

Obstructive Sleep Apnoea/Hypopnoea Syndrome and Hypertension

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متلازمة انقطاع النفس النومي الكامل/الجزئي وعلاقتها بارتفاع ضغط الدم

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الملخص: متلازمة انقطاع النفس النومي الكامل/الجزئي اضطراب شائع يصيب 2-4% من البالغين. توجد علاقة وثيقة بين متلازمة انقطاع النفس النومي الكامل/الجزئي وارتفاع ضغط الدم وذلك وفقا للدراسات التي اجريت على الحيوانات والدراسات الوبائية الكبيرة وكذلك الدراسات التدخلية. اظهرت الدراسات الوبائية علاقة طردية بين معدل انقطاع النفس النومي والخطر من ارتفاع ضغط الدم مستقبلا. هناك أسباب عديدة يمكن أن تؤدي الى ارتفاع ضغط الدم عند المصابين بمتلازمة انقطاع النفس النومي الكامل/الجزئي. فنشاط الجهاز العصبي الودي عند هؤلاء يزيد اثناء النوم وفي اليقظة. هذه الزيادة في نشاط الجهاز العصبي الودي عند هؤلاء الأشخاص ربما تكون ناتجة عن تنشيط مستقبلات الضغط والمستقبلات الكيميائية في الأوعية الدموية نتيجة التيقظ المتكرر ونقص أكسجين الدم الناتج عن انقطاع النفس الكامل/الجزئي أثناء النوم. تبين أن جهاز ضغط الهواء الموجب الذي يستعمل لعلاج متلازمة انقطاع النفس النومي الكامل/الجزئي يخفض كلا من نشاط الجهاز الودي وضغط الدم. بالإضافة إلى ذلك قد يساعد الخلل في وظائف الأغشية البطانية للأوعية الدموية في ارتفاع ضغط الدم عند المصابين بمتلازمة انقطاع النفس النومي الكامل/الجزئي. قد يكون نقص إنتاج غاز اكسيد النيتريك وزيادة إنتاج الجذور الحرة مسؤولا عن اختلال توسع الأوعية الدقيقة عند هؤلاء الأشخاص نتيجة نقص الاكسجين. أظهرت الدراسات أن العلاج بجهاز ضغط الهواء الموجب يساعد على إعادة وظائف الأغشية البطانية بشكل فعال.

مفتاح الكلمات: أفعال الضغط الانعكاسية. ضغط الدم. الأفعال الكيميائية الانعكاسية. وظائف الاغشية البطانية، ارتفاع ضغط الدم، متلازمة انقطاع النفس النومي الكامل/الجزئي، نشاط ودي.

ABSTRACT The obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is a common disorder, affecting around 2–4% of the middle-aged population. There is a strong association between OSAHS and hypertension, based on animal, large epidemiological and interventional studies. The epidemiological studies have shown a dose-response relationship between apnoea/hypopnoea index (AHI) and the risk of developing hypertension. Different mechanisms may have a role in the process of elevated blood pressure in OSAHS. Sympathetic activity is increased in OSAHS patients during sleep and wakefulness. This increase in sympathetic activity is probably due to activation of baroreflexes and chemoreflexes by frequent arousals and hypoxaemia a result of apnoea or hypopnoea events. Continuous positive airway pressure (CPAP) has been shown to reduce sympathetic stimulation and blood pressure in OSAHS patients. Altered endothelial function may also have a role in the pathogenesis of hypertension in OSAHS subjects. Reduction of nitric oxide (NO) production and increase in the formation of free radicals may be responsible for the impairment of the vasodilatation of micro-vasculature in these subjects as a result of hypoxaemia. It has been shown that effective CPAP therapy has a reversible effect on endothelial dysfunction.

Keywords: Baroreflex; Blood pressure; Chemoreflexes; Endothelial function; Hypertension; OSAHS (Sleep apnoea/hypopnoea syndrome); Sympathetic activity.

THE OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA syndrome (OSAHS) is a disorder characterised by repetitive upper airway collapse during sleep in association with daytime sleepiness

that has an estimated prevalence of 2% among middle-aged women and 4% among middle-aged men.¹ It was recognised only quite recently, although it has been extensively researched in the last 30 years.

