Review Article

Cardiovascular function during sleep apnoeas

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Introduction

The sleep apnoea syndrome (SAS) is recognized as a common disorder which may have both mental and physical effects.^{1,2} It is an excellent example of the close interaction between respiratory and cardiac function. It is claimed that among SAS patients there is an increased risk of sudden death during sleep.³ The literature which states this is very limited, but it seems that these patients run an increased risk of developing systemic hypertension, cardiac diseases and strokes.^{4–6}

The main pathophysiological mechanisms that are implicated in the haemodynamic changes during sleep in patients with SAS are firstly the cessation of breathing and the consequent hypoxia, and secondly the development of extreme negative intrathoracic pressures (obstructive apnoea). These two mechanisms which differentiate patients with SAS from other groups of patients who experience severe hypoxaemia during sleep but without any cessation of breathing,⁷ lead to a reduction in cardiac output due to a decrease in stroke volume and in heart rate, and an increase in systemic and pulmonary arterial pressures.

Stroke volume

Direct measurements of the stroke volume during sleep apnoea are very difficult, because of the short duration of the apnoeas, and because accurate measurements are prevented by the progressive changes in heart rate.⁸ The majority of the information is derived from holding of breath or Mueller manoeuvres during wakefulness. But even then the methodological differences make the findings rather contradictory. Lin *et al.*⁹ using impedance cardiography, found that during breath-holding the stroke volume increased. In other studies,¹⁰ based on systolic time intervals, the stroke volume was found to decrease during breath-holding. It is possible that the events following simple breath-holding are similar to those in central apnoeas, but with obstructive apnoeas

the whole process is quite different. The explanation for this difference is the greatly negative intrathoracic pressure during obstructed breathing, which may be as low as $-80 \text{ cm H}_2\text{O}$ ¹¹ leading to an increase in venous return to the right atrium.¹²

The increase in venous return augments the end-diastolic volume of the right ventricle (preload). It thus causes an increase in stroke volume of the right ventricle¹³ and also a displacement of the intra-ventricular septum to the left,¹⁴ with a consequent reduction of left-ventricular compliance.¹⁵ The results of this mechanism are an increase in the pulmonary vascular and left atrial pressures¹⁶ and a decrease in the end-diastolic volume and, thus, a reduction of the stroke volume of the left ventricle^{17,18} (Figure 1).

During the Mueller manoeuvres the end-systolic volume (afterload) of the left ventricle is increased as a result of an increase in cardiac^{19,20} and aortic transmural pressure.¹⁶ According to Permutt,²¹ during dynamic changes of intrathoracic pressure, the transmural pressure of the left ventricle more accurately reflects the left ventricular afterload than the systolic aortic pressure. The situation is exacerbated by the use of β -blockers which, by influencing the relationship between pressure and volume (contractility), can further increase the end-systolic volume of the left ventricle and decrease the stroke volume.¹³ This is of great interest in view of the fact that many hypertensive patients with SAS are treated with β -blockers. Unfortunately there are no haemodynamic studies in this field known to the author.

The pressure in the interstitial space following the changes in intrathoracic pressure becomes greatly negative during sleep apnoea. This negative pressure may induce transvascular fluid filtration^{22,23} especially in addition to the increase in left atrial pressure, which augments the wedge pressure. In some patients with sleep apnoea the wedge pressure has been found to be high enough to cause pulmonary oedema.²⁴

As the intrathoracic pressure continues to decrease, the pressure in the right atrium becomes progressively more negative and, when it approaches values of -5 to -7 mm Hg , the intrathoracic veins collapse and the stroke volume and cardiac output decrease fur-

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Figure 1 The effects of negative intrathoracic pressure on cardiac function during obstructive apnoea. ↑ = increased; ↓ = decreased.

ther.^{8,12,25} This critical point seems to give temporary relief to the congestive pulmonary circulation. With the return of ventilation a large amount of blood enters the heart and the cardiac output increases as a result of an increase in both the stroke volume and heart rate.

