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

Jin-Gun Cho and John R Wheatley

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%. 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. 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 (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 and snoring, leading to a viewpoint that sleep is the “new cardiovascular frontier”. In spite of this, OSA remains an under-diagnosed condition for more than 85% of patients with moderate to severe OSA.

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.

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\(^{11,12}\), and sudden death\(^{16}\). 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\(^{17}\), and continuous positive airway pressure (CPAP) treatment appeared to reduce this risk\(^{16}\).

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\(^{17,19}\). 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\(^{22}\), 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\(^{16}\) (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/snooring on the carotid arteries\(^{27}\). It is proposed that the vibrations from heavy snoring may have detrimental effects on the carotid artery endothelium\(^{25,28,31}\).

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\(^{33}\) and smoking\(^{34}\). 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.
The association of carotid artery disease with snoring and obstructive sleep apnoea: definitions, pathogenesis and treatment

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. 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 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. 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, and this may lead to vibration-induced damage of the endothelial cells lining the carotid artery with resultant endothelial dysfunction, 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. 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

Fig. 4: Therapeutic options in obstructive sleep-disordered breathing, 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 from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force for further information.

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. 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. 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.

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.  

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.

References

1. Australia’s health 2008. Australian Institute of Health and Welfare 2008. Cat. no. AUS 99.Canberra: AIHW.
2. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikki K, Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. BMJ (Clin Res Ed) 1987; 294: 16–9.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328: 1200–3.
4. Somers V, White D, Amin R, Abraham W, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Circulation 2008; 118: 1080–1111.
5. Yaggi HK, Concato J, Kurnan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353: 2034–41.
6. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365: 1046–53.
7. Partinen M, Palomaki H. Snoring and cerebral infarction. JAMA 2000; 283: 1829–36.
8. Naughton M. Heart failure and obstructive apnoea. Sleep Med Rev 1998; 2: 93–103.
9. Gami AS, Pressman G, Caples SM, Kanagarala R, Gard JJ, Davison DE, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004; 110: 364–7.
10. Monahan K, Storfer-Isser A, Mehr R, Shahar E, Mittleman MA, Rotman J, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol 2009; 54: 1797–804.
11. Arzt M, Young T, Finn L, Skatrud J, Bradley T. Association of sleep disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005; 172: 1447–51.
12. Yaggi HK, Concato J, Kurnan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353: 2034–41.
13. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005; 352: 1706–14.
14. Hu F, Willet W, Manson J, Colditz G, Rimm E, Speizer F, et al. Snoring and the risk of cardiovascular disease in women. J Am Coll Cardiol 2000; 35: 308–13.
15. Shafer H, Koehler U, Ewig S, Hosper E, Tasci S, Luderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. Cardioiology 1999; 92: 79–84.
16. Moon T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep disordered breathing in men with coronary artery disease. Chest 1996; 109: 659–63.
17. Kaynak D, Goksan B, Kaynak H, Degirmenci N, Daglioglu S. Is there a link between the severity of sleep-disordered breathing and atherosclerotic disease of the carotid arteries? Eur J Neurol 2003; 10: 487–93.
18. Friedlander A, Yueh R, Littner M. The prevalence of calcified carotid artery atheromas in patients with obstructive sleep apnea syndrome. J Oral Maxillofac Surg 1998; 56: 950–4.
19. Friedlander A, Friedlander I, Yueh R, Littner M. The prevalence of carotid atheromas seen on panoramic radiographs of patients with obstructive sleep apnea and their relation to risk factors for atherosclerosis. J Oral Maxillofac Surg 1999; 57: 516–22.
20. Hedner J, Wilcox I, Sullivan C. Speculations on the interaction between vascular disease and obstructive sleep apnea. In: Saunders N and Sullivan C, editors. Sleep and Breathing. New York: Marcel Dekker; 1994.
21. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, et al. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results from the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163: 19–25.
22. Rahangdale S, Campana L, Malhotra A, Not So Good Vibrations. Commentary on Lee, et al. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep 2008; 31: 1204–5.
23. Lee S, Amis T, Byth K, Larcos G, Kairatis K, Robinson T, Wheatley J. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep 2008; 31: 1207–13.
24. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szko M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study, 1987–1993. Am J Epidemiol 1997; 146: 83–94.
25. O’Leary D, Polak J, Kronmal R, Manolio T, Burke G, Wolfson S. Oral Maxillofac Surg 1999; 57: 516–22.
26. Lakka T, Salonen R, Kaplan G, Salonen J. Blood pressure and the progression of carotid atherosclerosis in middle-aged men. Hypertension 1999; 34: 51–6.
27. Wagenknecht L, D’Agostino R, Savage P, O’Leary D, Saad M, Haffner S. Duration of diabetes and carotid wall thickness: the insulin resistance atherosclerosis study (IRAS). Stroke 1997; 28: 999–1005.
28. Diez-Roux AV, Nieto FJ, Comstock GW, Howard G, Szko M. The
relationship of active and passive smoking to carotid atherosclerosis 12–14 years later. *Prev Med* 1995; 24: 48–55.

