INTERACTION OF SLEEP APNOEA SYNDROME WITH VARIOUS DISEASES

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INTERAKCIA SYNDRÓMU SPÁNKOVÉHO APNOE S RÔZNYMI CHOROBAMI

Abstract

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Sleep disordered breathing (SDB), particularly their clinically most serious and at the same time common form-sleep apnoea syndrome-caused by structural or functional abnormalities in the area of upper airways, are frequently linked with other diseases. The accompanying respiratory, cardiovascular, neuropsychic, sympathoadrenal and endocrine-metabolic disorders and their variable intensity determine the character and severity of patients complaints. The coincidence of SDB with alteration in one or another system produces mutual potentiation of their negative effects appearing as serious, not rarely even life threatening acute complications or chronic consequences manifesting exactly in the area of the afflicted system. The paper illustrates on several examples the development of pathological signs of SDB concerning practically all medical branches and at the same time demonstrating the multidisciplinary character of sleep medicine. *(Fig. 1, Ref. 27.)*
Key words: interaction of diseases, multidisciplinary co-operation, sleep apnoea syndrome, sleep disordered breathing.

Abstrakt

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Spánkové poruchy dýchania (SPD), najmä ich klinicky veľmi závažná a pritom častá forma, akou je syndróm spánkového apnoe spôsobená štruktúrnymi, či funkčnými abnormalitami v oblasti horných dýchacích ciest, sa často vyskytujú súčasne s rôznymi inými chorobami. Sú to hlavne najrôznejšie pridružené poruchy respiračné, kardiovaskulárne, neuropsychické, sympatoadrenálne a endokrinno-metabolické, ktoré predurčujú charakter a zvyšujú závažnosť ťažkostí pacienta. Koincidencia SPD a postihnutie príslušného systému spôsobuje, že ich účinky sa vzájomne podporujú a prejavujú sa vážnymi, často život ohrozujúcimi akútnymi komplikáciami a chronickými následkami práve v oblasti postihnutého systému. Práca na mnohých príkladoch ilustruje rozvoj patologických prejavov SPD zasahujúcich prakticky do všetkých oblastí medicíny, a súčasne poukazuje na multidisciplinárny charakter spánkovej medicíny. *(Obr. 1, lit. 27.)*
Kľúčové slová: interakcia chorôb, multidisciplinárna spolupráca, spánkové apnoe, spánkové poruchy dýchania.

So called sleep disordered breathing (SDB) often originates during sleep. It represents various stages of the development of a pathologic process generally also termed *"heavy snorers' disease"* (Lugaresi et al., 1990). SDB involves various forms, such as simple and habitual snoring, upper airway resistance syndrome, sleep apnoea syndrome (SAS), Pickwickian syndrome and others (Guilleminault and Partinen, 1990; Kryger et al., 1994; Saunders and Sullivan, 1994; Tomori et al., 1998). Qualitative and quantitative characteristics of individual symptoms of SDB depend on the degree of airflow limitation in the respiratory tract and on the subsequent hypoventilation, which determine severily of the pathological process. Hypoventilation of a lesser degree originates due to the decrease in the tidal volume below 50 % of the standard value (hypopnoea), or in the case of its drop to 0—20 % apnoea occurs.

Considering frequent occurrence and serious health and social-economic impacts, SDB represents a pressing problem being solved by sleep medicine. This was considerably developed mainly in countries of Western Europe and North America during the last 20 years. However, only a little attention was paid to these problems in our country in the past. In the last 3 years, within the framework of the Tempus-Phare project: *"Sleep related breathing disorders in Slovakia"*, which is co-ordinated by us, the situation has been improved in our country, too. The following actions have contributed to this: 1) Introduction of sleep medicine teaching at the Medical Faculties in Košice, Bratislava and Martin. 2) Establishment of sleep laboratories at all three medical faculties, which along with the National Institute for Tuberculosis and Respiratory Diseases in Podunajské Biskupice serve as co-ordination centres.