Heart rate

During sleep apnoea marked bradycardia occurs, as a result of interaction between the respiratory centre and the cardiac autonomic centres in the central nervous system.²⁶ The onset of bradycardia is rapid, occurring within two or three cardiac cycles after the cessation of breathing.^{27,28} The bradycardia is mediated by vagal nerve activity, which predominates in the heart while the sympathetic nervous system output is enhanced in the periphery and the peripheral vascular resistance is increased.²⁹ The decrease in intrathoracic pressure causes bradycardia, as proved by the Mueller manoeuvre.³⁰ It has also been shown that during breath-holding, for a given lung volume the heart rate decreases with increasing negativity of the intrapleural pressure.³¹

Meanwhile, the oxygen saturation (SaO_2) decreases and the degree and rate of this reduction are directly related to the duration of apnoea and on the O_2 consumption³² and inversely to the preapnoeic SaO_2 values and the alveolar O_2 store.³³ The resulting hypoxaemia stimulates the peripheral chemoreceptors, which enhance the peripheral vasoconstriction³⁴ through the sympathetic nervous system,³⁵ but cause vasodilatation in the most vital organs^{36,37} through the parasympathetic system.³⁴ The stimulation of peripheral chemoreceptors also has a positive ino-

tropic effect on the heart³⁸ and intensifies the bradycardia which has already become established as a result of the cessation of breathing. When the breathing is unobstructed, the stimulation of chemoreceptors causes hyperventilation and tachycardia develops through the pulmonary stretch receptors as the ventilation increases.³⁰ In the event of apnoea the action of peripheral chemoreceptors remains unopposed by the action of the stretch receptors and the net result is bradycardia. The bradycardia is mainly related to the duration of apnoea and the degree of hypoxaemia. Denervation of carotid bodies,^{10,39} or administration of O_2 ^{40,41} or atropine,⁴² will eliminate bradycardia caused by hypoxaemia.

PaCO_2 increases rapidly at the beginning of apnoea^{32,43} but then rises very slowly because of the Haldane effect.³³ There is some controversy about the effect of increased PaCO_2 on the heart rate. Some authors suggest that it has no influence⁴⁴ or causes bradycardia,³⁰ while others have found that an acute, even minor, increase in PaCO_2 ameliorates bradycardia caused by breath-holding and by hypoxaemia. However, the acceleration of the heart rate is limited and the overall result is still marked bradycardia.²⁸ The action of increased PaCO_2 is believed to be due to the secondary acidosis which potentiates catecholamine release from the adrenals.^{28,45} When the apnoea has ended, tachycardia is invariably observed. This is mainly due to the decrease in the previously enhanced parasympathetic activity⁴⁶ as the tachycardia remains essentially unchanged after β -adrenergic blockade, but it is counteracted by the administration of atropine.⁴⁷ Another mechanism which may contribute to tachycardia after apnoea is the increase in venous return, which stimulates the stretch receptors of the atria and elicits the Bainbridge reflex, and thus increases the heart rate and presumably the cardiac contractility via the sympathetic system.⁴⁷ On the other hand the hyperventilation which follows apnoea stimulates the pulmonary stretch receptors and their action by overriding the effects of chemoreceptors on the heart evokes acceleration of the heart rate and vasodilatation.^{48,49}

The cyclic alternations of bradycardia-tachycardia are so characteristic of SAS that serious suspicions of SAS can be aroused from 24-hour ambulatory Holter monitoring of the heart rate. The findings are similar to the classical sick sinus syndrome and the differential diagnosis against this syndrome can be based on the occurrence of the latter phenomenon exclusively during sleep.⁵⁰ Only patients with very short apnoeas or impairment of the autonomic nervous control of the heart (autonomic neuropathy, Shy-Drager syndrome, heart transplantation) do not exhibit the phenomenon.⁴¹ During bradycardia the heart rate is usually between 30 and 50 beats/min, while during tachycardia it is between 90 and 120.⁵¹

In addition to this marked sinus arrhythmia, with sometimes extreme sinus bradycardia⁵² which is a consistent finding in patients with sleep apnoea,⁵³ severe sinus pauses of up to 17 seconds have been reported,²⁴ as well as various types of atrioventricular (AV) blocks,^{51,54,55} paroxysmal atrial tachycardia and atrial fibrillation.²⁴ Premature ventricular contractions (PVCs), of various degrees of severity, and ventricular tachycardia have been found to be more frequent during sleep in patients with SAS.³³ Miller⁵¹ noted no difference in the occurrence and grade of PVCs between wakefulness and sleep. It seems that the incidence of PVCs in sleep apnoea is related to the degree of oxyhaemoglobin desaturation, since Shepard *et al.*⁵⁶ observed that they were 173% more numerous when the SaO_2 values were below 60% than when SaO_2 was above 90%. Similar observations have been made in patients with chronic obstructive pulmonary disease⁵⁷ and in patients with Cheyne-Stokes breathing.⁵⁸

