24]. Pressure drop was greater in subjects with longer CPAP use (>3.5 hr/night) and those with >20 4%-oxygen-desaturations per hour of sleep. Still another parallel group study involving very severe OSA patients (mean AHI >60/h) showed a significant reduction of mean blood pressure of 9.9 mm Hg [25]. In a small study involving patients with OSA and refractory hypertension, introduction of CPAP treatment led to sharp reduction of blood pressure in sleep [26]. A 2006 Cochrane Systematic Review concluded, that 24 hr systolic and diastolic blood pressure were lower in patients with CPAP treatment compared to controls [27]. However, in a study of 35 non-sleepy, hypertensive patients with OSA, CPAP treatment did not significantly reduce blood pressure compared to sham-CPAP treatment [28]. Moreover, CPAP did not modify quality of life, objective sleepiness, vigilance, attention, memory, or arterial blood pressure in non-sleepy patients with a remarkably pathologic AHI (30 and more apnoeas/hypopnoeas/hr) [29]. Therefore, sleep fragmentation, hypersomnolence and "mediators" may play an important role for the pathogenesis of hypertension in OSA [29]. Moreover, patient history seems to be crucial for treatment indication in patients with an elevated AHI. Controlled studies of the effect of nasal CPAP on blood pressure are given in table 1.

Cardiovascular and cerebrovascular disease (CVD)

Since 1992, a cohort of patients with OSA was followed with record of the incidence of new fatal and non-fatal cardiovascular events (stroke and myocardial infarction). The results were published in 2005 by Marin et al. [6]. Mean follow-up time was 10 years. The cohort included 264 healthy men, 377 snorers without OSA, 403 with untreated mild to moderate OSA, 235 with severe OSA and no treatment, and 372 with OSA and adequate treatment. Although all patients were offered treatment, some, even with severe OSA, refused it and were therefore suitable as a control group. Mean (SD) AHI in mild-moderate OSA was 18.2(3.5), in severe untreated and treated OSA, AHI was 43.3(5.7) and 42.4(4.9), respectively. The incidence of fatal as well as non-fatal events in untreated patients with severe OSA was significantly higher than in otherwise healthy age- and body mass index (BMI)-matched individuals. A dose effect for this association was postulated. Simple snoring without apnoeas was not identified as a risk factor. Treatment with CPAP significantly reduced the risk for fatal and non-fatal cardiovascular events. Odds ratios for fatal cardiovascular events per 100 person-years are given in figure 2. As treatment allocation was done by preference of the patient and not randomly, confounding factors could not be excluded. Nonetheless, these data may remain unique for some time to come, because from an ethical point, the evidence of the beneficial effects of CPAP precludes withholding of this treatment to a randomised control group for a period long enough to study cardiovascular effects.

The effectiveness of OSA treatment was also tested in a consecutively followed sleep clinic cohort of 182 middle-aged men over 7 years. The incidence of at least one cardiovascular event was observed in 37% of cases with OSA compared to 7% of subjects

Table 1

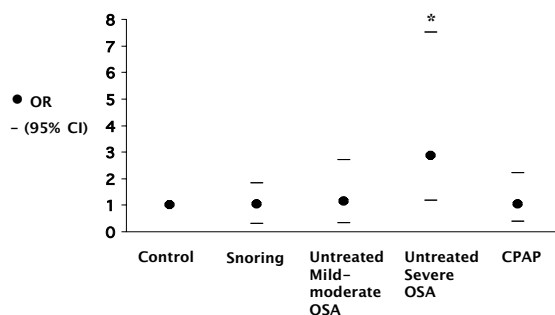
Controlled studies of the effect of nasal CPAP on blood pressure

