The association of carotid artery disease with snoring and obstructive sleep apnoea: definitions, pathogenesis and treatment

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Introduction

Cerebrovascular disease was the third most common cause of death among Australian males in 2005, accounting for 6.9% of all deaths and the second most common cause in females at 10.8%[1]. Carotid atherosclerosis contributes the majority of the burden of cerebrovascular disease. Although traditional risk factors for carotid atherosclerosis such as smoking, hypertension and hyperlipidaemia have been well-established, an emerging risk factor is sleep-disordered breathing. This is a condition which describes a wide spectrum of disorders ranging from snoring, partial upper airway collapse and reduction in inspiratory airflow during sleep, to obstructive sleep apnoea (OSA) with periods of complete airway collapse leading to cessation of airflow. This review will focus on the association of sleep-disordered breathing and carotid atherosclerosis, in particular as related to the epidemiology of carotid disease and stroke in this population, exploring possible pathogenic mechanisms, the role of ultrasonography and reviewing treatments available for sleep-disordered breathing.

Sleep-disordered breathing

OSA is characterised by repetitive collapse of the upper airway (behind the soft palate and tongue) during sleep, resulting in a reduction (hypopnoea) or cessation (apnoea) of breathing and is usually terminated by arousal from sleep, leading to restoration of ventilation. However, as a consequence, the recurrent arousals from sleep may disturb normal sleep quality leading to excessive daytime sleepiness, impaired memory and concentration, inability to stay awake and contribute to a poor quality of life. The frequency of these obstructive events during sleep can be quantified during an overnight sleep study (polysomnography) where the number of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index, AHI) is used to grade the severity of the sleep-disordered breathing (Table. 1). If the sleep study shows apnoeas and hypopnoeas occurring at a rate of more than five times per hour of sleep and is accompanied by excessive daytime sleepiness, a clinical diagnosis of obstructive sleep apnoea-hypopnoea syndrome (OSAHS) can be made.

Snoring is very common in the community, occurring regularly in more than 30% of the adult population[2]. While OSA has been demonstrated in 24% of adult males and 9% of women, OSAHS has a prevalence of 4% in adult males and 2% in adult females[3] (Fig. 1). Although snoring has long been regarded as a social problem of noise pollution, recent evidence has demonstrated adverse cardiovascular consequences of both sleep-disordered breathing[4–6] and snoring[2,7,8], leading to a viewpoint that sleep is the "new cardiovascular frontier"[9]. In spite of this, OSA remains an under-diagnosed condition for more than 85% of patients with moderate to severe OSA[10].

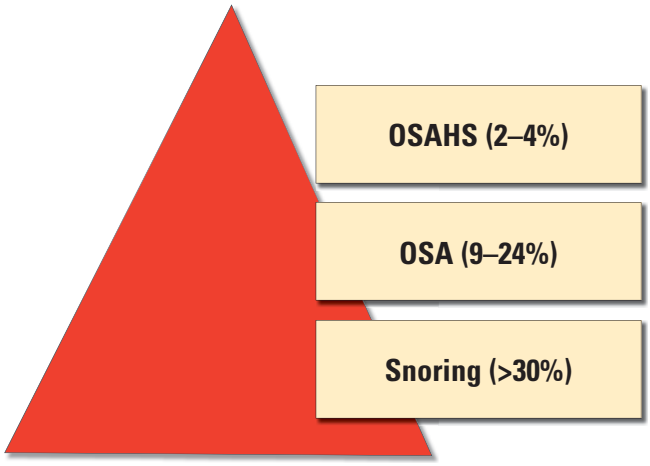

Fig. 1: Prevalence of sleep-disordered breathing in adults. The pyramid of sleep-disordered breathing encompassing snoring, obstructive sleep apnoea (OSA) and the obstructive sleep apnoea hypopnoea syndrome (OSAHS) highlighting the common nature of this condition in the general population.

Table. 1: Severity of Sleep-Disordered Breathing based on the Apnoea-Hypopnoea Index.
As the frequency of apnoeas and hypopnoeas per hour of sleep (AHI) increases, the severity of OSA increases. Severe OSA is classified as an AHI greater than 30 events per hour of sleep while less than 5 events per hour of sleep is considered within normal limits.