After studying 24-hour Holter electrocardiograms of 400 patients with SAS, Guilleminault *et al.*⁵⁹ concluded that cardiac arrhythmias usually appear in association with marked desaturation and always during the second half of the apnoeic events. Ninety eight per cent of cardiac dysrhythmias occur during obstructive apnoeas or during the obstructive components of mixed apnoeas. On the other hand, Shepard *et al.*⁵⁶ observed that during prolonged apnoeas the heart rate remained slow and PVCs occurred immediately after the termination of apnoea when cardiac acceleration occurred and SaO_2 increased. In the generation of ventricular ectopic activity after apnoea, the withdrawal of vagal tone, the increase in sympathetic tone in combination with myocardial hypoxia, and acidosis are all implicated,³³ while the imbalance in sympathetic-parasympathetic activity has been considered to be involved in the origin of conduction disturbances.

Extreme cardiac dysrhythmias related to apnoeas are potential causes of sudden death.³ Although this cause of death is not well documented and there is no agreement as to whether cardiac pauses or ventricular extrasystolic activity is the most life-threatening factor, it is well recognized that patients with SAS, especially those who experience long apnoeas and severe hypoxaemia, run an increased risk of death during sleep. Tracheostomy has been reported to effectively eliminate all kinds of cardiac dysrhythmias related to obstructive apnoeas.^{42,59,60} The influence of the application of continuous positive airway pressure (CPAP) remains to be evaluated.

Pulmonary hypertension

Cor pulmonale and right heart failure are well known features of the pickwickian syndrome.^{61,62} Cor pul-

monale has also been described in patients with upper airway obstruction.⁶³⁻⁶⁵ It is reversible after effective treatment.^{65,66} During apnoea the pulmonary arterial pressure (PAP) rises rapidly and the highest values are recorded when pulmonary ventilation is resumed a few seconds after the nadir of PaO_2 . The systolic pressure increases to a greater extent than the diastolic, with the consequent increase in pulse pressure.⁶⁷ These events are repeated cyclically during sleep and values as high as 80 mmHg for systolic and 54 mmHg for diastolic PAP have been reported.²⁴

The greatest increase in PAP occurs in patients with high apnoeic index, and according to Schroeder *et al.*⁶⁸ the increase is more pronounced in obstructive than in central apnoeas. PAP is closely related to the pulmonary vascular resistance, which is mainly located in the precapillary pulmonary arteries. The pulmonary vasoconstriction is induced by low O_2 tension both in the alveoli and in the capillaries^{69,70} and is potentiated by acidosis.⁷¹

The incidence of cor pulmonale and right heart failure in patients with the sleep apnoea syndrome is not yet well established, nor are the pathogenic factors. It is still not certain whether these transient, even severe episodes of hypoxaemia during sleep are able to increase PAP permanently. Studies in animals exposed to intermittent hypoxia and hypercapnia revealed that under these conditions increases in haematocrit, right ventricular weight and right ventricular systolic pressure and pulmonary hypertension occurred.^{72,73}

According to some authors, the prevalence of permanent pulmonary hypertension in patients with SAS is as high as 52%²⁵ and is dependent on the frequency and degree of oxyhaemoglobin desaturation, irrespective of the daytime level of PaO_2 .⁷⁴ Others suggest that daily hypoxaemia also co-exists, a condition which usually occurs in association with chronic obstructive pulmonary disease.^{75,76}

