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OBSTRUCTIVE SLEEP APNEA AND HYPERTENSION

J.P. Baguet[a], K. Narkiewicz[b] and J.M. Mallion[a]
From [a]Department of Cardiology and Hypertension, Grenoble University Hospital, Grenoble, France and [b]Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland

Correspondence: Jean-Philippe Baguet, Cardiologie et Hypertension artérielle, CHU de Grenoble - BP 217, 38043 Grenoble Cedex 09, France, tel +33476765440, fax +33476765559, JPBaguet@chu-grenoble.fr

Introduction

At present there are many epidemiological and clinical arguments in favour of an increase in cardiovascular risk linked to sleep apnea syndrome (SAS) [1]. Several studies have contributed important information to support this theory, particularly concerning the role played by SAS in cardiovascular morbid-mortality, even when the number of nocturnal apnea episodes is limited. Many pathophysiological mechanisms are suggested to explain morbid associations between SAS and cardiovascular diseases. Cardiovascular responses to apneas are acute - following each respiratory episode - and chronic [2].

Epidemiology and diagnosis of SAS

SAS is a common disease affecting around 5% of the general population, preferentially affecting men [3]. The clinical picture includes four main symptoms: diurnal hypersomnolence, frequent nocturnal arousals with nycturia, morning asthenia with or without headache, and severe snoring. Factors promoting SAS are not only obesity, age, smoking and consumption of alcohol, but also and above all, anomalies of the upper respiratory airways promoting snoring in these patients. Polysomnography is the standard examination for diagnosis of nocturnal respiratory arrest. It simultaneously records sleep, quantified air flow (nasal pressure), thoracic and abdominal respiratory movements, electroencephalogram and haemoglobin oxygen saturation. A respiratory polygraphy without sleep record is also used in establishing a diagnosis of SAS. Apnea may be obstructive (persistent respiratory effort), central (no respiratory effort) or mixed (starts as central type and ends as obstructive type). The number of apneas (airflow stops completely) and obstructive hypopneas (reduction of more than 50% in inspiratory flow or 30% linked to more than 3% desaturation and/or microarousals) lasting more than 10 seconds per hour of sleep (apnea-hypopnea index or AHI) can then be calculated. When the sensitive instruments described above are used, the threshold of 15 events per hour of recording is usually applied for SAS diagnosis.

Pathophysiological aspects of interactions between SAS and the cardiovascular system

Patients suffering from SAS will display permanent oscillations in their haemodynamic parameters during the night. The heart rate, blood pressure (BP) and cardiac output will therefore vary incessantly because of the repeated respiratory events and rapid changes in state of vigilance (cortical microarousals) induced by these respiratory anomalies. BP falls at the start of each episode of apnea then gradually increases to a peak pressure just at the moment when respiration starts again, with systolic BP possibly increasing by 15 to 80 mmHg during a cortical microarousal. These variations in BP occur under the influence of four stimuli: O2 desaturation, increase in PaCO2, increased respiratory effort, and microarousal at the end of the apnea. Respiratory resumption linked to arousal does not last for long with a new episode of apnea occurring as soon as the patient has gone back to sleep.

Repetition of these stimuli every night leads to chronic changes in the cardiovascular system response and structural modifications. All these stimuli, in particular desaturation-reoxygenation, are a source of sympathetic stimulation [4, 5]. This type of stimulation is well revealed by plasma or urinary catecholamines assay and microneurography data [6-8]. Moreover, SAS patients exhibit impaired baroreflex sensitivity to a hypotensive stimulus [9, 10]. This baroreflex adaptation may also contribute to the increase in resting autonomic tone observed in SAS patients. The chronic increase in sympathetic tone, alterations in baroreflex sensitivity and associated deficit in vascular relaxation lead to elevated peripheral vascular resistances in SAS [11]. Other potential mechanisms include abnormal peripheral chemoreceptor function [12], inflammation [13], endothelial dysfunction [14], increased levels of endothelin [15] and stimulation of the renin-angiotensin system [16].

Prevalence and characteristics of hypertension in SAS

The links between SAS and hypertension are more than a simple association, SAS being accepted by many authors, and acknowledged in the American JNC 7 recommendations for treating hypertension, as a cause of hypertension [17]. There are many predisposing factors for both pathologies however, particularly overweight and its associated hyperinsulinism [18]. The first major epidemiological study, performed in 1985 on 7,511 subjects, showed that the relative risk of hypertension in snorers compared with non-snorers was 1.94 in men and 3.19 in women [19]. At present, the prevalence of hypertension in SAS patients is estimated at nearly 60%. As has been well demonstrated by the Sleep Heart Health Study in 6,132 subjects, this prevalence increases constantly with the AHI [20]. This dose-effect relationship was also detected in another large study involving 2,677 subjects examined for suspected SAS [21]. In this last study, any increase in an event (apnea or hypopnea) per hour of sleep was linked independently to a 1% rise in the relative risk of hypertension and any 10% fall in nocturnal O2 saturation increases the risk of hypertension by 10%. Another study, the Wisconsin Sleep Cohort Study, with 709 subjects not treated for sleep anomalies, found a relative risk of hypertension after 4 years follow-up of 1.42 for an AHI < 5 and 2.89 when the AHI is > 15 [22]. In a recent study performed on 59 apnea sufferers not known to be hypertensive, we found a 42% prevalence of hypertension by clinical measurement and 76% using ambulatory BP monitoring over 24 hours (ABPM) [23]. In SAS patients, daytime systolic BP is generally not different to that of control subjects when matched for age and BMI [24]. On the other hand, using office BP recording and ABPM even more, it has now been well demonstrated that SAS patients have a high prevalence of isolated diastolic hypertension [23, 25, 26]. Taking these data into account, ABPM could be proposed for SAS patients whose clinical BP does not display any abnormality. According to the various studies published to date, nearly 30% of hypertensive patients suffer from SAS [27, 28]. This prevalence is even greater in refractory hypertension, particularly before the age of 50 [29, 30]. The severity of the hypertension also seems to be in proportion with that of the SAS [25].