AHI	Severity of OSA
0–5	Normal
6–15	Mild
16–30	Moderate
> 30	Severe

Snoring and OSA are more prevalent in males than females. Although the cause is often multifactorial, risk factors include upper body obesity, neck circumference > 42 cm in males, a family history of OSA, nasal or pharyngeal obstruction, craniofacial abnormalities and alcohol. OSA may present with symptoms and signs including loud snoring, witnessed apnoeas, gasping during sleep, daytime sleepiness and unrefreshing sleep. However, some individu-

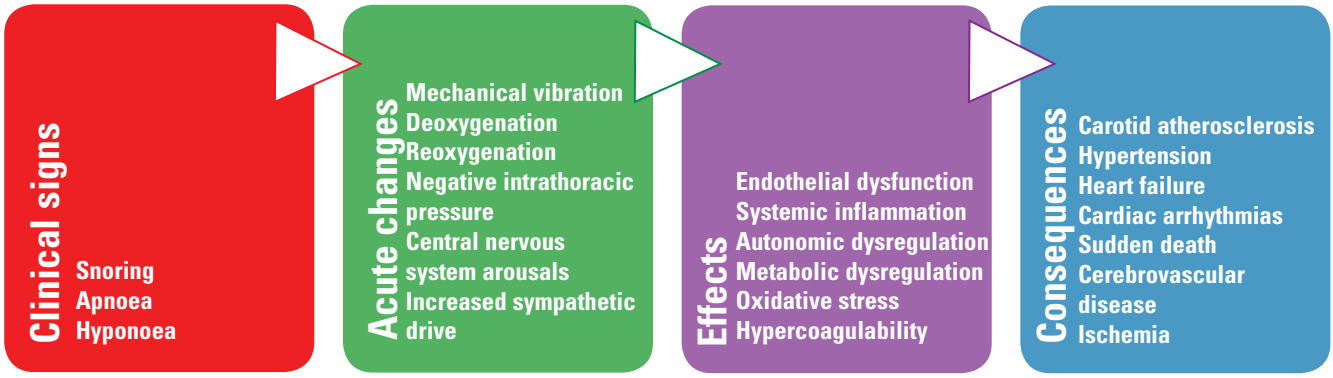

Fig. 2: Potential mechanisms of vascular disease in sleep-disordered breathing.

als with significant OSA may be relatively asymptomatic apart from snoring.

It is generally recommended that patients with cardiovascular disease be evaluated if symptoms of OSA are present, given the significant associations of OSA with the conditions of hypertension, atrial fibrillation and nocturnal angina[4]. If this recommendation were extrapolated to cerebrovascular disease, for example following detection of plaques on carotid ultrasound, evaluation for OSA and/or snoring should also be undertaken in this patient group.

Vascular consequences of snoring and OSA

Untreated sleep-disordered breathing has been linked with hypertension[11,12], cardiac failure[13], cardiac arrhythmias[14,15], cerebrovascular disease and stroke[16,17], and sudden death[18]. In patients followed for 6 to 10 years, there was a significant increase in the risk of fatal and non-fatal cardiovascular events among subjects who had severe obstructive sleep apnoea[6,17], and continuous positive airway pressure (CPAP) treatment appeared to reduce this risk[6].

In relation to stroke, several questionnaire-based retrospective studies have demonstrated a higher incidence of cerebral infarction among habitual snorers with a relative risk ranging between 1.3 and 10.3[2,7,19]. In addition, prospective studies have also demonstrated an increased risk of stroke or sudden death (hazard ratio 3.3) from severe obstructive sleep apnoea, even after accounting for the presence of other cardiovascular risk factors[17].

Mechanisms leading to cerebrovascular disease in snoring and OSA

A number of studies have highlighted the association of obstructive sleep apnoea with coronary artery disease[20,21], cerebrovascular disease[16], and carotid plaques[22–24]. However, it has been difficult to demonstrate that sleep-disordered breathing independently leads to cardiovascular disease and death, due to the presence of many other risk factors in this population including obesity and the metabolic syndrome (i.e. hypertension, dyslipidaemia and impaired glucose tolerance).

Mechanisms proposed to cause stroke in OSA include carotid artery endothelial dysfunction, altered cerebral blood flow autoregulation, increased blood coagulability, reduction in overall cerebral blood flow during sleep-disordered breathing, and other vascular complications related to OSA such as atrial fibrillation and hypertension. Increased sympathetic activation from repetitive arousals during sleep, intermittent hypoxia and sleep deprivation leading to systemic inflammation, increased oxidative stress from intermittent hypoxia and insulin resistance may also be contributory factors[4] (Fig. 2).

An alternative novel mechanism proposed as a cause of vascular disease, is the contribution of vibration energy from snoring to the development of carotid atherosclerosis[25]. In the Sleep Heart Health Study[26], the risk of stroke was greater than the risk of myocardial infarction in severe OSA patients, raising the possibility of a site-specific effect of obstructive sleep apnoea/snoring on the carotid arteries[27]. It is proposed that the vibrations from heavy snoring may have detrimental effects on the carotid artery endothelium[25,28,43,44].

