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Sleep apnea syndrome and its complications

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Das Schlaf-Apnoe-Syndrom und seine Komplikationen

Zusammenfassung. In diesem Artikel fassen wir die Informationen über die Epidemiologie, die Pathophysiologie wie auch über die Risikofaktoren und Komplikationen vom Schlaf-Apnoe-Syndrom (SAS). Bekannt sind die zentrale, obstruktive and die gemischte Form von SAS, die obstruktive Form ist aber (begründet durch die hohe Prävalenz vom Übergewicht) auf jedem Fall die häufigste. Die letzten Jahre der experimentellen und klinischen Forschung haben die Wichtigkeit dieser schlafbezogenen Atmungsstörung aufgezeigt. Die hohe Prävalenz und vor allem die kardiovaskulären Komplikationen (z. B. systemische und pulmonale Hypertonie, Aterosklerose, Arrhythmien) haben zu dem gegenwärtigen Wissen über SAS beigetragen. Künftige Studien sollten uns mit neuen Informationen versorgen, die mehr Licht in die versteckten Geheimnisse des SAS bringen.

Schlüsselwörter: Schlaf-Apnoe-Syndrom, Pathophysiologie, kardiovaskuläre Komplikationen, Hypertonie, Übergewicht, schlafbezogene Atmungsstörung.

Summary. In this article we summarize the available information regarding the epidemiology, the pathophysiology as well as the risk factors and complications of the sleep apnea syndrome (SAS). Central, obstructive and mixed forms of SAS are known, however, the obstructive form is (resulting from the actual high prevalence of obesity) definitely the most frequent. Latest years of experimental and clinical research have pointed towards the clinical importance of this sleep related breathing disorder. High prevalence in the population and especially the cardiovascular complications (e. g. systemic and pulmonary hypertension, atherosclerosis, arrhythmias) have contributed to the recent increase in knowledge about SAS. Nevertheless, there are numerous unsolved problems and unanswered questions in the pathophysiology of SAS. Future studies should, thus, provide us with more information and shed light on regarding the hidden mysteries of SAS.

Key words: Sleep apnea syndrome, pathophysiology, cardiovascular complications, hypertension, obesity, sleep related breathing disorder.

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Introduction

Sleep is a physiological process necessary to keep the health status of most living organisms. The mechanism of this protective effect is despite the boom in sleep biomedicine far from being completely understood. It is a recent finding that one third of the human population suffers from variable kind of sleep disorders. The high prevalence might be due to the contemporary life style, increased stress exposure, decreased physical activity and resulting epidemic spread of obesity. A further reason is related to social changes in the biological clock due to traveling far distances across time zones and working in the night shift.

Important issues of sleep medicine are the sleep related breathing disorders. These entities are often divided according to their causal relationship either to the sleep or to diseases of the respiratory system. Sleep apnea syndrome (SAS) belongs to the first group [19]. Apnea is defined arbitrary as a breathing cessation for more than 10 seconds. On contrary, hypopnea is a hypoventilarory event with a decrease of respiratory volume by 50 % for more than 10 seconds. The average number of apneas and hypopneas during one hour of sleep is the so-called apnea/hypopnea index (AHI) or respiratory disturbance index (RDI). If this index exceeds the value of 10, SAS is diagnosed. AHI of more than 20 represents an important clinical problem. A recent effort to quantify the seriousness of SAS is the oxygen desaturation index (ODI) based on the hypoxic status of the patient during the apnea periods. The clinical value of this index must, however, though clear pathophysiological substantiation, be evaluated yet.

For the clinical praxis it is important to bear this diagnosis in mind as a life threatening disorder. Complica-

tions of SAS include daytime sleepiness (resulting in increased incidence of car accidents and work injuries), acute (dysrhythmias, sudden cardiac death) and chronic cardiovascular diseases (pulmonary hypertension, cor pulmonale, atherosclerosis) as well as stroke and cognitive decline.

