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Pathophysiology of obstructive sleep apnoea syndrome: a review

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الفيزيولوجياالمرضية لملازمة إنقطاع النفس الانسدادي أثناء النوم: مراجعة

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الخلاصة: تعتبر متلازمة إنقطاع النفس الانسدادي أثناء النوم من الأمراض الشائعة وتشكل خطراً صحياً كبيرًا وذلك لما تسببه من زيادة في نسبة المراضه والوفيات من أمراض شرايين القلب والدماغ . من أعراض هذه المتلازمة النوم المفرط أثناء النهار ، الارهاق والضعف العام ، الاكتئاب ونقص في الرغبة الجنسية الى جانب اضطرابات الغدد الصماء . ويكثر هذا المرض عند أصحاب السمنة المفرطة وخاصة الرجال في أواسط العمر كما أن له عوامل وراثية . وبالرغم من الاهتمام المتزايد الذي لاقاه هذ ا المرض مؤخرا في الغرب كونه من المشاكل الصحية الكبيرة فإن الاهتمام به ما زال في الدول النامية أقل من المطلوب. في هذه المراجعة نقوم بالتعريف بالأمراض التنفسية أثناء النوم ونتعرض لمناقشة الفيزيولوجيا المرضية لمتلازمة إنقطاع النفس الانسدادي أثناء النوم في ضوء المعرفة الحالية الى جانب الخبرة السريرية للمؤلفين .

ABSTRACT: Sleep apnoea syndrome is a common disorder and a major health hazard that affects many body systems. It is particularly associated with increased cardiovascular and cerebrovascular morbidity and mortality. Among its other manifestations include increased daytime somnolence, fatigue, depression, reduced sexual libido and endocrine dysfunction. The main risk factors are obesity, male gender, middle age and heredity. Despite being a recognised major health problem in the industrialised countries, this condition has not yet received its due importance in the developing world. This review introduces breathing disorders during sleep and discusses the pathophysiological features of obstructive sleep apnoea syndrome in the light of the currently available literature and the authors' own clinical experience.

KEY WORDS: sleep; apnoea; obstructive; mortality; cardiovascular; airway

Disordered breathing during sleep is a common condition with an estimated prevalence of up to 24% in men and 9% in women in North America.[1] It is associated with excessive morbidity and increased mortality from cardiovascular and cerebrovascular events and increased risk of road traffic accidents.[2] The condition can be suspected clinically in the presence of classic symptoms such as snoring, daytime hypersomnolence, obesity and male gender. The diagnosis is confirmed by polysomnography. Continuous positive airway pressure (CPAP) has been the mainstay of treatment although various other modalities are still being investigated.

The most important among these disorders is Obstructive Sleep Apnoea Syndrome (OSAS), also known as Sleep Apnoea Hypopnoea Syndrome (SAHS). This condition is so much linked to excessive morbidity and mortality that it is considered a public health hazard at par with smoking.[3] This review details the pathophysiological mechanisms and clinical effects of this condition.

PATHOPHYSIOLOGY

UPPER AIRWAY FEATURES IN PATIENTS WITH OSAS

An apnoea is complete cessation of breathing, either due to the failure of the central nervous system to initiate breathing stimulus (*central apnoea*), or more commonly due to obstruction of the upper airways (*obstructive apnoea*). Concurrent occurrence of central and obstructive apnoeas is called *mixed apnoea*. The term *hypopnoea* refers to 50% reduction in breathing.[4]

Most, if not all, obstructive apnoeas are caused by a collapse of the pharyngeal airway. Pharyngeal patency depends critically on the action of dilator muscles, which contract during each inspiration to prevent the upper airway from being closed by suction. Muscle tone decreases

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throughout the body during sleep, and the upper airway dilating muscles relax. In many individuals, this results in considerable upper airway narrowing during inspiration, and causes the turbulent flow and vibration of snoring.[5]