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OSAHS-related features include excessive daytime sleepiness,^{2,3} neurocognitive impairment,⁴ and increased motor vehicle accidents.⁵⁻⁷ It has also been associated with adverse cardiovascular consequences such as hypertension and impairment of cardiovascular variability. Treating OSAHS is very rewarding, for the benefit to the patient is enormous in improving the quality of life as well as preventing long-term sequelae.

There is strong evidence that patients with sleep apnoea might be at increased risk of cardiovascular disease. Patients with sleep apnoea are often hypertensive^{8,9} and up to one-third of hypertensive patients may have sleep apnoea.¹⁰ Several cross-sectional studies have shown that the prevalence of hypertension increases progressively with the severity of OSAHS.¹¹⁻¹³ How hypertension is associated with OSAHS is not fully understood. However, repetitive episodes of airway occlusion during sleep, with consequent hypoxia, hypercapnia, dramatic changes in intrathoracic pressure and repeated arousals, may provoke a number of autonomic, haemodynamic, humoral and neuroendocrine responses. This review focuses mainly on the epidemiological link between OSAHS and hypertension and the autonomic responses that might occur in OSAHS patients. Other aspects of the possible vasculopathy in OSAHS will also be briefly reviewed.

EPIDEMIOLOGY

OSAHS and hypertension have common risk factors, such as obesity, alcohol intake, age, gender and lack of exercise, which makes causation impossible to prove, using epidemiology alone. However, several epidemiological studies have revealed a strong association between OSAHS and hypertension.¹¹⁻¹⁷

OSAHS IN THE GENERAL POPULATION

Early studies of the association between hypertension and snoring came from Norton et al. and Koskenvuo et al., who found that snoring was a risk factor for hypertension.^{14,15} Subsequent studies found that sleep apnoea was an independent risk factor for the development of hypertension, similar to age and obesity.¹⁶ A large epidemiological study showed that sleep apnoea significantly contributed to hypertension, independent of other risk factors.¹¹ Each apnoeic event per hour of sleep added 1% to the risk of having hypertension. More evidence linking OSAHS with hypertension is provided by the Wisconsin Sleep Cohort study, which

showed a dose-response association between OSAHS and *de novo* hypertension after 4 years of follow-up independent of confounding factors although the number of new hypertensive subjects was small.¹³ In the original report, patients with an apnea-hypopnea index (AHI) > 25 had a fivefold risk of hypertension.¹⁷ The increase in risk of hypertension was greater in thinner patients who had abnormal breathing. After correction for confounding factors, those with an AHI >15 had a 2.9-fold greater chance of developing hypertension in the following four years. A similar relationship between OSAHS and hypertension was found in the Sleep Heart Health Study.¹² In this study of 6,000 middle-aged and older adults, the prevalence of hypertension (defined as a resting BP \geq 140/90 mmHg or the use of anti-hypertensive drugs) increased progressively with the severity of OSAHS. After adjusting for the confounding factors, including obesity, the odds ratio in the group with severe OSAHS (AHI >30) was 1.37 (95% confidence interval (CI), 1.03-1.83; $p = .005$) compared with those with lowest AHI (< 1.5). A cross-sectional study in a normal population by Bixler et al. also indicated an association between hypertension and sleep apnoea independent of other risk factors. The association was strongest in young subjects, and decreased with age.¹⁸

OSAHS IN THE HYPERTENSIVE POPULATION

Epidemiological studies of hypertensive patients have also suggested an association between sleep apnoea and hypertension. Hypertensive patients had a greater prevalence of sleep apnoea than normotensive subjects.¹⁹ Grote et al. found that OSAHS was a risk factor for poor blood pressure control in younger hypertensive patients.²⁰ A greater prevalence of obstructive sleep apnoea is found in adults with drug-resistant hypertension (BP > 140/90 who require a combination of three or more antihypertensive drugs)²¹ supporting the idea of an etiological role of OSAHS in the cause of hypertension.