Study	n	AHI/DI*	ESS	Outcome	Remarks
Becker et al. [25]	32	64	14	↓ mean BP by 9.9 mm Hg	Randomised controlled trial, sham-CPAP versus CPAP
Pepperell et al. [23]	95	37	16	↓ mean BP by 3.3 mm Hg	Randomised parallel trial subtherapeutic versus therapeutic
Dimsdale et al. [45]	38	48	NA	↓ nocturnal BP by 5 mm Hg	Randomised parallel trial subtherapeutic versus therapeutic
Faccenda et al. [24]	68	35	15	↓ diastol. BP by 1.5 mm Hg	Randomised placebo tablet randomised controlled cross-over trial
Monasterio et al. [46]	125	20	13	no effect on BP	Multicentre randomised trial, control group: lifestyle modification
Barnes et al. [47]	28	13	11	no effect on BP	Two centres randomised crossover trial, CPAP, mandibular device, placebo tablet
Barbé et al. [29]	55	56	7	no effect on BP	Multicentre randomised, placebo-controlled, parallel group study
Robinson et al. [28]	32	28*	5	no effect on BP	Prospective randomised sham-CPAP controlled trial
Campos-Rodriguez et al. [48]	68	58	15	no effect on BP	Parallel, randomised placebo-controlled, OSA patients pretreated with antihypertensive medication

AHI: apnoea-hypopnoea index; BP: Blood pressure; CPAP: Continuous Positive Airway Pressure; DI: Desaturation Index; ESS: Epworth Sleepiness Score; OSA: Obstructive Sleep Apnoea

Figure 2

Odds ratios (95%CI) for cardiovascular death associated with diagnosis, adjusted for possible confounding factors such as age, hypertension, diabetes, smoking status and lipid status. Odds ratio for untreated severe OSA was 2.87 (1.17–7.51) $p < 0.05$ (*), all other were n.s. compared to controls; Data from [6].



without the condition ($p < 0.001$). In the OSA group, incidence of cardiovascular disease was observed in 57% of incompletely treated cases compared with 7% of efficiently treated subjects ($p < 0.001$). It was concluded, that effective treatment of OSA reduces the excess risk for cardiovascular disease, even in relatively mild OSA, and in contrast to other studies, without regard to daytime sleepiness [30].

In a retrospective long-term observational study (7.5 yr), 168 patients with OSA were followed, 107 accepted CPAP, and 61 did not. Cardiovascular death occurred in 14.8% of the untreated and in 1.9% of the treated group ($p < 0.009$) [31]. As a general limitation, data taken from cohort studies are subject to potential selection bias by uneven treatment allocation.

In a prospective, open trial, CPAP treatment during 18 months in patients with an AHI > 20 afforded significant protection against new vascular events after ischaemic stroke [32]. However, these favourable results were not reproduced in a most recent randomised controlled trial [33] and difficulties of using CPAP after stroke have consistently been recognised [5, 33]. Thus, early detection and treatment of sleep apnoea as primary prevention has to be emphasised.

Heart failure

The hypothesis, that treatment of OSA with continuous positive airway pressure in patients with heart failure improves left ventricular systolic function was tested in patients with decreased left ventricular ejection fraction (LVEF 45 percent or less) despite best medical therapy. Patients were randomly assigned to either continuing medical treatment or additional CPAP therapy for one month. Compared to conventional treatment, CPAP significantly improved LVEF by 9% [34].

The effect of CPAP was also tested in a randomised controlled study involving 40 OSA patients with daytime symptoms of sleepiness (Epworth Sleepiness Scale score of 9–11) and heart failure. CPAP was capable to significantly increase LVEF (from 38 ± 3 to $43 \pm 0\%$; $p < 0.05$) and to lower nocturnal urinary norepinephrine levels [35].

Sleep apnoea depresses cardiac response to exercise which is important for quality of life. Three months of CPAP therapy improved stroke volume and cardiac output in a prospective controlled trial [36].

However, treating OSA in patients with heart failure has not yet been shown to improve mortality. Therefore, CPAP treatment is not justified in patients with OSA and heart failure but no complaint of daytime fatigue for an exclusive prognostic indication.