These events were thought to be clinically important only if they resulted in occlusion of the airway, cessation of airflow, and apnoea.[6,7] However, more recent studies have indicated that these same effects may result from episodes of hypopnoea which effect continued but reduced ventilation.[8] Recent investigations suggest that episodes of airway narrowing that result in increased ventilatory effort without diminution of ventilation may also produce symptoms of the so-called Upper airways resistance syndrome (UARS). Typical findings of UARS on sleep study are: (1) repetitive arousals from EEG sleep coinciding with a (2) waxing and waning of the respiratory airflow pattern and (3) increased respiratory effort as measured by oesophageal pressure monitoring.[9] There may be few, if any, obvious apnoeas or hypopnoeas with desaturation, but snoring may be a very prominent finding.[10] Arousals usually restore upper airway dilating muscle tone and the patient gasps, takes a few deep breaths, and falls back to sleep, at which point the upper airway dilating muscles relax again and the cycle starts off once more. These episodes of upper airway narrowing, terminated by arousal, may recur many hundred times in a night. This recurrent sleep disruption accounts for the daytime symptoms and clinical features of the condition.[11]

The narrowest point of the upper airway in awake normal subjects is behind the soft palate especially when the person is supine. During sleep, airway narrowing occurs in normal subjects. About 50% of normal subjects display the largest increase in resistance at the level of the palate, and the other 50% in the hypopharynx.[11] Similarly, half the OSAS patients have obstruction at palatal level and half have it at hypopharyngeal level.[12] It is not clear whether anatomical or physiological factors are the main determinants of the primary site of occlusion during sleep, nor is it clear why only some individuals have upper airway obstruction during sleep.

The main anatomical factors that predispose to upper airway narrowing are obesity and facial structure.[7] Patients with OSAS tend to have narrower airways than normal subjects when awake, although there is considerable overlap.[13] Much of this narrowing may be due to fat deposition around, and particularly lateral to, the upper airways. Palatal enlargement with increased fat and muscle bulk and facial structure abnormalities with retroposition of the mandible and /or maxilla, have also been found in OSAS.[14] However, the relative importance of differences in bony structure and fat deposition between OSAS patients and the normal population is not known and could vary with patient type. For instance, facial structure perhaps is important in thinner patients, and the location of fat deposits more critical in the obese. Around 50% of OSAS patients have body mass indices > 30 kg/m^2.[15]

The physiological factors that inhibit the function of upper airway dilating muscles are sleep, alcohol[16] and hypnotics.[17] Narrowing of the nose or nasopharynx calls for extra effort to breathe, and thus generate an increase in upper airway pressure during inspiration, and further predisposes to upper airway narrowing and collapse.[14]

The upper airways of OSAS patients are not only narrower, but also more compliant both during wakefulness and sleep.[18] The reason for this increase in compliance is unclear and cannot be accounted for by differences in muscle tone or in upper airway calibre. If the upper airway dilating tone is above normal in OSAS patients when awake,[15] then deflatory compliance of the airway would be expected to decrease rather than to increase. Conversely, if narrowing of the upper airway by fat deposition or by retroposition of the jaw is the factor, expiratory compliance would be expected to decrease, but not increase in patients with OSAS. Pharmacologic enhancement of serotonergic transmission by serotonin uptake inhibition has been suggested as one approach to improve upper airway patency, and thus nocturnal breathing in patients with OSAS.[19] In our view, more work is required to explain the discrepancies found in such patients before firm conclusions could be drawn.

FACTORS PREDISPOSING TO OSAS

GENDER

Any explanation of the pathogenesis of OSAS has to encompass the main predisposing factors: male sex, middle age, and obesity. It is far from clear why 85% of patients presenting with OSAS are men.[20] There seems to be no consensus in the literature regarding upper airway calibre differences between the genders.[21–23] The upper airways in men seem to have different physical properties, with bigger changes in airway size with fluctuations in lung volumes,[22] and on lying down.[23] It is not clear if these differences are the result of anatomical factors or from differences in the upper airway dilating muscle function. In addition, the effects of gender on these factors are unclear. Although androgens have been reported to induce OSAS, anti-androgen drugs given for one week did not significantly affect OSAS severity.[24] It is possible that androgens' effects on fat deposition in the neck or on upper airway muscle function were not evident within one week. Men have thicker necks than women even when matched for body mass index.[1] This difference could cause increased mass loading on the airway in men when they lie down, predisposing to upper airway narrowing during sleep. Another gender-related puzzle is that, although 85% of individuals presenting to sleep clinics with OSAS are male, recent epidemiological studies have consistently found that men are only twice as likely

as women to have abnormal breathing during sleep.[1,25] Clarification is required as to whether this discrepancy results from referral bias or from differences between the sexes in the severity of symptoms resulting from a given degree of irregular breathing during sleep.