HYPERTENSION IN OSAHS SUBJECTS

Animal models

In dogs, obstructive sleep apnoea leads to the development of sustained hypertension.²² Obstructive sleep apnoea (OSA) was produced in four dogs using an occlusion valve attached to an endotracheal tube through which the dog could breathe. Obstruction of the airway by the valve was controlled by telemetry of elec-

trocardiogram (ECG) and electromyography (EMG) signals from the dog during a one to three month period. In the same dogs, sleep fragmentation was also induced. Arterial blood pressure was monitored for 12 hours every night. Obstructive sleep apnoea (OSA) caused a progressive increase in night-time mean arterial BP in each of the four dogs. There was no difference between the change in night-time BP caused by sleep fragmentation and that caused by OSA ($p = 0.4$). In contrast, the change in daytime BP caused by sleep fragmentation was significantly less than the change during OSA ($p = 0.001$). There were no changes in night-time or daytime heart rates during either OSA or sleep fragmentation. In another dog study of chronic OSA by Parker et al., acute airway occlusion during sleep increased left ventricular (LV) afterload and decreased fractional shortening. Chronic OSA caused a sustained decrease in LV systolic performance, caused by systemic hypertension and/or transient increases in LV afterload during episodes of airway obstruction.²³

Human studies

A case-control study found that patients with OSAHS had higher blood pressure than matched control subjects. Diastolic blood pressure in patients with OSAHS was significantly greater than controls during the daytime, night-time, and overall. OSAHS patients also had significantly greater night-time systolic BP ($p = 0.01$), although daytime and overall systolic blood pressure did not differ from control subjects.⁸ Direct evidence that OSAHS causes hypertension is provided by intervention studies, in which continuous positive airway pressure (CPAP) reduced BP.^{24, 25} Nevertheless, in order to understand the pathophysiology of hypertension in OSAHS, the mechanism of blood pressure elevation is discussed below.

OSAHS AND BLOOD PRESSURE

In healthy subjects, blood pressure normally decreases by 10% to 15% from its daytime value during sleep. This circadian drop in BP has been called dipping. However, some patients with OSAHS do not show nocturnal dipping of BP and are thus called non-dippers.²⁶ This may relate to apnoeas and hypopnoeas, which cause repeated nocturnal increases in BP, which consequently increase the mean sleeping BP.²⁷ The greatest pressure peaks occur after apnoea and may be 100 mmHg above the baseline value.^{28, 29} These acute nocturnal changes may lead to persistent daytime hypertension

as a long-term consequence²⁹ with an increased risk of target organ damage.³⁰ In a case-control study, sleep apnoea patients had significantly increased mean diastolic BP during both the daytime and night-time, and systolic BP was higher among OSAHS patients at night compared with controls. The nocturnal dip in BP was smaller in patients with OSAHS than in matched control subjects.⁸

Hypoxia may explain partly these variations in BP in sleep apnoea patients. In animals, repetitive episodic hypoxia causes diurnal elevation in BP in rats.³¹ Similarly rises in daytime blood pressure follow induced apnoeas in dogs and are probably related to hypoxaemia rather than arousal, because noise-induced arousal did not cause daytime hypertension in the same dogs.²² Increased sympathetic activation, perhaps induced by hypoxaemia, may be a key factor in causing long-term BP changes.³² However, other factors may be implicated in the development of hypertension in OSAHS patients, such as endothelial dysfunction, as discussed below.

SYMPATHETIC ACTIVITY IN OSAHS PATIENTS

DURING SLEEP

Normal sleep is physiologically divided into rapid eye movement (REM) and non-rapid eye movements (NREM) sleep. NREM is further divided into 4 stages from Stage 1 to 4. In normal sleep, heart rate, blood pressure, and sympathetic nerve traffic usually decrease.^{33, 34} This reduction of sympathetic activity appears to increase progressively from Stage 1 to Stage 4 sleep.²⁸ However, during REM sleep, sympathetic activity increases, to as much as double that of wakefulness.³⁴ Blood pressure and heart rate during REM are variable, but average about the same as during wakefulness.²⁸