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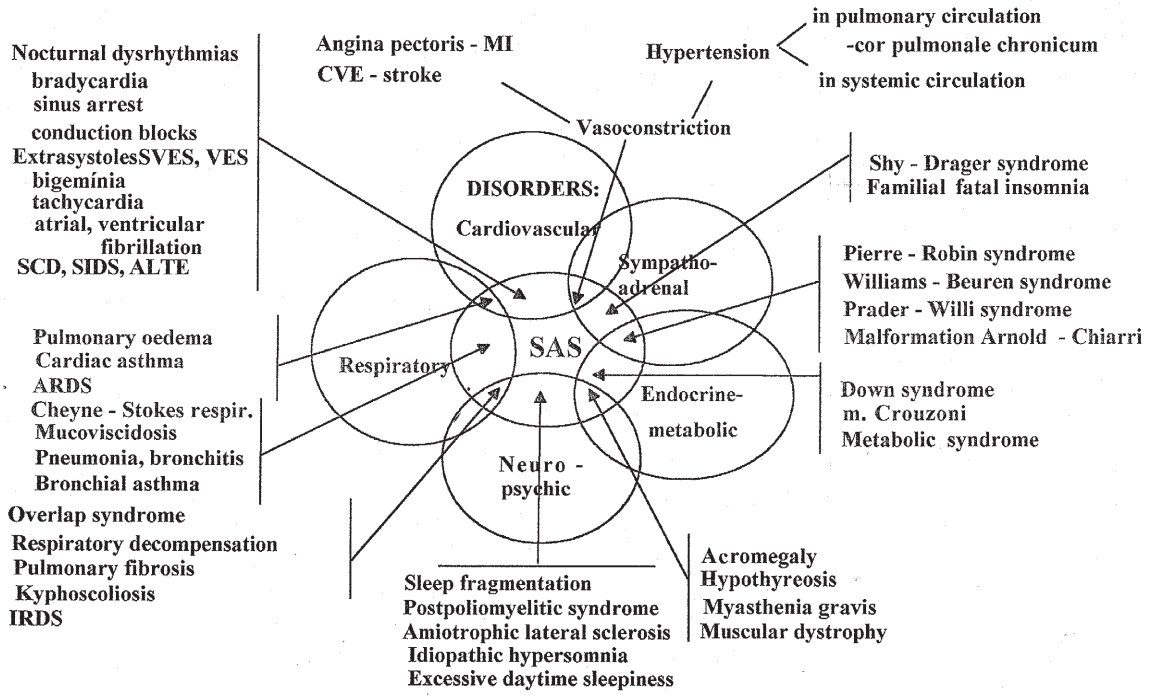

Fig. 1. Interaction of sleep apnoea syndrome with various diseases. Abbreviations: ALTE — Apparently Life Threatening Event, ARDS — Adult Respiratory Distress Syndrome, CVE — cerebrovascular event, IRDS — Idiopathic Respiratory Distress Syndrome, m. — morbus (disease), MI — myocardial infarction, SAS — Sleep Apnoea Syndrome, SCD — Sudden Cardiac Death, SIDS — Sudden Infant Death Syndrome, SVES — Supraventricular Extrasystole (premature beat), VES — ventricular extrasystole.
Obr. 1. Interakcia syndrómu spánkového apnoe s rôznymi chorobami. Slovenské skratky sú v texte.

3) Improvement of postgraduate education of physicians from various branches by organising lecture cycles in sleep medicine at conferences of the relevant professional societies and at the meetings of medical associations, as well as in the form of publications in scientific journals. 4) Training the workers of sleep laboratories in the form of short-term visits to the partner institutions in Antwerp, Dublin and Strassbourg, respectively. 5) Improvement of therapeutical-preventive care of patients suffering from SDB by multidisciplinary co-operation of various specialists, mainly on the basis of sleep laboratories.