Recent ultrasound studies on intima-media thickness, carotid plaques and sleep disordered breathing

Due to the recognised association of sleep disordered breathing with stroke, carotid ultrasound has been used to demonstrate the presence of carotid atherosclerotic plaques in patients with both heavy snoring[28] and OSA[22,26].

In addition to the conventional ultrasound assessment for carotid vascular disease, recent non-invasive ultrasonography methods have been developed to enable detection of early, pre-clinical atherosclerosis. The main technique employed involves measurement of the carotid intima-media thickness (IMT) using B-mode ultrasound. The intima and media layers of the carotid artery have been shown to increase in thickness in association with cardiovascular risk factors such as age[29,30], hypertension[31], diabetes[32], hyperlipidaemia[29] and smoking[33]. In addition, increasing carotid IMT has been shown to be a strong predictor for adverse cardiovascular and cerebrovascular events[34]. The advantages of using B-mode ultrasound to assess carotid IMT (Fig. 3) include low cost, non-invasive nature of the test, reproducibility of results for less experienced users by employing semi-automated border detection programs[35], and the ability to assess cardiovascular risk longitudinally following treatment of risk factors.

What evidence supports sleep-disordered breathing as a cause of carotid artery disease, that may help to explain the increased prevalence of stroke in this population? First, five case control studies evaluating carotid IMT in severe OSA subjects (mean AHI > 40 events/hour) compared to subjects without sleep-disordered breathing (AHI < 5 events/hour) have all demonstrated significant increases in carotid IMT in the OSA groups (36–40), even after matching for potential confounders such as age, BMI, smoking, hypertension and diabetes mellitus. Thus it is likely that the severity of sleep-disordered breathing is an independent predictor of increasing carotid IMT.

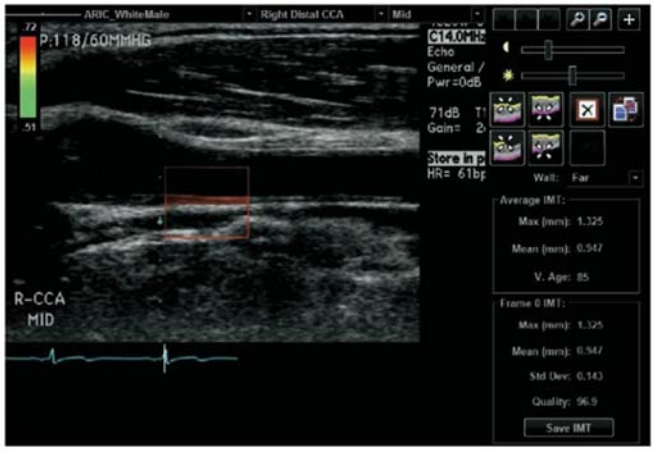

Fig. 3: Semi-automated IMT measurements of the carotid artery. Segment of carotid artery with box highlighting intima and media for automated measurement. Semi-automated IMT measurements may improve the reproducibility of results for less experienced users. From Clinical Use of Carotid Intima-Media Thickness: Review of the Literature. R. Todd Hurst, Daniel W. C. Ng, Chris Kendall, and Bijoy Khandheria. *J Am Soc Echocardiogr* 2007; 20: 907–14.

Secondly, the frequency and degree of nocturnal oxygen desaturation may have detrimental effects on the carotid artery. In a cross sectional study of 167 patients presenting to a sleep laboratory, both the AHI and nocturnal desaturation due to sleep apnoea were significantly associated with carotid IMT[41]. The severity of oxygen desaturation due to obstructive sleep apnoea was also predictive of increased carotid IMT and plaque occurrence in a prospective study of 83 subjects with severe OSA[42] without known cardiovascular risk factors.

In addition to obstructive sleep apnoea and its associated oxygen desaturation, the role of direct snoring vibration damage to the carotid artery has also been examined. In a study of heavy snorers, the prevalence of carotid atherosclerosis was 64% (as measured via ultrasound) compared with 20% in mild snorers, even when conventional risk factors (e.g. hypertension, hyperlipidaemia and smoking) were taken into account[28]. Furthermore, in these subject groups, there was no difference in the prevalence of femoral atherosclerosis which supported a site-specific effect of the snoring. In support of this hypothesis, it is known that snoring vibrations are transmitted to the carotid artery wall and lumen[43], and this may lead to vibration-induced damage of the endothelial cells lining the carotid artery with resultant endothelial dysfunction[44], which is considered a precursor to the development of atherosclerosis.