AGE

OSAS affects all age groups, but there is no obvious reason for it to be commonest in middle age.[26] Although upper airway resistance has been reported to increase with age in men,[27] a recent study indicates that the pharyngeal lumen in awake men becomes greater as they get older.[28] This study also showed that the electromyographic response of the tongue to negative upper airway pressure was greater in subjects aged 60–79 years than in either 20–39 or 40–59-year-olds.[28] Thus, there is no convincing evidence of either structural narrowing or functional impairment of upper airway dilating muscles in middle age. Nevertheless, a common observation in clinical practice is that a young snorer is likely to become a middle-aged patient with OSAS.[29]

OBESITY

The association with obesity is easier to explain. Indirect evidence of increased fat deposition in the neck comes from the observation that patients with OSAS tend to have large necks.[27] Magnetic resonance imaging (MRI) studies have shown that patients with OSAS have increased fat deposition adjacent to the pharyngeal airway,[23] especially posterolateral to the airway at the level of the soft palate, so that there is squashing of the lateral aspects of the upper airway.[15] MRI studies have also shown fat deposition in the soft palate itself.[16] Morphological studies have shown increased fat deposition in the soft palates and uvulae of OSAS patients.[28] Deposition of fat could narrow the upper airways and predispose to critical airway narrowing during sleep.

INHERITANCE

There were early case-reports that OSAS cluster among family members.[30] However, this might have been due to familial occurrence of obesity alone. Studies in families of non-obese patients with OSAS have shown definite family clustering of OSAS, with evidence of abnormal facial structure, narrowed upper airways, and enlarged uvulae compared with weight, height, and sex matched controls.[31] It remains to be determined if these abnormalities are causal and inherited or whether they are consequences of the abnormal breathing during sleep.

CLINICAL EFFECTS OF OSAS

The severity of daytime sleepiness relates poorly to the frequency of either respiratory events or electroencephalographic (EEG) arousal during the night.[32,33] The fragmented sleep invariably causes daytime somnolence which may be associated with impaired cognitive function, fatigability and morning headaches.[33] What constitutes a clinically significant arousal from sleep or even whether any cortical EEG change is needed for an event to contribute to subsequent daytime sleepiness is not well understood.[14] The degree of effort to breathe seems to act as the stimulus for arousal to terminate an apnoea. But does the threshold to arousal vary between subjects, or are there qualitative differences in arousals between subjects that could account for the disparity between respiratory event frequency and sleepiness? Unlike sleepiness, impaired daytime cognitive function does relate to the severity of sleep disruption and particularly to the frequency of brief cortical EEG arousals. The large individual variation calls for better quantification of sleep fragmentation.

Untreated patients with OSAS are at increased risk of cardiovascular and cerebrovascular events. There is conflicting evidence on whether OSAS patients have higher daytime blood pressure than do normal subjects matched for age, sex, weight, and alcohol consumption.[34] However, each apnoea or hypopnoea is associated with a transient rise in systemic blood pressure which occurs at the time of the arousal. This rise may occur even when there are no obvious EEG changes.[35] It is tempting to speculate that the excess of cardiovascular and cerebrovascular disease among OSAS patients probably results from hundreds of these blood pressure rises occurring every night for years or even decades although the natural history of these consequences are ill understood. Apart from its effects on the systemic circulation, OSAS results in raised pulmonary arterial pressure in about 25% of patients,[36] and this might predispose to cor pulmonale, especially in patients with co-existing lung disease.

EFFECTS OF OSAS ON THE CARDIOVASCULAR SYSTEM

1. SYSTEMIC HYPERTENSION

Systemic blood pressure normally decreases by 5–14% in non-rapid eye movement (non-REM) sleep compared with awake resting values.[37] Blood pressure fluctuates considerably during REM sleep and is on average 5% higher than the preceding non-REM sleep. In patients with sleep disordered breathing there are brief phasic changes in blood pressure superimposed on a cyclical pattern which coincide with the upper airways obstruction. The brief phasic changes in blood pressure are secondary to the large changes in intrathoracic pressure during obstructed respiration. Systemic blood pressure may increase by up to 20% during OSAS and is maximal immediately after termination of apnoea.[38] The mechanism of the cyclical pattern in blood pressure during OSAS is probably multifactorial in origin. Hypoxaemia,

hypercapnic acidosis, increased respiratory effort and the increased sympathetic activity associated with awakening have all been proposed.[39] Hypoxaemia does not appear to be a major causative factor as blood pressure remains unchanged in patients with OSA during supplemental oxygen therapy.[40] Both sympathetic nervous output and catecholamine production increase during OSAS.[41,42] Catecholamine secretion decreases following effective treatment with either tracheostomy[43, 44] or nasal CPAP therapy.[45] Systemic hypertension occurs in 40–60% patients with OSAS,[46] and its severity is related to apnoea severity.[38]