Sleep disordered breathing manifests frequently by an episode of obstructive sleep apnoea. Their negative effects are more frequent, rapid and intensive if the patient suffering from SAS also suffers from some other cardiovascular, respiratory, neuromuscular or endocrine-metabolic disorders. Due to this coincidence of SAS and disorders of other systems, their consequences are mutually increased. Schematic Fig. 1 illustrates their participation in development of various pathological manifestations of SDB, and at the same time demonstrates multidisciplinary nature of sleep medicine, above all in the field of diagnostics and therapy.

Pathogenetical relationships between SAS and dysfunctions of various systems

During apnoic and hypopnoic episodes, a temporary increase of blood pressure in pulmonary and systemic circulation occurs in patients suffering from SAS. This is caused by vasoconstriction, which is a result of interaction of the sympatheto-adrenal and cardiovascular systems. Vasoconstriction is produced mainly by the activity of sympathetic fibres supplying the relevant vessels. It is induced by a complex action of various factors initiated by an apnoic-hypopnoic episode. The most important factors are following: 1) central and peripheral action of hypoxaemia, 2) strong fluctuations of pressure in the airways, or in thorax during obstructive sleep apnoea, 3) arousal phenomenon or stress and 4) hypocapnia induced by compensatory hyperventilation. Local effect of hypoxia and acidosis (a local alveolocapillary reflex of hypoventilation of the afflicted alveoli in order to reduce perfusion of the relevant parts of lungs) contributes to constriction of arterioles and venules in lungs.

The short-lasting activation of the efferent sympathetic fibres and a transient vasoconstriction after mechanical irritation of the upper airways (UA) have been proved both in experimental animals and men (Tomori and Widdicombe, 1969; Sellgren et al., 1992). In patients suffering from obstructive sleep apnoea syndrome (OSAS) there is an increased activity of sympathetic fibres supplying vessels of striated muscles and increased secretion of catecholamines even during the day (Hedner et al., 1995). These findings explain the 3 times higher occurrence of arterial hypertension in patients suffering from OSAS (50—70 %) in comparison with the control group (18 %) and demonstrates the contribution of sympathetic nerves to its development. On the other hand, about 43 % of hypertonics suffer at the same time from OSAS and approximately 20 % of patients suffering from OSAS also suffer

from pulmonary hypertension (Krieger, 1990). Chronic irritation of the sympathetic-adrenal system in the case of frequently repeated stresses caused by obstructive sleep apnoea (up to 400 times during each night) may contribute to the development of systemic and pulmonary hypertension and cor pulmonale chronicum. However, the mechanisms of the development of hypertension are very complex.

In the case of ischaemic heart disease (IHD) or coronary and cerebral artery disease, apnoic-hypopnoic episodes, mainly during REM sleep, cause expressive desaturations of oxyhaemoglobin with subsequent nocturnal myocardial or cerebral ischaemia, which can induce more serious complications. According to epidemiological studies, the occurrence of e.g. angina pectoris and of cerebrovascular events (CVE) is increased 1.5-2 times in patients with habitual snoring. The risk of myocardial infarction in patients suffering from SAS is many times higher and the risk of sudden cardiac death will be increased by 33 % (Verrier et al., 1997). Cerebral blood flow in patients suffering from SAS is distinctly reduced during N-REM sleep and considerably increased during REM sleep, which results in a frequent occurrence of cerebrovascular events mostly of the ischaemic type during early morning hours (Hajak et al., 1995). The increased incidence, high intensity and rapid development of the above mentioned pathological processes can be attributed to the following mechanisms: 1) Vasoconstriction and changes in cardiac activity and in blood pressure induced by the increased activity of the sympathetic nerves, which is caused by complex effects of OSAS. 2) Mental stress that induces, according to findings in patients suffering from coronary artery disease, both fatal and non-fatal heart attacks 2.8 times more frequently than physical exercise (Wei Jiang, 1996). 3) Reduced saturation of blood by oxygen and restricted supply of O_2 to the relevant areas due to apnoic or hypopnoic episodes occurring during sleep in these people.

