



Obstructive Sleep Apnoea: Increasing Evidence of Cardiovascular Complications

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2005.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common form of sleep disordered breathing (SDB) characterised by repetitive episodes of partial or complete upper airway obstruction causing sleep fragmentation and symptoms.¹ It is equally common among the middle-aged male Caucasian and HK Chinese populations with a prevalence of at least 4%.^{2,3} OSAS may cause disabling daytime sleepiness, impaired cognitive function, poor quality of life, and increase the risk of road traffic accidents.¹ Sleep-induced loss of upper airway muscle tone and obesity are the major factors in the pathogenesis of OSAS. However craniofacial abnormality may play an important role especially in the Asian populations. While Asian patients with OSAS are generally less obese than the Caucasian counterparts, craniofacial abnormalities such as a low hyoid bone and retro-position of the maxilla or mandible are common predisposing factors in the Chinese populations.^{4,5} Other predisposing factors in the pathogenesis of OSAS in adults include inappropriate use of benzodiazepine or alcohol (further reduction in muscle tone), endocrine causes such as hypothyroidism (macroglossia, mucopolysaccharide deposits in upper airway, myopathy, neuropathy) and acromegaly (macroglossia, central sleep apnoea), smoking (airway inflammation), and enlarged tonsils and adenoids (mechanical obstruction) in the paediatric cases.⁶

Obstructive sleep apnoea and cardiovascular complications

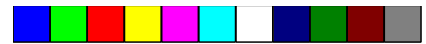
In recent years, there are growing data linking SDB to cardiovascular complications. Several epidemiological studies have shown an independent association between SDB and hypertension after controlling for confounding factors such as age, body mass index (BMI), sex, alcohol and smoking.⁷⁻⁹ Patients with OSAS have increased ambulatory diastolic blood pressure (BP) both day and night and increased systolic BP at night compared to controls matched for age and BMI.¹⁰ The US Sleep Heart Health Study cohort has shown the effects of SDB on various manifestations of cardiovascular diseases, and relatively SDB was more strongly associated with reported

stroke and heart failure than with coronary artery disease.¹¹ A 7-year longitudinal study of otherwise healthy patients with OSAS has shown a higher incidence (56.8%) of at least one cardiovascular complication in patients incompletely treated than those effectively treated, who have a low incidence (6.7%) similar to the normal controls.¹²

Cerebrovascular disease is an important cause of morbidity and mortality worldwide. Several overseas studies have reported a high prevalence of SDB predominantly of obstructive nature in patients following stroke in the acute phase and rehabilitation phase.^{13,14} A case-controlled study in HK has shown a high prevalence of OSA in Chinese patients admitted with acute ischaemic stroke (49% vs 24% in a control group).¹⁵ Two recent studies in Europe have shown that patients with both OSA and stroke have lower survival rates than those with stroke alone.^{16,17} Atherosclerosis of the carotid arteries is an important cause of ischaemic stroke. In recent years, carotid artery intima-media thickness (IMT), measured by B-mode ultrasound, has been shown to correlate with traditional vascular risk factors and may predict the likelihood of acute coronary events and stroke.¹⁸ In a study of 167 Japanese patients referred for screening of OSAS, Suzuki et al¹⁹ have shown that the severity of OSA is independently related to the carotid artery IMT, and that the severity of OSA-induced hypoxaemia is more important than the frequency of obstructive events. The findings have been strengthened by a case-control study in Germany.²⁰ OSA-related arousals are closely linked to increases in sympathetic activity. A case-controlled study recently conducted in HK has shown that OSAS, through repeated episodes of arousals, may lead to platelet activation. Platelet activation is an important step in the pathogenesis of ischaemic stroke but its activity can be reduced by nasal continuous positive airway pressure (CPAP) treatment.²¹

In addition to hypertension, other mechanisms for the association between SDB and cardiovascular complications are not fully understood but there is strong evidence indicating a role for the sympathetic nervous system in the pathophysiological process. Multiple, potentially intertwined mechanisms are proposed to link OSA with chronic cardiovascular diseases, and these include tonic elevation of sympathetic neural activity, vascular endothelial dysfunction, oxidative stress,





inflammation, and metabolic dysregulation.²² In addition to cascades of increased vasoactive peptides and proinflammatory factors, repetitive surges of sympathetic activity may directly promote endothelial/vascular injury and enhanced coagulability. Platelet aggregability, increases in haematocrit, fibrinogen levels, and blood viscosity may also predispose to clot formation and atherosclerosis in patients with OSAS.²²