SAS forms

Central SAS is based on a failure in cerebral respiratory control (Fig. 1). Respiratory muscles do not get any commands from the brain leading to a lack of respiratory movements and to a breathing cessation [4]. The etiology is mostly cerebrovascular secondary to cardiologic or neurologic diseases. Resulting acute hypoxia of specific parts of the central nervous system, especially in medulla oblongata is usually the cause of this SAS form. A hypoventilatory state can, however, be also induced by a number of psychopharmaceuticals causing apnea.

Obstructive SAS is characterized by the presence of breathing movements but by a lack of airflow [3]. Episodes of complete or partial obstructions of upper airways during sleep are often accompanied with loud snoring, daytime sleepiness, arousals, sleep fragmentation and intermittent hypoxia and hypercapnia. Snoring or gasping is usually a symptom of intermittent obstructions in men in the 4th and 5th decade. Deviation of the nasal septum, adenoid vegetation, hypetrophic tonsils, but also benign nasal polyps and other tumors in this region often cause snoring.

Mixed SAS represents a combination of both previously mentioned SAS forms. An episode of mixed SAS begins as a central SAS. After the recovery of respiratory musculature activity it continues as obstructive SAS due the missing activity of pharyngeal dilatators. Acromegaly frequently causes mixed SAS. Macroglossy is related to the obstructive SAS and disorders in the pons and medulla oblongata to central SAS. An interesting symptom that can be found in this situation is a pathological orbitoocular reflex.

Pathogenesis of SAS

The basis of all forms of SAS is the intermittent breathing interruption in sleep. During these events the alveolar ventilation is diminished resulting in changes in blood gas concentrations [16]. Disorders in the function of heart and other organs are the end-point in the acute phase. The grade of arterial oxygen desaturation is dependent not only on the duration of apnea, but also on the basic values of pO_2 before the sleep. These are influenced by a variety of respiratory and other diseases like chronic obstructive pulmonary disease, asthma, obesity etc. Continual registration of arterial blood oxygen saturation is a very useful information about the origin, seriousness and the progress of hypoxia in SAS.

The dynamics of hypoxia as well as the consequences can be followed by the polysomnographic record of oxygen saturation and other parameters like EEG and ECG changes occurring especially during the REM sleep phases. The horizontal position during sleep and high inspiratory effort during the apnoic episodes of obstructive and mixed SAS forms trigger the increase of venous

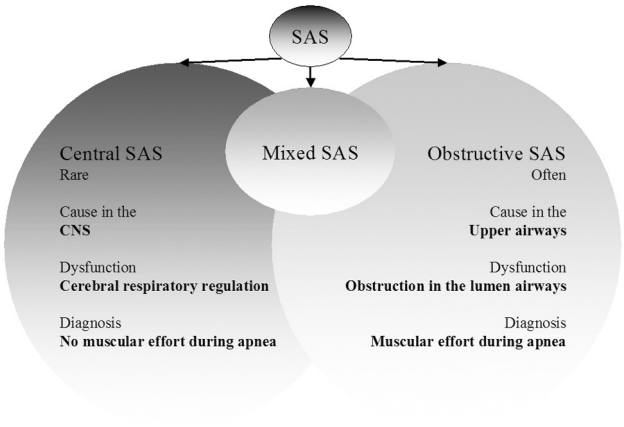

Fig.1.

blood return to the heart. This raised preload increases the pulmonary circulation flow. In patients suffering from asthma bronchiale the induced changes in pulmonary circulation together with the congestion of the mucous layer of respiratory tract can induce a severe asthma attack. An important symptom found in SAS is the cyclic variation of heart rate. During the apnoic episodes bradycardia arises, the following reactive hyperventilation induces tachycardia.

The pathogenesis on molecular level is a mixture of puzzle pieces that need to be arranged correctly in the near future. A hypothesis of the molecular interactions leading to the cardiovascular complications of SAS has been published recently [8]. The crossroad of the subcellular pathways seems to be the hypoxia inducible factor (HIF). Hypoxia response elements are the targets for HIF at DNA. Numerous genes have been reported to be regulated by this mechanism. Nevertheless, the "molecular SAS" is a great challenge for future research.