In cardiomyopathies and after myocardial infarction and other damages to myocardium, various dysrhythmias such as extreme bradycardia and cyclic variation of heart rate in the form of bradycardia-tachycardia occur. They represent manifestations of changes in vagal and sympathetic tone, and accompany the apnoea — hyperventilation episodes. Hypoxia of the conductive system of the heart is often manifested by various disorders of impulse conduction such as sinus arrest and AV blocks of various degrees. These occur mainly in the apnoic stage, while extrasystoles are more frequent in the hyperventilation stage (Peter, 1990). Myocardial hypoxia and acidosis contribute to the development of dysrhythmias (supraventricular and ventricular extrasystoles, bigeminia, trigeminia, tachycardia, atrial or ventricular fibrillation even with the possibility of sudden cardiac death). Similar peracute cardiorespiratory failure with fatal end occurs in the case of SIDS (Sudden Infant Death Syndrome). Similar acute Apparently Life Threatening Event (ALTE) occasionally occurs in paediatric practice, where the event is noticed and the threatening death could be prevented by prompt resuscitation. These clinical observations are supported by the finding based on model experiments on anaesthetised animals. Extreme hypoxaemia accompanied with hypercapnia induced in these experiments more frequent and more serious cardiac dysrhythmias and ECG changes, which required urgent resuscitation, than hypoxaemia with normocapnia or hypocapnia, (Tomori et al., 1997). Close interaction of cardio-respiratory functions is also documented by the fact that approximately 40 % of patients suffering from cardiomyopathy have at least 100 apnoic episodes during one night (Peter, 1990).

In the case of congestive heart disease, symptoms of failure of cardiovascular and respiratory systems of various degrees will develop according to the speed of blood transfer to the pulmonary circulation (Fig. 1). Due to SDB characterised by hypoventilation in sleep, provocation or intensification of bronchial spasms will take place in an asthmatic, or escalation of breathlessness will develop in patients suffering from acute bronchitis or mucoviscidosis. In the case of evident blood stagnation in lungs, more serious sleep disordered breathing will produce transfer of fluid into the interstitial and alveolar spaces, which can be manifested by a development of cardiac asthma, or even pulmonary oedema. The development of ARDS (Adult Respiratory Distress Syndrome also named as shock or wet lungs) can have dangerous effects on patients suffering from SAS. In case of failure of the left ventricle of the heart along with extension of circulation time, frequent central apnoic pauses and periodic breathing of the Cheyne-Stokes type will appear, which are bad prognostic signs with probable death within 6 months (Quaranta et al., 1997).

During sleep, as a rule, there is a general reduction of ventilation. Therefore, each respiratory disorder accompanied with hypoxaemia in conscious state threatens with acute respiratory failure during hypoventilation in sleep (Fig. 1). This is valid mainly for patients suffering from OSAS. Hypoventilation during sleep threatens by the development of stronger hypoxaemia and hypercapnia in patients suffering from obstructive ventilatory disorders. Simultaneous occurrence of OSAS and chronic obstructive bronchopulmonary disease, so called overlap syndrome requires artificial ventilatory support, mainly during the night. In the case of various restrictive disorders such as chest deformities (kyphoscoliosis), fibroses and pneumonia, but also IRDS (Idiopathic Respiratory Distress Syndrome), a more distinct hypoventilation with subsequent hypoxaemia may develop due to serious disorders in mechanics of breathing. This condition can require administration of oxygen, artificial ventilation and prompt therapy of the developing respiratory failure.