In contrast, sympathetic activity is increased during sleep in OSAHS patients and the sympathetic and the haemodynamic state during sleep is determined primarily by the duration and severity of apnoea rather than by the sleep stage itself.²⁹ Repetitive episodes of obstructive apnoea, hypoxia and hypercapnia probably act through chemoreceptor reflexes and other mechanisms to increase sympathetic drive.³⁵ Furthermore, resumption of breathing results in increased venous return and increased cardiac output. This increased cardiac output is delivered into a severely constricted peripheral vasculature, with surges in BP.³⁵

EFFECTS OF AROUSAL FROM SLEEP ON BP

Normal spontaneous arousals from sleep are associated with transient increases in blood pressure, heart rate and ventilation.³⁶ These increases are caused by changes in sympathetic activity caused by the arousal. In a study in dogs,³⁷ ventricular stroke volume (SV) remained constant when apnoea ended, if there was no arousal. However, with arousal from apnoeas, heart rate and cardiac output increased, although SV decreased. Arousal increased the systemic, but not the pulmonary arterial pressure, in response to obstructive apnoea. The increase in systemic blood pressure was more marked during NREM sleep than in REM sleep.³⁷ In a large population-based study, sleep fragmentation index (SFI), calculated as the total number of awakenings or shifts to Stage 1 divided by the total sleep time per hour, was significantly associated with systolic, but not diastolic blood pressure, during wakefulness in individuals with AHI < 1. However, sleep fragmentation and blood pressure were not associated in those with AHI > 1 after controlling for the influence of the AHI. The authors concluded that sleep fragmentation was independently associated with a greater systolic blood pressure during wakefulness.³⁸ Noda et al.³⁹ found that end-apnoeic arousal and hypoxic asphyxia and the subsequent sleep fragmentation might contribute to nocturnal and diurnal elevation of BP. The rise in blood pressure with arousal might be caused by an increase in sympathetic activity. Sympathetic outflow remained elevated for a substantial period even after a hypoxic stimulus was removed;³⁵ nevertheless, it is unwise to conclude that sleep arousal is the sole contributor to sustained hypertension in awake sleep apnoea patients. However, in patients with higher AHI, sleep disruption may modulate the BP along with other effects such as hypoxaemia and changes in intrathoracic pressure, which may overcome the effects of arousal.³⁸

DURING WAKEFULNESS

Greater sympathetic activity in OSAHS patients may be present even during daytime wakefulness, when subjects are breathing normally and both arterial oxygen and carbon dioxide levels are normal.^{29, 40} Circulating catecholamines⁴¹ and muscle sympathetic nerve activity⁴² were greater in patients with OSAHS compared with normal subjects, probably because of baroreflex dysfunction, chemoreflex excitation and endothelial dysfunction. Greater sympathetic drive in

these patients may contribute, to a certain extent, to chronic elevation of resting BP. The mechanism underlying the sustained increase in sympathetic drive is not clear. Morgan et al. suggested that combined hypoxia and hypercapnia evoke long-lasting sympathetic activation.³⁵ This may explain in part the increased daytime sympathetic drive in OSAHS patients. However, repeated BP increases, acting via the baroreceptors, may reset the baroreflex, permitting a higher level of sympathetic activity and BP even during wakefulness. To understand the role of the chemoreflexes and baroreflexes in BP control in OSAHS patients, these two aspects are explained in detail below.

CHEMOREFLEXES

The chemoreflexes are important and powerful modulators of sympathetic activation. Hypoxia, which acts primarily on the peripheral chemoreceptors located in the carotid bodies,⁴³ and hypercapnia, acting on the central chemoreceptors located in the brain stem, trigger reflex increases in minute ventilation as well as sympathetic activity. Patients with OSAHS have an enhanced vascular response to hypoxia.⁴⁴ In a double-blind, randomised, controlled trial, it was found that muscle sympathetic nerve activity (MSNA) and mean arterial pressure were significantly reduced in OSAHS patients compared with control subjects during chemoreflex deactivation by 100% oxygen;^{44, 45} however, the enhancement of peripheral chemoreflexes is selective to autonomic, haemodynamic and ventilatory responses in normotensive OSAHS.⁴⁴ Furthermore, this enhancement of the reflex response to hypoxia is not explained by obesity, since obese subjects who are otherwise healthy with no OSAHS have chemoreflex responses similar to those seen in control subjects.^{44, 46} Nevertheless, obese patients have a greater response to hypercapnia.^{46 - 48} Both hypoxia and hypercapnia have local vascular effects, causing vasodilation, which lowers the blood pressure initially, which in turn increases sympathetic activity and catecholamine release.⁴⁹ During apnoea, sympathetic activity rises gradually, reaching its peak at the end of the apnoea, when oxygen desaturation and carbon dioxide retention are most marked.^{34, 45} On release of the airway obstruction and resumption of breathing, increased cardiac output, together with the constricted peripheral vasculature, result in a marked increase in blood pressure.³⁴ There is also a carry-over effect to the tonic activation of the peripheral chem-