Risk factors of SAS

The typical SAS patient is a middle aged obese man. Recent epidemiological research has shown that the prevalence of SAS is in adult population about 4 % in men and 2 % in women. SAS in children was not considered, as the pathophysiology of this disorder in infancy differs

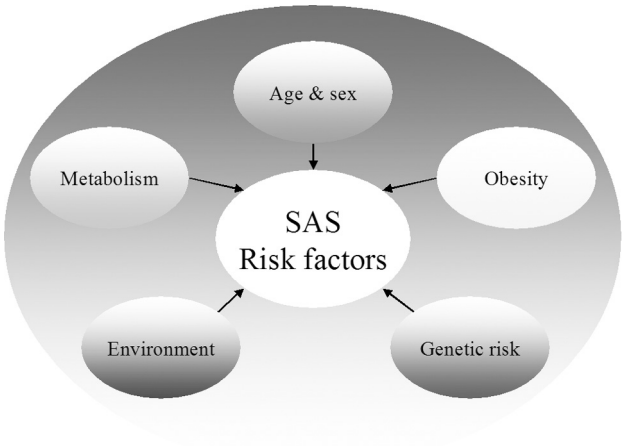

Fig. 2.

considerably [6]. The most important risk factor for the development of SAS is surely obesity. Other risk factors are often dependent on the characteristics of the soft and hard tissues of the upper respiratory tract and on factors influencing the respiratory control [5]. A number of these risk factors are changing with the age. It must be noted, that the borderlines between risk factors, complications and obesity related diseases are difficult to draw [14]. Thus further aspects of the SAS pathophysiology (although not determined as clear risk factors) should be mentioned – diabetes mellitus, hypertension, cardiopulmonary diseases, but also environmental influences (alcohol, smoking, allergens, drugs etc.) and genetic dispositions take a part on the development and progress of SAS (Fig. 2).

Age and sex

The higher incidence of SAS in men is often explained by the male form of fat distribution that includes the neck region. Androgens (especially testosterone) affect respiratory and neuromuscular activity of the upper respiratory tract as well. Whether higher androgen levels are involved in the pathogenesis of SAS is unclear yet. Progesterone and estradiol as the main female sex hormones are reported to have a stimulatory effect on the central nervous respiratory control. Their role in SAS pathophysiology should be also further studied.

A clear sex difference in the prevalence of SAS is noticeable especially between 25 and 50 years of age. Women of this age with SAS are mostly morbidly obese with BMI of more than 30 kg/m^2. Anatomical characteristics are thus suspected to play the central role, as lean women are "protected" against SAS. The sex difference nearly disappears in prepubertal and postmenopausal population groups, suggesting once more some unknown role for sex hormones.

Obesity and fat distribution

Obesity quantified as BMI > 28 kg/m^2 is found in 60–90 % of SAS patients. Thus, the risk to develop SAS is 10–14 times higher in obese patients. On the other hand, the loss of weight – even moderate – can considerable improve the symptoms of SAS. Especially the central form of obesity contributes to acceleration or exacerbation of the process of SAS development due to the deposition of adipose tissue in the neck region and around the upper airways [12]. A consequence of this mechanism is the collapse of upper respiratory tract lumen during sleep and the development of obstructive sleep apnea syndrome (OSAS). Abdominal fat deposits play a role in SAS by inducing hypoventilation. The central form of obesity is more frequent in men. Women develop this type of obesity mostly in the postmenopausal period.

Genetic risk

Some of the risk factors like obesity and morphology of the anatomical structures in the neck region have a known or supposed genetic basis [9]. This is used to explain the increased incidence of SAS in some families. Complex genetic syndromes can be linked to SAS. Marfan syndrome can cause SAS through the pathologically increased compliance of connective tissue, thus facilitating the collapse of upper airways. In Down syndrome tissues are accumulated in the pharyngeal region (macroglossy, tonsilar hypertrophy), central form of obesity occurs and the brachycephaly as a morphological abnormality of the cranial development also plays a part in the SAS progress. Cranio-facial deviations and micrognacy are responsible for SAS and snoring in Pierre-Robin syndrome. Although the genetic mechanisms seem not to be cause of SAS in most patients, their understanding can help in recognition of the pathophysiology of SAS.