Many neurological and psychiatric diseases (Fig. 1) often affect negatively the sleep and its quality, which contributes to the fact that nowadays up to one third of people suffer from various sleep disorders. Practically the sleep disorder can manifest as insomnia, hypersomnia, parasomnia, changes in sleep architecture, or frequent interruptions — fragmentation of the sleep due to patient's repeated awakening (arousal). Arousal from sleep can result from respiratory stimuli (for example marked hypoxaemia and hypercapnia, as well as strong and fast fluctuation of negative pressure in the respiratory tract achieving during snoring up to — 80 cm of H_2O). Arousal can also occur due to non-respiratory stimuli (e.g. movements of extremities and of the entire body, noise, etc.).

The insufficient quality and fragmentation of sleep result in morning headaches, physical and mental distress, exhaustion and decrease of the total efficiency that reduce considerably productivity and life quality of patients. In case of epilepsy, mainly in children, the sleep breathing disorders can often occur in the form of apnoic episodes, which accompany the absence seizure, but also some other forms of epilepsy. In case of idiopathic or recur-

rent hypersomnia occurring in the course of various NS diseases (encephalitis of various types, and so on) the excessive daytime sleepiness occurs. Sleepiness of the imperative nature associated with cataplexy is typical for narcolepsy. Excessive daytime sleepiness causing a 3 time increase of injuries, traffic accidents and catastrophes occurs in OSAS patients suffering also from various neuromuscular disorders. For example in the case of postpoliomyelitic syndrome, muscular dystrophy, amyotrophic lateral sclerosis and myasthenia gravis, the efficiency of respiratory muscles is restricted with possible development of hypoventilation due to their fatigue, mainly during sleep or in narcosis.

Very serious SDB also originates *in diseases of the autonomous or sympathetic-adrenal system* (Fig. 1). The Shy-Drager syndrome represents an polysystemic disorder, which will be manifested by autonomous insufficiency. In addition to the frequent occurrence of central and obstructive apnoic episodes, cyclic changes in heart rate variability are missing, and a distinct orthostatic hypotony occurs as a result of a sympathetic disorder. In case of fatal familial insomnia due to degeneration of the thalamic nuclei, the inhibitory effect of higher centres on the hypothalamus, and a predominance of dopaminergic mechanisms is established. This is manifested by extreme insomnia, increased salivation, sweating, fever, excessive sympathetic nerve irritation and complete exhaustion followed by death within 9-18 months (Kryger et al., 1994; Lugaresi et al., 1994; Nevšímalová and Šonka, 1997).

Various endocrine-metabolic disorders (Fig. 1), often genetically determined, may cause serious SDB. In addition to several congenital defects in the craniofacial area, such as micrognathia, retrognathia, Arnold-Chiari malformation, Pierre-Robin syndrome, Crouzoni malformation, etc., also a serious disorder of nasal breathing with excessive snoring occurs. In the case of the Williams-Beuren syndrome, very large adenoid vegetations associated with the high position of the palatal arch and with facies adenoidea cause difficulties in breathing during sleep or even asphyxia. Extreme obesity in the Prader-Willi syndrome is associated with nocturnal hypoventilation. The Down syndrome is also characterised, in addition to other manifestations, by macroglossia, muscular hypotony and obstructive apnoic episodes. In acromegaly, macroglossia occurs and in hypothyreosis, infiltration of the pharyngeal wall by a myxomatous liquid occurs, which narrows the upper airway lumen and impedes breathing during sleep.

Obesity is also linked with SDB. According to various data, the simultaneous occurrence of obesity and OSAS is approximately 35 % and their mutual relationship is reciprocal. Due to frequent arousal and considerable limitation of the 3rd and 4th stage of N-REM sleep in patients suffering from OSAS, production of lipolytic hormones acting both lipolytically (somatotropic hormone, cortisol) and anabolically (testosterone, growth hormone) is reduced. Therefore, SDB and especially OSAS contribute to the development of central obesity (Grunstein, 1997). Deposition of fat even in the neck area, especially in men with central type of obesity contributes to upper airway obstruction and to easier development of apnoic episodes during sleep (Horner et al., 1989). In case of metabolic syndromes, disorders in carbohydrate and lipid metabolism, diabetes mellitus, obesity, hypertension and often SDB occur (Grunstein, 1997).