oreceptors, even during normoxia, which may partly explain the increased sympathetic activity during the daytime (see above). However a double-blind study suggested that hyperoxia can suppress peripheral chemoreceptors in OSAHS patients, shown by a decrease in blood pressure and slowing of heart rate.⁴⁴

BAROREFLEX AND HYPERTENSION

There is evidence that the cardiac baroreflex is impaired if blood pressure is increased, in both humans^{50,51} and animals.⁵² Floras et al. found that the arterial baroreflex could buffer acute changes in blood pressure in subjects with WHO Stage 1 hypertension. However, this ability is weakened if the baroreflex sensitivity (BRS) is reduced. With the development of clinically evident cardiac adaptation to hypertension (WHO Stage 2), the contribution of the arterial baroreflex to the regulation of blood pressure is no longer detectable and the influence of cardiac and somatic afferents to reflex circulatory adjustment to activity may predominate.⁵⁰ Furthermore, Lantelme et al. found that hypertensive rats have impaired cardiac baroreflex responses, characterised by a range-independent decreased gain, which is not caused by cardiac hypertrophy.⁵² The impaired baroreflex may even precede the development of hypertension. Baroreflex inhibition of muscle sympathetic nerve activity is reduced in adolescents with a family history of hypertension, even when they are normotensive, which may lead to the development of hypertension by increasing sympathetic vasomotor tone.⁵³ This could also be a factor for hypertension in OSAHS patients, although there is no evidence for this so far.

BAROREFLEX IN SLEEP APNOEA

Patients with OSAHS have baroreflex dysfunction. Narkiewicz et al. used phenylephrine to activate baroreceptors and nitroprusside to deactivate them. Normotensive patients with OSAHS had an impaired response to baroreceptor deactivation, but not to baroreceptor activation. They suggested that the reduced baroreflex sympathetic modulation in patients with sleep apnoea was not accompanied by any impairment of baroreflex control of heart rate.⁴² In addition, OSAH patients have impaired baroreflex responses to a hypotensive stimulus.⁵⁴ Using sequence method analysis, it has been noted that baroreflexes are impaired in OSAHS patients compared with

healthy controls.^{55,56}

EFFECT OF TREATING SLEEP APNOEA ON SYMPATHETIC ACTIVITY AND BP

CPAP is the treatment of choice for majority of OSAHS patients. In addition to improvement of symptoms, CPAP treatment may also reduce sympathetic activity. Nasal CPAP was found to reduce catecholamines.⁵⁷ Somers et al. found that CPAP treatment caused an acute and marked reduction in nocturnal sympathetic nerve traffic.²⁹ However, CPAP does not reduce daytime blood pressure acutely, although it significantly reduces the large oscillations in blood pressure seen overnight in patients with untreated sleep apnoea.⁵⁸ Nevertheless, a small fall in night-time systolic BP was seen in OSAH patients after 2 weeks of treatment,⁵⁹ with some improvement in daytime mean arterial blood pressure in non-dippers after 3 weeks of CPAP treatment compared with the placebo.⁶⁰ However, when effective CPAP treatment was given for a longer period (8 weeks) in a before-and-after non-placebo controlled design, there was a significant fall in both systolic and diastolic BP, independent of changes in body weight.⁶¹ Thus, long-term treatment with CPAP may be needed to attenuate sympathetic activation and consequently reduce BP. This idea is supported by the findings that CPAP treatment reduced the muscle sympathetic nerve activity (MSNA) in otherwise healthy OSAHS patients, although the reduction was evident only after one and a half years of treatment.⁴⁷ Furthermore, in a randomized placebo-controlled crossover study, Faccenda et al. found that CPAP therapy reduced 24-hour diastolic blood pressure in comparison with the placebo, although the overall reduction was small, averaging 1.5mmHg over the 24 hours. The decrease was greater during the early morning period that is at 2:00 a.m. As predicted *a priori*, the decrease was greater in those with more nocturnal hypoxaemia (> 20% desaturations/hour).²⁴