Finally, in support of the link between sleep-disordered breathing and carotid artery pathology, a recent study demonstrated that effective treatment of a group of severe, hypoxic OSAHS patients with nasal CPAP for four months resulted in a significant decrease in carotid IMT compared with untreated control OSAHS subjects, supporting the concept that OSA is an independent risk factor for carotid atherosclerosis[45]. However, it must be noted that effective CPAP treatment reverses all of the effects of sleep-disordered breathing including the raised AHI, nocturnal oxygen desaturation and snoring, and thus the relative contributions of each of these factors to any carotid artery pathology cannot be established based on this trial.

Increasingly, carotid IMT is being used to stratify risk and as an end point in clinical intervention studies, because of its ability to predict future clinical cardiovascular endpoints. Technical details of performing carotid IMT by ultrasound and current guidelines as to its use are beyond the scope of this review, and readers are recommended to refer to the consensus statement[46] from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force for further information.

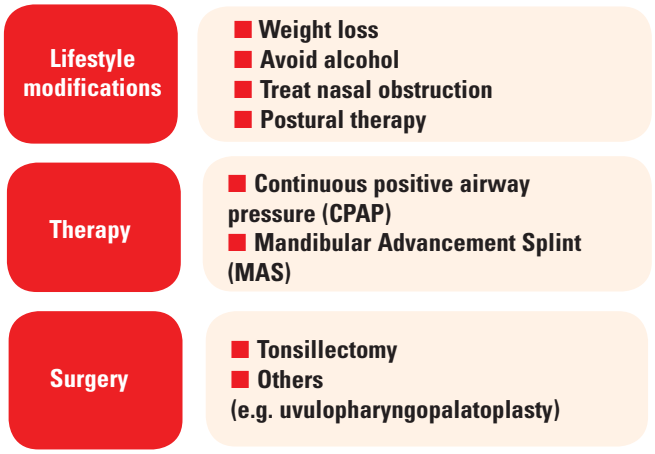

Fig. 4: Therapeutic options in obstructive sleep-disordered breathing.

Treatment for snoring and OSAHS

The treatment for snoring and OSAHS involves a combination of lifestyle modifications, postural therapy during sleep, medical devices such as mandibular advancement splints (MAS) and continuous positive airway pressure (CPAP) devices, and surgery. There are no medications in routine clinical use for treating obstructive sleep apnoea syndrome. (Fig. 4).

Lifestyle modification encompasses weight loss in overweight and obese patients, avoidance of alcohol close to bedtime and avoidance of sleep deprivation. Chronic nasal congestion or obstruction may exacerbate sleep disordered breathing and should be actively treated[47]. In patients who predominantly have snoring and OSA while sleeping on their back, sleeping in the non-supine posture may be of benefit using postural aids such as a tennis ball T-shirt[48]. However, for the majority of patients with OSAHS, lifestyle modifications and/or postural treatment are not sufficiently effective and devices to treat sleep-disordered breathing will also be required.

Treatment of OSAHS is best achieved using continuous positive airway pressure (CPAP) which provides a pneumatic splint to the airway using a nasal or oro-nasal face mask at night with the patient breathing at a positive air pressure to maintain airway patency. Although there is no doubt as to its effectiveness, compliance with CPAP therapy in the long term remains a problem for many patients, especially those without symptoms of unrefreshing sleep and daytime sleepiness.

Mandibular advancement splints (MAS) are oral appliances inserted into the mouth at night which pull the lower jaw forward to increase the size of the airway, much like the jaw thrust manoeuvre in an unconscious patient. The MAS is more effective in non-obese subjects with primarily snoring or mild to moderate OSAHS. Despite being less effective than CPAP, many patients prefer MAS to CPAP therapy[49].

Finally, surgery for snoring and OSAHS (involving

removal of tissue within the throat by excision or laser) has been trialled but a systematic review found little evidence to support the use of surgery as a permanent cure for OSAHS[50].

Summary

1 Snoring and OSA are very common in the adult community.
2 Snoring and OSA have been linked to adverse cardiovascular outcomes such as stroke, hypertension and myocardial infarction. Heavy snoring itself may not be a benign entity and may be a risk factor for carotid atherosclerosis.
3 The presence of carotid plaques in combination with features such as thick neck, excessive daytime sleepiness and history of loud snoring should alert the health professional to a possible diagnosis of obstructive sleep apnoea.
4 Clinical trials suggest regression of early carotid atherosclerosis with CPAP treatment in patients with OSAHS.
5 Carotid intima-media thickness (IMT) measured via B-mode ultrasound is increasingly used to evaluate carotid artery disease, assess vascular risk and treatment outcomes in clinical trials involving OSAHS patients. Semi-automated border detection programs may improve reproducibility in less experienced centres.

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