Metabolic and vascular diseases

Many consequences of SAS can also be considered as risk factors for SAS development. Hypertension and diabetes mellitus belong to the factors that seem to increase the incidence of SAS. Although typically hypertension is often reported as a complication of SAS, the use of various antihypertensives increases the apnoic activity by 20 %. Chronic increase of blood pressure can alter the neural reflexes and the integration of neural signals in cerebral stem. This may cause the respiratory instability symptomatic for SAS.

Vascular disorders influence negatively both, cardial and cerebral functions leading to the impairment of respiratory controls and thus to SAS [18]. Diabetic status and insulin resistance are often linked to the central obesity and can thus further aggravate the progress of SAS.

Environmental factors

Alcohol, smoking and irritations of airways can be seen as risk factors of SAS. Smoking and allergens exposure lead to the muco-cutaneus congestion of upper respiratory tract. The development of secondary chronic pulmonary diseases further supports the progress of sleep related breathing disorders, especially if linked to the decrease of pulmonary capacity. Alcohol decreases the tone of the smooth musculature that is responsible for the stability of the lumen of upper airways. The sedative and hypnotic effect of alcohol intake therefore decreases the respiratory activity leading to worsening of SAS.

Complications of SAS

A majority of specialists share the opinion that obstructive SAS is much more dangerous than other forms of SAS. The main reason is the higher occurrence of serious cardiovascular complications (Fig. 3). Obstruction of the upper airways, hypoventilation and arousals – typical for obstructive SAS – play a key role in the pathogenesis of cardial arrhythmias, arterial hypertension, heart failure etc. Articles concerning the epidemiology of SAS report that obstructive SAS is a risk factor for cardiovascular diseases especially in obese patients of older age that smoke and consume alcohol frequently [7]. Cardiovascular complications include also spasms of vessels in coronary and cerebral vasculature. Patients with obstructive SAS have a double risk for myocardial infarction, angina pectoris and stroke. About 20 % of these patients with worse forms of SAS develop a stagnation of blood in the pulmonary circulation leading to left ventricular heart failure and pulmonary edema. Preexisting chronic

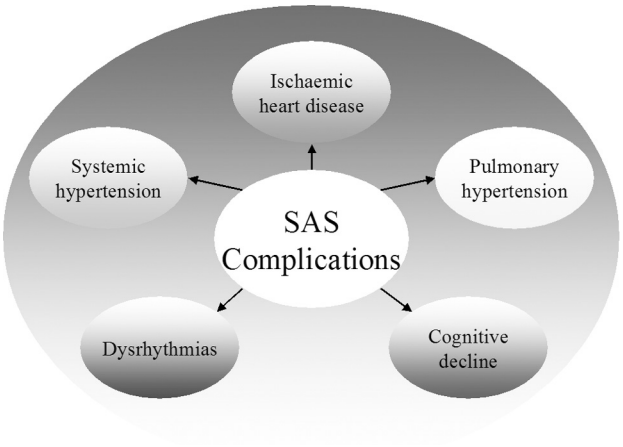

Fig. 3.

heart failure is of course a further contributor to this process. Serious disorders of the heart rhythm, particularly an extreme sinus bradycardia, sinus arrest, malign tachycardia and sudden cardiac death can also occur. Recently, complications affecting the central nervous tissue have been recognized. Considerably accelerated age-related cognitive decline, decreased memory and also disordered development of various cognitive abilities belong to the reported psychological changes induced by SAS [11].