Systemic hypertension

The prevalence of systemic hypertension (SH) among patients with SAS is very high. According to some authors, two-thirds of the patients with SAS have this condition.^{77,78} Conversely, it has been found that 22-48% of patients with essential SH have SAS.⁷⁹⁻⁸² There is also a significant relationship between snoring^{67,83} and daily hypersomnolence,⁸⁴ both of which are well known clinical features of SAS patients, with hypertension. Among hypertensive patients, the prevalence of SAS seems to be higher in those with an increased body mass index. The observation that hypertension in obese patients is associated with fat accumulation in the abdomen and chest rather than in the gluteal and femoral regions⁸⁵ may have

some connection with SAS. Williams *et al.*⁸² suggested two possible interrelations: Firstly, that obesity may give rise to both systemic hypertension and SAS independently, and secondly, that obesity may lead to SAS and subsequently to systemic hypertension. Two patients with obstructive apnoeas and an arterial blood pressure of 130/80 mmHg and 160/94 mmHg during wakefulness had arterial pressures of 200/120 mmHg and 280/170 mmHg respectively, after 5 hours of sleep and repetitive apnoeas.²⁴ The more severe the SAS is, the higher and more refractory to treatment is the SH.⁷⁹ After tracheostomy the arterial blood pressure of the patients improved.⁶⁵ Blood pressure increases progressively during apnoea and reaches its highest levels when the ventilation of the lungs starts again.⁶⁸ The systolic pressure increases more than the diastolic, with a consequent rise in pulse pressure. A fall in pulse pressure during sleep apnoea is only seen in severely ill newborn babies and has a very poor prognostic implication.⁸⁶ When the apnoeas are of high frequency, the blood pressure remains continuously at higher levels than those during wakefulness²⁴ contrary to the situation in normal people, who have lower blood pressure during sleep.

The initial progressive increase in blood pressure is possibly due to stimulation of the peripheral chemoreceptors, which might increase the blood pressure through peripheral vasoconstriction when their action is unopposed by a rise in ventilation.⁴⁹ Immediately on resumption of ventilation, a rapid increase in blood pressure is observed as a result of the increase in cardiac output (increased venous return and heart rate), while the sympathetic nervous activity is greatly elevated consequent to the arousal.⁸⁷ The electroencephalographic arousals which almost invariably occur at the end of the apnoeic episodes are caused by hypoxaemia, hypercapnia,⁶⁸ an increase in inspiratory resistance, and obstruction of large airways.^{88,89} The idea of influence of increased sympathetic activity is supported by the decrease in the duration of cardiac electromechanical systole corrected for heart rate (QS₂I), which is an indicator of enhanced adrenergic activity. It is also corroborated directly by the observed increase in urinary and plasma catecholamine levels in 24-hour measurements,⁹⁰ as well as during sleep,^{91,92} in contrast to the reduction which occurs in normal subjects during sleep.¹

Recently, it was reported that the pressure of the cerebrospinal fluid increases dramatically⁹³ and that the blood flow in the common carotid artery is reduced by 50% during sleep apnoeic episodes.⁹⁴ According to these observations, which have been made in only a small number of patients, it is possible that the increase in blood pressure might be due to the release

of the Cushing reflex. In that case the rate of increase in intracranial pressure is very important, as the acute changes affect the cerebral blood flow more than the chronic ones.⁹⁵ The increase in intracranial pressure influences the blood flow in the upper brain stem before that in the lower brain stem and the Cushing response can be seen as being of great importance in maintaining blood flow to the medulla oblongata where the respiratory centre is located.⁹⁶

Although there are some clues to the causes of increased blood pressure during sleep apnoea, the mechanisms by which the systemic hypertension becomes permanent remain obscure.

There is experimental evidence in animals that an extreme increase in sympathetic tone as a response to behavioural demands decreases renal blood flow and increases renal activity and the reabsorption of sodium and water by the proximal tubules.^{97,98} The same observations have been made in young men and an increase in arterial blood pressure has been observed especially in those with a genetic predisposition to hypertension.^{99,100} It is possible that extreme and/or paroxysmal sympathetic activation during sleep even at night is responsible for the permanent systemic hypertension in the same way that intermittent hypoxaemia causes pulmonary hypertension. It seems that reduction of the sympathetic activity during normal sleep¹⁰¹ is of great importance in maintaining the homeostasis of the human organism.

Conclusions

During sleep apnoeas, pronounced changes in the cardiovascular function occur, predisposing to arrhythmias and pulmonary and systemic hypertension. The result is that SAS patients have a high incidence of adverse cardiovascular events. Even in mild cases of SAS the threat of systemic hypertension is high.

Human beings spend one-third of their life sleeping. Thus, it is important to consider the sleep habits when taking a patient's history. The sleep apnoea syndrome is a danger hidden by the darkness of the night.

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