The association between sleep disordered breathing and systemic hypertension appears to be mainly due to similar risk factors for both conditions. It is important to consider the diagnosis of sleep disordered breathing in patients with systemic hypertension, especially those resistant to therapy, but further diagnostic studies are not indicated in the absence of other features of sleep disordered breathing.

2. Cardiac Function

There is a variation in cardiac output during episodes of apnoeas/hypopnoeas. It drops during bradycardia and increases with the rebound tachycardia and it has been hypothesised that this would result in left ventricular hypertrophy or dysfunction.[47] There are several reports of echocardiography in patients with OSAS. Hedner and associates[48] excluded patients with systemic hypertension and found a larger left ventricular mass in patients with OSAS compared with control subjects. However, results of controlled study showed no difference in left ventricular size or function between snorers and OSA patients.[49] In our own observation, normotensive patients OSAS failed to dip their blood pressure during sleep and had increased LV mass.[50] Cardiovascular variability is altered in patients with OSAS. This alteration is evident even in the absence of hypertension, heart failure, or other disease states, and may be linked to the severity of OSAS. Abnormalities in cardiovascular variability may be implicated in the subsequent development of overt cardiovascular disease in patients with OSAS.[51]

3. Ischaemic Heart Disease

OSAS has been shown to be a significant risk factor in the development of ischaemic heart disease.[52] The combined effects of systemic hypertension, hypoxaemia and increased sympathetic activity during sleep are thought to promote the development of atherosclerosis.[53] ST depression is relatively common in patients with OSAS during overnight ECG monitoring, and the duration of this is reduced by nasal CPAP therapy.[54] This ST depression may reflect myocardial ischaemia or non-specific changes associated with OSAS. Myocardial ischaemia is reported to have occurred during polysomnography in five of 20 patients with combined ischaemic heart disease and OSAS.[55] New evidence suggesting a role for vascular endothelium in the development of vascular disease in OSAS is now emerging.[56]

4. Cardiac Arrthythmias

Cardiac rate normally decreases by 5–10% during non-REM sleep, with a slight increase during REM sleep.[47] In patients with sleep disordered breathing the vagal stimulation caused by inspiring against the upper airway obstruction results in sinus bradycardia during the apnoea followed by a reflex tachycardia at apnoea termination.[57] The degree of bradycardia is related to the severity of the associated arterial oxygen desaturation.[58] Cardiac arrhythmias during sleep occur in up to 50% of patients with OSAS.[59] These arrhythmias are more frequent when OSAS is associated with arterial oxygen desaturation, and resolve following effective treatment of the OSAS. The cyclical changes in heart rate seen in patients with sleep disordered breathing can be confused with sick sinus syndrome, and could result in inappropriate treatment such as cardiac pacing.[60]

5. Cerebrovascular Disease

Patients with OSAS have increased cerebrovascular mortality and morbidity.[61] One report described 53% of male patients with a cerebrovascular accident (CVA) to be chronic snorers.[62] Of these, 35% had CVA during sleep and snoring was the only factor which correlated with the diurnal variation in the time of CVA. A case controlled study of patients admitted to hospital with a CVA showed that snoring was an important risk factor for the development of a CVA and adversely affected the prognosis.[60,61]

6. Pulmonary hypertension/Right heart failure

Pulmonary artery pressures usually remain relatively unchanged during sleep in normal subjects. In contrast, pulmonary artery pressure increases by up to 100% during REM sleep in patients with OSAS.[63] The cyclical changes in pulmonary artery pressure parallel the changes in systemic blood pressure. These changes are due to the effects of obstructed inspiratory efforts on pulmonary and cardiac dynamics, and hypoxic pulmonary vasconstriction. Pulmonary pressor response to hypoxia was augmented (> 10 mm Hg) by hypercapnia in patients with OSAS but not in normal subjects.[64]

Pulmonary hypertension occurs in a substantial proportion of patients with sleep disordered breathing. The prevalence of pulmonary hypertension in patients with OSAS has been reported to be between 10% and 20%, but may be as high as 55% in moderate to severe disease.[65] The presence of pulmonary hypertension and

associated right heart failure in patients with sleep disordered breathing is invariably indicative of severe disease which requires prompt diagnosis and treatment. It is important to consider the diagnosis of sleep disordered breathing in patients with unexplained pulmonary hypertension. However, further diagnostic studies are not indicated in the absence of other features of sleep disordered breathing.