RR interval variability is decreased and BP variability is markedly increased in patients with SAS [27, 31]. This variability is well assessed by ABPM but even more by non-invasive continuous BP measurement, cycle by cycle, using a digital sensor. The fall in BP which occurs during the night in a normal subject is often absent in apnea patients [32, 33]. In the study discussed previously, we found that 41% of apnoeic patients did not experience a fall of 10% or more in nocturnal BP (non dippers) [23]. If this anomaly is observed during an ABPM analysis in a hypertensive patient, it must suggest the possibility of SAS.

Deleterious role of the association of SAS with hypertension

The high prevalence of hypertension in SAS and the close relations between these two pathologies partly explains the high incidence of

cardiovascular events in apnoeic patients. Angina pectoris, myocardial infarction, heart failure (SAS often central), arrhythmia, cardiac conduction disorders and cerebrovascular events are often encountered during follow-up of apnoeic patients [19, 34-44]. Therefore, it was found that when the AHI was above 20, cardiovascular mortality was around 40% after 8 years in men [45]. Apart from these cardiovascular events, SAS is a major source of social handicap because of the snoring and non-recuperative aspect of the sleep obtained. A diagnosis of SAS, suggested by a questionnaire (the Epworth questionnaire in particular) [46] confirmed by polysomnography or respiratory polygraphy, is therefore an essential step, because treating this pathology seems to reduce the risk of later cardiovascular complications.

Left ventricular hypertrophy and SAS

Left ventricular hypertrophy (LVH) seems to be more common in cases of SAS, even after taking the BP into account [47, 48]. The frequency of occurrence of LVH rises with severity of SAS [49]. The greater prevalence of LVH in apneoeic patients appears to be related to postload elevation during apnea episodes and sympathetic hyperstimulation [49]. However, these data should be taken with care because of the difficulty in obtaining reliable measurement of left ventricular mass in SAS patients who are often overweight.

Effects of SAS treatment on BP

The first treatment for SAS was tracheotomy, which had a beneficial effect on BP values and cardiovascular morbi-mortality [50]. Today, therapeutic strategies for SAS include sleep postural changes, avoiding sleeping on the back, weight loss, avoidance of alcohol and sedative hypnotics, mandibular advancing device and upper airway surgical procedures. The most widely used treatment consists of continuous positive airway pressure (CPAP) administered during the night. CPAP treatment prevents airway collapse during inspiratory efforts. Effective long-term treatment of SAS by CPAP has been shown to decrease sympathetic activity and improve baroreflex control of heart rate [51, 52] and to improve BP control. Thus, several recent studies have shown that CPAP has a beneficial effect on BP levels. After a period of 7 days to 9 months, depending on the study, CPAP led to a reduction in both daytime and nocturnal BP with a fall in mean BP of around 5 to 10 mmHg [53-56]. The favourable effect of CPAP on BP therefore seems to be felt rapidly. This fall in BP with CPAP is also noted in patients suffering from refractory hypertension [57]. The fall in nocturnal BP with CPAP is greater when the patients use their device for more than 3.5 hours per night and when the SAS is severe [58]. This fall in BP with CPAP is parallel to that obtained for plasma and urinary norepinephrine [59]. The absence of antihypertensive drugs and the initial BP level have both been found to be significant, independent predictors for the lowering effect of CPAP therapy on systolic and diastolic BP [60]. The mechanism suggested to explain the efficacy of this treatment is the reduction in nocturnal BP peaks and microarousals by CPAP. Concerning medication, hypertension in apnea patients seems to be more sensitive to beta-blockers than other classes of antihypertensives [61]. The beneficial effect of this type of medical treatment can be explained by its inhibitory action on the sympathetic system.

Conclusion

SAS is a pathology which is both common and under-estimated, which cannot be summed up as a simple association of snoring and obesity. Its prognosis is closely linked to the occurrence of cardiovascular accidents. The causal link between cardiovascular events and SAS is only formally established for hypertension. There are many pathophysiological mechanisms which may explain the morbid association between SAS and hypertension, with sympathetic hyperactivity in the lead. SAS must be suggested in principle for any hypertensive patient, particularly if the hypertension is refractory to treatment, predominantly diastolic or linked to a non-dipper profile. The beneficial effect of treating SAS with CPAP with respect to BP seems to be well established.

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