Treatment

Nasal CPAP is the most effective treatment for OSAS with robust evidence in support of its efficacy in improving symptoms, cognitive function, and quality of life.¹ Several randomised placebo-controlled studies have shown that nasal CPAP can reduce day and night BP in patients with OSAS.^{23,24} Pepperrell *et al*²³ have shown a 3.3 mmHg reduction in 24 hr mean systemic BP among sleepy patients with OSAS in the therapeutic vs the sub-therapeutic CPAP arm, and the beneficial effect of CPAP on BP was seen mostly in those with more severe OSAS. More recently, Becker *et al*²⁴ have shown that patients with severe OSAS in the active CPAP treatment arm achieved a reduction in mean systemic BP of 9.9 mmHg over a period of 9 weeks. This magnitude of reduction in mean BP with nasal CPAP is predicted to reduce coronary heart disease event risk and stroke risk by 37% and 56% respectively.²⁴ Other favourable effects of CPAP include reduction of sympathetic activity and hypoxic/oxidative stress,^{25,26} with improvement of vasodilator response and endothelial function.²⁷ In patients who are not able to tolerate nasal CPAP, dental appliance in the form of mandibular advancement device can improve symptoms²⁸ and reduce mean 24-hr diastolic BP by 1.8 mmHg after 4 weeks of treatment.²⁹ These data have important therapeutic implications, and compliance with nasal CPAP or dental device may reduce the risk of cardiovascular complications associated with OSAS.

References

- Engleman HM, Douglas NJ. Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. *Thorax* 2004;**59**:618-622.
- Ip MS, Lam B, Launder JJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest* 2001;**119**:62-69.
- Hui DS, Chan JK, Ko FW, et al. Prevalence of snoring and sleep-disordered breathing in a group of commercial bus drivers in HK. *Intern Med J* 2002;**32**:149-157.
- Hui DS, Ko FW, Chu AS, et al. Cephalometric assessment of craniofacial morphology in Chinese patients with OSA. *Respir Med* 2003;**97**:640-646.
- Lam B, Ooi CG, Peh WC, et al. Computed tomographic evaluation of the role of craniofacial and upper airway morphology in obstructive sleep apnea in Chinese. *Respir Med*. 2004;**98**:301-307.
- Hui DS, Choy DK, Ko F, et al. Obstructive sleep apnoea syndrome: treatment update. *HK Med J* 2000;**6**:209-217.
- Lavie P, Herer P, Hoffstein V: Obstructive sleep apnoea as a risk factor for hypertension: population study. *Brit Med J* 2000;**320**:479-482.
- Nieto FJ, Young TB, Lind BK, et al. Association of Sleep-disordered breathing, Sleep Apnea and hypertension in a large community-based study. *JAMA* 2000;**283**:1829-1836.
- Peppard P, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**:1378-1384.
- Davies CW, Crosby JH, Mullins RL, et al. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. *Thorax* 2000;**55**:736-740.
- Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;**163**:19-25.
- Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med* 2002;**166**:159-165.
- Wessendorf T, Teschler H, Wang YM, et al. Sleep-disordered breathing among patients with first-ever stroke. *J Neurol* 2000;**247**:41-47.
- Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med* 2000;**161**:375-380.
- Hui DS, Choy DK, Wong KS, et al. Prevalence of Sleep-disordered breathing and CPAP compliance. Results in a group of Chinese patients post first-ever Ischemic Stroke. *Chest* 2002;**122**:852-860.
- Turkington PM, Allgar V, Bamford J, et al. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. *Thorax* 2004;**59**:367-371.
- Parra O, Arboix A, Montserrat JM, et al. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J* 2004;**24**:267-272.
- O'leary DH, Polak JF, Kronmai RA, et al. Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;**340**:14-22.
- Suzuki T, Nakano H, Maekawa J, et al. OSA and carotid artery intima-media thickness. *Sleep* 2004;**27**:129-133.
- Schulz R, Seeger W, Fegbeutel C, et al. Changes in extracranial arteries in obstructive sleep apnoea. *Eur Respir J* 2005;**25**:69-74.
- Hui DS, Ko FW, Fok JP, et al. The effects of nasal CPAP on platelet activation in OSA. *Chest* 2004;**125**:1768-1775.
- Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: Implications for cardiac and vascular disease. *JAMA* 2003;**290**:1906-1914.
- Pepperrell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and sub-therapeutic nasal continuous positive airway pressure for obstructive sleep apnea: a randomized prospective parallel trial. *Lancet* 2002;**359**:204-210.
- Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal CPAP on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003;**107**:68-73.
- Ohga E, Tomita T, Wada H, et al. Effects of OSA on circulating ICAM-1, IL-8, and MCP-1. *J Appl Physiol* 2003;**94**:179-184.
- Yokoe T, Monoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and IL-6 in patients with OSAS are decreased by nasal CPAP. *Circulation* 2003;**107**:1129-1134.
- Ip MS, Tse HF, Lam B, et al. Endothelial function in OSA and response to treatment. *Am J Respir Crit Care Med* 2004;**169**:348-353.
- Gotsopoulos H, Chen C, Qian J, et al. Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. *Am J Respir Crit Care Med*. 2002;**166**:743-748.
- Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep* 2004;**27**:934-941.