7. Psychological / psychiatric consequences

Intellectual deterioration, personality and behavioural changes are well recognized features of sleep disordered breathing. Interpersonal relationships at work and at home are affected. Psychological testing in patients with sleep disordered breathing show significant impairments in thinking, perception, memory and the ability to learn.[66] Dysfunction of cognitive behaviour is related to the severity of the sleep hypoxaemia[67] and sleep fragmentation.[68] Treatment of OSAS may improve psychological status and result in reduced anxiety and depression.[69] Sleepiness, as assessed by the Epworth Sleepiness Scale, has an important impact on general health and functional status, specifically influencing self-perceptions regarding energy and fatigue.[70–72]

8. Endocrine

Decreased libido and impotence are frequently associated with sleep disordered breathing.[46] Of 50 patients with severe OSA, 44% were reported to have either diminished sexual interest or performance.[46] This sexual dysfunction is probably related in part to the daytime sleepiness or depression associated with sleep disordered breathing. There are however, two reports that suggest that sleep disordered breathing causes hypothalamic pituitary dysfunction, which is reversible following effective treatment.[73] This reversible neuroendocrine dysfunction might contribute to the decrease in libido and impotence in OSAS.[74] In postmenopausal women, the incidence of OSAS increases and changes in reproductive hormones might have a role in this condition.[75] Treatment with testosterone has been reported to cause OSAS in men.[76] Some patients with acromegaly may develop OSAS which may be related to changes in facial features. Interestingly OSAS responds to growth hormone lowering drugs.[77] OSAS and hypothyroidism overlap in symptoms and signs. The sleep-disordered breathing that accompanies hypothyroidism could lead to significant risk of misdiagnosis of sleep apnoea among patients referred to sleep clinics who have undiagnosed hypothyroidism.[78] Nevertheless routine thyroid testing in OSAS is not recommended except in clinically relevant cases.[79] Similarly routine sleep studies in all hypothyroid patients.[80] Good clinical judgement alone is the important in diagnosing and managing both conditions in a cost effective way.

Melatonin has a strong circadian rhythm with high values during the night-time and low values in the afternoon and it was hypothesized that sleep disordered breathing may change the circadian rhythm of melatonin which may have diagnostic implications.[81] Even though exogenous melatonin has proven to have clear phase-shifting effects,[82] and can influence sleep and circadian parameters, low endogenous melatonin is not related to sleep disturbances, nor does it predict response to melatonin therapy.

9. Renal

Atrial natriuretic peptide concentrations are increased during sleep in patients with sleep disordered breathing and decrease with nasal CPAP therapy.[82,83] Patients with sleep disordered breathing commonly complain of nocturia which could improve with effective treatment.[84] The frequent nocturia in patients with sleep disordered breathing is probably related to diuresis and natriuresis caused by the recurrent hypoxaemia. Patients with sleep disordered breathing are also more prone to have proteinuria[85] which improves with effective treatment. The mechanism of this proteinuria is unclear.[87]

10. Mortality

There are limited retrospective data on the mortality associated with OSAS, but most studies suggest a decreased long term survival.[88] Guilleminault and colleagues[89] reported decreased five year survival in patients with untreated OSA compared with both patients treated by tracheostomy and CPAP. The US age adjusted survival curve was the same. There is a decreased survival in patients with untreated OSAS with an apnoea index of >20/hour.[90] This difference was most evident in patients below 50 years of age.[91] The major cause of increased mortality in sleep-disordered breathing appears to be cardiovascular in nature.[92] There is no difference in the long term survival of patients with OSA treated with either corrective upper airway surgery or nasal CPAP.[93]

CONCLUSION

Obstructive sleep apnoea syndrome is a multi system disorder and a major health hazard, which has gained its due recognition in the developed world. Unfortunately this recognition is still largely lacking in developing countries. Although treatment is effective and relatively simple, the fundamental abnormality which initiates the cascade of events described above remains to be identified.

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