Systemic arterial hypertension

The incidence of arterial hypertension in obstructive SAS is reported to be 40–70 %. Beginning as a transient repeated increased blood pressure it slowly develops to the full clinical picture of fixed hypertension. Although the detailed mechanisms are unknown endothelial damage and the decrease in NO bioavailability seem to play a major role. Under physiological conditions the blood pressure decreases up to 10 % in comparison to the daytime average values. This phenomenon is called dipping. Increased secretion of endorphins and decreased levels of adrenalin and other hormones related to the sympathetic activity are thought to be responsible for the lower blood pressure during sleep in healthy population. Blood pressure decreases with the depth of the sleep in the non-REM phase. In REM phases the blood pressure undergoes a great dynamic variability with high amplitude that coincide with irregular breathing. Early in the morning the blood pressure is increasing due to the corticoid rise, probably, to prepare the organism for the awakening. Hormones like catecholamines, vasopressin, rennin, angiotensin and endothelin are increased in this period. In patients with SAS two peaks of blood pressure can be found during one apnoic event – during the apnea and just after the apnea during the restored breathing. The cause of this rise is the activation of the sympathetic nervous system due to the restoration of ventilation and of intrathoracal pressure. A further characteristic feature of blood pressure profile of patients with obstructive SAS is the absence of the sleep or night related decrease [10]. This "non-dipping" is also related to an increased variability of blood pressure during the sleep phase due to the oscillations during every apnea-hyperventilation period. Pathogenetic mechanisms important for the development of arterial hypertension include activation of sympathetic autonomous nervous system, endocrine changes related to the regulation of water and electrolyte milieu, metabolic shifts towards insulin resistance, obesity, dyslipidemia and local disorders of vasotonus regulation.

Chronic intermittent and repeated hypoxemia in SAS represents a stress situation for the organism with a following inadequate vasopressin secretion. Induced changes in fluid volume homeostasis lead to chronic modifications of the rennin-angiotensin-aldosterone system [20]. Secretion of rennin is low in SAS patients. The suppression of rennin secretion can be explained by the stimulation of cardiopulmonary volume receptors during apnea. Decreased rennin levels during sleep lead to central hypovolemy and a subsequent overproduction of rennin during the following day. This situation is similar to that in patients with essential low-rennin hypertension. During apnea aldosterone levels are also decreased. An optimal therapy can, however, reverse these changes and normalize the hormonal levels. Endothelial dysfunction leads after repeated hypoxia to a dysbalance between vasoconstriction (TXA_2, endothelin) and vasodilatation (NO, EDGF, PGE_2, adenosine) inducing cytokines. The dysfunction of local vasotonus regulation amplifies the vasoconstriction effect of sympathetic activity during hypoxia. Fluctuations of glycaemia induce activation of the sympathetic nervous system and the rennin-angiotensin-aldosteron cascade, but they also increase the sensitivity of the vascular wall vasoconstriction stimuli. Hyperinsulinemia stimulates the growth of the muscular layer of the vessel wall. This vascular hypertrophy and the stimulation of endothelin production increase the peripheral resistance.

Pulmonary hypertension

Pulmonary hypertension begins as transient disorder during the apnoic phases, but becomes fixed with the progress of SAS. During the apnoic episodes the oscillations of intrathoracal pressure can lead to acute right ventricular heart failure – cor pulmonale acutum. Fixed pulmonary hypertension often ends in cor pulmonale chronicum.

The real prevalence of pulmonary hypertension in obstructive SAS patients is unknown. Literature information varies considerably between 17 % and 73 %. The reason lies in the diagnostic methods used. About 10 % of patients, however, suffer from right ventricular heat failure. Previous epidemiological studies have shown that SAS alone can lead to pulmonary hypertension without any "help" from other pulmonary diseases. The highest incidence of pulmonary hypertension has been found in patients suffering from both, obstructive SAS and chronic obstructive broncho-pulmonary diseases – so-called overlap syndrome.