OSAHS AND ENDOTHELIAL DYSFUNCTION

The endothelium is the cell layer lining the blood vessels. It is one cell thick and senses changes in haemodynamic states.⁶² The endothelium responds to physical and chemical stimuli by synthesis or release of substances such as nitric oxide (NO), prostacyclin, endothelins, endothelial cell growth factors, inter-

leukins, adhesion molecules, and fibrinolytic factors.⁶³ Therefore, the endothelium can greatly influence vascular tone and structure by releasing NO. Impaired endothelium dependent function and endothelium independent function in the forearm vascular bed is associated with an increased risk of acute cardiovascular events, including cardiac death.^{64, 65} The endothelium is a major target of oxidative stress, and this stress may play a role in the pathophysiology of vascular disease. In OSAHS, recurrent episodes of hypoxaemia followed by re-oxygenation may trigger endothelial damage, via oxidative stress, superoxide radical formation.⁶⁶ The combination of superoxide radical with nitric oxide and reducing nitric oxide bioavailability in the vessel wall leads to vasoconstriction. More recent studies have shown that oxidative stress and lipid preoxidation do not appear to be the key mediator for the cardiovascular diseases in OSAHS.^{67, 68} This finding contradicts the results of other studies which showed that OSAHS patients have an increased status of oxidative stress such as thiobarbituric reactive substances and peroxides⁶⁹ and decreased antioxidant capacity which could be reversed by CPAP treatment.^{70, 71} Only a few studies have shown increased expression of adhesion molecules⁷² and production of reactive oxygen species in leukocytes of sleep apnoea patients.^{73, 74} Pro-inflammatory factors such as interleukins, C-reactive protein and leukocyte adhesion molecules such as CD15⁷³ might also contribute to the pathogenesis of developing cardiovascular diseases and merit further evaluation. In addition, prothrombotic factors⁷⁵ such as fibrinogen, plasminogen activator inhibitor, and reduced fibrinolytic activity with enhanced platelet activity, may play a role in the process.⁷⁶ In a randomized double-blind placebo controlled crossover trial, it was shown that OSHAS is associated with endothelial dysfunction using venous occlusion plethysmography during intra-arterial infusion of endothelium-dependent (acetylcholine and substance P) and endothelium-independent (sodium nitroprusside) vasodilator. Vasodilatation was significantly impaired in subjects with oxygen desaturations (20 dips of 4% desaturations/hr) compared to non-desaturators ($p < 0.05$) In the same study, treatment with CPAP for 6 weeks improved forearm blood flow to all vasodilators in comparison to results after sham CPAP ($p < 0.05$ for all vasodilators).⁷⁷

CONCLUSION

Obstructive sleep apnoea/hypopnoea syndrome is a common condition and its association with hypertension is very strong. Clinically, it is essential to understand the relationship between OSAHS and hypertension for the benefit of patients in order to prevent long-term sequelae and optimise treatment. The mechanisms behind the elevation of blood pressure in OSAHS are mainly due to autonomic changes that occur as a result of recurrent arousal and hypoxia. Impairment of baroreflex and chemoreflexes may lead to sustained activation of sympathetic activities. Endothelial dysfunction may also have a role in the process of development of hypertension in sleep apnoea subjects. Effective CPAP therapy has been shown to reverse these changes and may prevent its occurrence. Further studies are required to explore the role of OSAHS in the pathogenesis of atherosclerotic changes and subsequently developing arterial stiffness. Randomised control trials are also needed to assess the effect of CPAP therapy in reversing or preventing these changes.

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