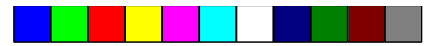
MCHK CME Programme Self-assessment Questions

Please read the article entitled "Obstructive Sleep Apnoea: Increasing Evidence of Cardiovascular Complications" by Dr. David SC Hui and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2005. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-5: Please answer T(True) or F(False). Questions 6-10: Choose the best answer.

- OSAS is more prevalent in Caucasians than Asians.
- OSAS may increase the risk of road traffic accidents.
- Enlarged tonsils and adenoids are commonly noted in adults with OSAS.





- 4) Retroposition of the mandible or maxilla is a predisposing factor in Chinese patients with OSAS.
- 5) Patients with stroke and OSAS have lower survival rates than those with stroke alone.
- 6) Which of the following factors may predispose to OSAS?
 - a) Sleep induced loss of muscle tone
 - b) Obesity
 - c) Craniofacial abnormalities
 - d) Inappropriate use of alcohol
 - e) All of the above
- 7) Which of the following treatment modalities is the most effective and evidence-based in improving symptoms such as sleepiness, cognitive function, and quality in OSAS ?
 - a) Mandibular advancement device
 - b) Palatal surgery
 - c) Weight reduction
 - d) Nasal CPAP
 - e) Sleep in lateral positions
- 8) Which of the following statements is INCORRECT concerning cardiovascular consequences in OSAS?
 - a) Patients with severe OSAS have higher daytime and nocturnal BP compared to controls matched for age and BMI
 - b) Central sleep apnoea is more common than Obstructive sleep apnoea in patients admitted with ischaemic stroke.
 - c) Carotid artery intima-media thickness is increased in patients with OSAS compared to controls.
 - d) Patients with OSAS not effectively treated have a higher incidence of developing cardiovascular complications
 - e) Platelet activation is increased in patients with OSAS
- 9) Which of the following statements is INCORRECT concerning nasal treatment for OSAS?
 - a) It can improve symptoms very effectively.
 - b) It can reduce 24 hr mean blood pressure.
 - c) It can improve endothelial function.
 - d) It can increase activity of the sympathetic nervous system.
 - e) It can reduce platelet activation.
- 10) In addition to improvement of symptoms, which of the following areas can dental device in the form of mandibular advancement splint improve in patients with OSAS?
 - a) Platelet activation
 - b) Systemic blood pressure
 - c) Sympathetic activity
 - d) Risk of car accidents
 - e) Endothelial function

ANSWER SHEET FOR MARCH 2005

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2005 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Answers to February 2005 issue

Changing Concept of Early Rheumatoid Arthritis

- 1. (i) T (ii) T (iii) T (iv) T (v) F 3. (i) F (ii) T (iii) T (iv) F (v) F
- 2. (i) T (ii) F (iii) F (iv) T (v) F