The most important factor for the vasoconstriction of small arteries and arteriols of the pulmonary circulation is the decrease of partial oxygen pressure in the alveolar space – alveolar hypoxia. This hypoxia-induced vasoconstriction induces the development of permanent pulmonary hypertension [15]. A further contributor is the hyp-

oxia-induced proliferation of smooth muscle cells inside the wall of pulmonary vessels. Thus, the development of precapillary pulmonary hypertension is a combination of two processes – hypoxic vasoconstriction and remodelation of the vessel wall. Atrial natriuretic factor (ANF) is a further interesting parameter. ANF levels are usually increased in patients with obstructive SAS due to the distension of the right atrium caused by an increased venous return and an increased intrathoracal pressure. ANF produced in right atrium is a protective factor. Hypoxemia contributes to the up-regulation of ANF secretion. Increased ANF causes a rise in nocturnal diuresis, hemoconcentration and an early morning hypovolemy. The exhaustion of this mechanism can further accelerate the pathological process of blood pressure increase – both, in the systemic and in the pulmonary circulation.

Ischaemic heart disease

Hypoxia, hypercapnia and acidosis represent a strong stressor for the heart. The subsequent stimulation of the sympathetic activity can help to normalize the situation. But under pathological conditions this process can uncover beginning heart diseases. Especially, the low arterial oxygenation and the increased requirements of the organism detect the borders of resources for the heart. Spasms of the coronary arteries are the result. Patients suffer from attacks of angina pectoris or myocardial infarction. It should be noted that these clinical pictures are reached by two different although coupled mechanisms – hypoxia due to low arterial oxygenation and ischaemia due to coronary spasms [17]. The incidence of heart attacks during the REM sleep is up to four times higher than during the non-REM phases.

Dysrhythmias

About 10 % of SAS patients suffer from heart rhythm disturbances. The dysregulation of autonomous nervous system is very probable the main causal factor. The switch between vagal parasympathetic and sympathetic activity is usually benign for the healthy heart, but in patients with pre-existing heart ischaemia these disturbances might have serious consequences with bad prognosis. The apnoic phase is accompanied with hypoxia induced parasympathetic activity and bradycardia. The following arousal with a huge activation of the sympathetic nervous system causes tachycardia. These changes repeat during the sleep while asystolic periods of more than 10 seconds can occur. The dysrhythmias in SAS patients include the whole spectrum between sinus bradycardia and ventricular tachycardia. Nevertheless, the detailed pathophysiology of heart rhythm disturbances in SAS is unclear. Due to the increased risk for sudden cardiac death the pathomechanisms are of considerable clinical importance.

Stroke and psychological changes

Apnoic phases and their vascular consequences are dangerous for the cerebral vasculature. Periodic oxygen desaturation can lead to ischaemic cerebral infarction. These changes are diagnosed by EEG as a part of polysomnography. Repeated arousals during sleep rapidly decrease the blood flow through the brain. Above-mentioned dysrhythmias can also contribute to the risk for stroke. This relationship is often explained by the known higher incidence of strokes during the first hours after awakening.

Neuropsychiatric disorders are linked to the arousals and the discontinous sleep. Best known is the daytime hypersomnia – sleepiness. In the beginning patients note increased fatigue and often fall asleep during passive daily activities like reading or TV-watching. During the progress of SAS the hypersomnia is worsening [2]. Probably the most dangerous is the micro-sleep while driving a car. Car accidents and work injuries belong to the factors that shorten the life duration expectancy considerably. Higher nervous functions are also affected. Especially memory, spatial orientation, intelligence and a number of other cognitive abilities were proved to deteriorate in patients with SAS [1]. Diagnosis like chronic fatigue syndrome, slight reduced intelligence, but also Alzheimer's disease are worsened due to sleep related breathing disorders like SAS.

Conclusion

In this article we have presented and summarized the recent knowledge about the epidemiology, incidence, the risk factors, as well as the consequences of obstructive SAS. The clinical importance of this entity lies in the high prevalence in the population and the recently recognized cardiovascular and central nervous complications. These are the reasons for the contemporary increased scientific and clinical interest. Therapy options of obstructive SAS include pharyngeal surgery or nasal continuous positive airway pressure [13]. The main clinical problem lies, thus, in the early and accurate diagnostics. Though the recent concentrations of expert authorities, further research is still needed to uncover the hidden pathomechanisms involved in the pathophysiology of SAS.

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