Heart rhythm disturbance

Atrial fibrillation: In an observational comparative study, patients with documented OSA ($n = 39$) and AF were followed after DC cardioversion. Of these, 12 were treated with adequate CPAP. The recurrence rate of AF after one year was 42% in the treated group, whereas recurrence rate in the control group was 53% ($p = \text{n.s.}$) and 83% ($p < 0.05$) in the untreated OSA group. It was concluded that pa-

tients with untreated OSA have a higher recurrence of AF after cardioversion than patients without a diagnosis of OSA and that appropriate treatment with CPAP in OSA patients was associated with lower recurrence of AF [22].

Brady- and tachyarrhythmia: Brady- and tachyarrhythmic events have also been associated with the

presence of OSA. While bradyarrhythmia seems to be REM sleep associated and occurred independently from coronary artery disease [37], tachyarrhythmias may predispose to sudden cardiac death, as was speculated in the study of Gami et al. [4].

Is screening for obstructive sleep apnoea indicated for patients at risk for cardiovascular disease?

Cardiovascular disease will remain the leading cause of death in civilised countries; therefore all effort to lower cardiovascular risk should be taken. An increasing body of evidence points to an association of OSA and adverse cardiovascular risk. The evidence supporting beneficial effects of treatment is steadily growing. However, indications to screen for OSA and target subgroups remain to be defined. Adults with drug-resistant hypertension, defined as “a clinic blood pressure of $\geq 140/90$ mm Hg, while taking a sensible combination of three or more antihypertensive drugs, titrated to maximally recommended doses”, have a high prevalence of OSA. In a study of 41 patients with drug resistant hypertension, 83% had an AHI of ≥ 10 . OSA was even more prevalent in men (96 vs 65%, $p = 0.014$) [38]. As a long-term beneficial effect of CPAP treatment could be

shown in a small group of drug-resistant hypertensive patients with OSA [26], screening seems warranted in these patients. Recently, screening using nocturnal oximetry for the detection of sleep-related breathing disturbances was recommended for patients with heart failure [40]. Simple clinical tests can help to identify patients at increased risk of OSA. Narrowing of the airway by the lateral pharyngeal walls, enlargement of the uvula, tonsils and tongue are significantly associated with OSA [40]. Body mass index and neck size have been consistently shown to predict sleep disordered breathing [12, 41, 42]. In a clinical update statement, experts in the field recommended considering OSA in high risk patients, especially obese ($\text{BMI} > 30 \text{ kg/m}^2$) with refractory hypertension and “non-dippers” [43].

Conclusion

Obstructive sleep apnoea is an independent risk factor for arterial hypertension and probably also for any cardiovascular disease. Nasal CPAP effectively lowers blood pressure, especially in patients with high AHI and severe daytime symptoms. A steadily growing body of evidence points to beneficial effects of CPAP treatment on cardiovascular risk factors. However, CPAP has not yet been tested in large, randomised, prospective controlled trials with the outcome of CVD events.

CPAP therapy only works when patients put their masks on. Patients who are not sleepy or do not feel an immediate benefit after initiation of therapy are very hard to convince to continue “just to improve their prognosis”. As a benefit of CPAP treatment in non-sleepy patients with increased AHI has not consistently been proven, there is no need to insist on treatment. Rather, all effort should be undertaken to treat subjects with daytime fatigue and

sleepiness and a high cardiovascular risk profile. Therefore, screening for OSA is recommended in patients at increased risk for cardiovascular disease and a high clinical pre-test probability of OSA only.

Alternatives to CPAP treatment should be offered if this treatment is not accepted [44]. Although, with the exception of bariatric surgery, reduction of body weight has only modest potential to revert OSA, weight control should always be attempted if appropriate.

Correspondence:

PD Dr. med. Robert Thurnbeier

Leitender Arzt Pneumologie

Kantonsspital

CH-8596 Münsterlingen

E-Mail: robert.thurnbeier@stgag.ch

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