34 Lorenz M, Markus H, Bots M, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; 115: 459–67.

35 Gepner AD, Korcarz CE, Aeschlimann SE, LeCaire TJ, Palta M, Tzou WS, Stein JH. Validation of a carotid intima-media thickness border detection program for use in an office setting. *J Am Soc Echocardiogr* 2006; 19: 223–8.

36 Silvestrini M, Rizzato B, Placidi F, Baruffaldi R, Bianconi A, Diomedi M. Carotid artery wall thickness in patients with obstructive sleep apnea syndrome. *Stroke* 2002; 33: 1782–5.

37 Altin R, Ozdemir H, Mahmutyazicioglu K, Kart L, Uzan L, Ozer T, Savranlar A, Aydin M. Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome. *J Clin Ultrasound* 2005; 33: 80–6.

38 Schulz R, Seeger W, Fegbeutel C, Husken H, Bodeker RH, Tillmanns H, Grebe M. Changes in extracranial arteries in obstructive sleep apnea. *Eur Respir J* 2005; 25: 69–74.

39 Drager L, Bortolotto L, Lorenzi M, Figueiredo A, Krieger E, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 613–18.

40 Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, Okada S, Ohta S, Naito H, Adachi M. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 625–30.

41 Suzuki T, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Yamauchi M, Kimura H. Obstructive sleep apnea and carotid-artery intima media thickness. *Sleep* 2004; 27: 129–33.

42 Baguet J, Hammer L, Levy P, Pierre H, Launois S, Mallion J, Pepin J. The severity of oxygen desaturation is predictive of carotid wall thickening and plaque occurrence. *Chest* 2005; 128: 3407–12.

43 Amatoury J, Howitt L, Wheatley JR, Avolio AF, Amis TC. Snoring-related energy transmission to the carotid artery in rabbits. *J Appl Physiol* 2006; 100: 1547–53.

44 Cho J, Witting P, Verma M, Amis TC, and Wheatley JR. Reduction of endothelial nitric oxide bioavailability in carotid arteries exposed to snoring-like vibratory energy. *Am J Respir Crit Care Med* 2009; 179: A3984 (abstract).

45 Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2007; 176: 706–12.

46 Stein J, Korcarz C, Hurst R, Lonn E, Kendall C, Mohler E, Najjar S, Rembold C, Post W. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008; 21: 93–111; quiz 189–90.

47 Lofaso F, Coste A, d’Ortho M, Zerah-Lancner F, Delclaux C, Goldenberg F, Harf A. Nasal obstruction as a risk factor for sleep apnoea syndrome. *Eur Respir J* 2000; 16: 639–43.

48 Cartwright, R, Ristanociv R, Diaz F, Caldarelli D, Alder G. A comparative study of treatments for positional sleep apnea. *Sleep* 1991; 14: 546–52.

49 Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnoea: a review. *Sleep* 2006; 29: 244–62.

50 Hensley M, Ray C. The treatment of the obstructive sleep apnoea-hypopnoea syndrome. In: Gibson P, editor. Evidence-based Respiratory Medicine. Oxford: Blackwell Publishing Ltd; 2005. pp 447–61.