Multidisciplinary aspects of SDB management

Problems, which cause the patients suffering from SDB to consult a general practitioner or to require examination by specialists or at the sleep laboratory are of very different nature. They belong to the *following branches of medicine* (estimated in percentage values): pneumology (20 %), otorhinolaryngology (20 %), neurology—psychiatry (17 %), cardiology (10 %), general medicine (8 %) and other areas, such as anesthesiology, nephrology, sexuology, and others (6 %). SDB also occurs in childhood, even in the neonatal age (7 %), and for its specific nature (perinatal asphyxia, SIDS, ALTE, gastro-oesophageal reflux and the like), it requires a special care. SDB is also frequent problem in gerontology and geriatrics (12 %), where it contributes considerably to polymorbidity of elderly people (Koval et al., 1996).

The multidisciplinary approach to SDB includes explanation of common pathogenesis of functional disorders of various systems, as well as their diagnosis, therapy and prophylaxis, which presumes *close co-operation of various specialists.* Malformations in the upper airway area and their management require primary participation of otorhinolaryngologists and stomatologists, mainly in correction of various abnormalities by special surgical interventions or by orthodontic aids (Nelson and Hans, 1997). Preserving patency of upper airways and sufficient ventilation during operation and cardio-respiratory failure under various circumstances are the primary tasks of anesthesiologists. Therefore, the development and therapeutical use of the optimum manner of ventilatory support and artificial ventilation is their main domain. The anesthesiologist must be aware that all complications, which threaten the patient suffering of SAS during sleep can also occur in general anaesthesia. Due to several possible complications including pulmonary oedema, cardiac dysrhythmias and sudden cardiac death, it is necessary to avoid administration of opiates and myorelaxants that could cause hypoventilation to risk patients during pre-operational preparation. It is necessary to select a suitable anesthetic agent and manner of artificial ventilation in order to assure sufficient saturation of the blood with oxygen and to extubate the patient only after achieving full consciousness.

During examination of the patient at the sleep laboratory data are collected for the determination of the pathogenesis of the disease, its acute complications and chronic consequences. These data are used for determination of diagnosis and optimum pathogenetical therapy. For all these reasons, the participation of a clinical physiologist in sleep laboratory is very important. *Multidisciplinary co-operation of various specialists on the basis of the sleep laboratory* is unavoidable mainly in treatment of those patients suffering from SAS, who also suffer from some of the discussed disorders of various systems. The success of therapy, which is mostly long-lasting, will depend in considerable degree on the level of this co-operation. At the same time, close co-operation of the relevant specialists will allow to continuously monitor the effect of therapy on the further course of disease, to catch timely undesired events and to optimise further treatment.

In developed countries, there is *one accredited sleep laboratory per one million inhabitants,* which co-ordinates and assures general care of patients suffering from SDB. There are significant shortcomings in this area in our country, which arise mainly from insufficient information of the public and even of the physicians,

including competent officials of health care facilities and insurance companies about significant importance and social-economic usefulness of sleep medicine. The significance of sleep laboratories built up within the framework of the Tempus-Phare programme, in spite of temporary problems, will also grow in a short period of time in our country. At the same time, a great perspective is given by the possibility of screening examination of patients at individual clinics and out-patient departments, or at home using portable instruments designed using the most sophisticated technologies. Connection of these out-patient departments to the computer network will enable the progress of sleep medicine in our country, too: in the future patients will not necessarily be sent to the sleep laboratory, but only results of their examination using e-mail will be analysed. The task of the sleep laboratory as a regional centre for sleep medicine will then be based mainly on coordination of educational, diagnostic, therapeutic-prophylactic as well as research activities.

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