ABSTRACT:

Sleep-related respiratory disorders are a singular risk factor for cardio-vascular diseases. Biomarkers, related to the cardiovascular diseases and heart failure as a their result with the morbidity increasing with the increase of patients’ longevity, are used as a diagnostic and prognostic factor. The study of patients with sleep-related respiratory disorders may help the construction of a panel of biochemical and instrumental tools, defining the cardiovascular risk of these patients.

Keywords: sleep-related respiratory disorders, cardiovascular risk, obstructive sleep apnea

Obstructive sleep apnea (OSA) is a clinical condition of alternation of episodes (desaturation of at least 4% and duration over 10 s) of apnea (reduction of the respiratory flow over 90%) and hypopnea (reduction of the respiratory flow with at least 50%) and repetition of the episodes 5-100 times per hour. The prevalence of OSA increases considerably, related to the global pandemic of obesity (5). OSA is found in about 8% of men and 4% in women, with highest prevalence in the fifth decade. The episodes of hypopnea and apnea disturb the sleep structure, the shallow phases being more than the deep phases.

The result is fragmentation of the sleep and daily sleepiness occurs with frequent episodes of falling asleep, especially in monotonous situations. The repeated episodes of hypoxia in situations of OSA cause activation of nervous, humoral, thrombotic, metabolic and inflammatory mechanisms, related to cardiac and vascular diseases.

OSA is related to many factors causing endothelial
### Terms and definitions

<table>
<thead>
<tr>
<th>Terms</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Apnea</td>
<td>Cessation of the respiratory flow for over 10s</td>
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<tr>
<td>Hypopnea</td>
<td>Decrease, but not cessation, of the respiratory flow up to less than 50% of normal, usually with a decrease of the oxyhemoglobin saturation.</td>
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<td>AHI</td>
<td>Incidence of apnea and hypopnea per hour, a measure for the severity of sleep apnea.</td>
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<tr>
<td>OSA and hypopnea</td>
<td>Apnea or hypopnea, a result of partial or total collapse of the pharynx during sleep-time.</td>
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<tr>
<td>CSA and hypopnea</td>
<td>Apnea or hypopnea, a result of partial or total loss of the central respiratory trigger towards the respiratory muscles during sleep-time.</td>
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<tr>
<td>Oxygen desaturation</td>
<td>Decreasing of the oxyhemoglobin saturation, mostly as a result of apnea or hypopnea.</td>
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<td>Syndrome of sleep apnea</td>
<td>At least 10 or 15 episodes of apnea per hour, associated with symptoms like snoring, restless sleep, nocturnal shortness of breath, morning headache, daytime sleepiness.</td>
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Interruption hypoxia is to be blamed for the atherosclerotic changes in OSA (21). The episodes of hypoxia and re-oxygenation form reactive oxygen radicals, that prompt inflammation and atherosclerosis. This condition correlates with the inflammatory markers like CRP, VEGF, cytokines (22). There exist data that vibration from snoring contributes to carotid atherosclerosis. The indirect mechanisms OSA uses to contribute to atherosclerotic progression are insulin dysfunction and atherosclerosis, as inflammation increases the endothelial growth factor, oxygen radicals, and the soluble adhesion molecules and coagulation. Endothelial dysfunction is a basic mechanism of atherosclerosis (33). Existing data in animal models (34) and human models (35) show that OSA leads to endothelial dysfunction that can be reversed by CPAP. Intermittent hypoxia causes endothelial dysfunction by many mechanisms – oxidative stress as well as hypertension and insulin resistance (33, 36, 37). Patients with OSA syndrome have elevated levels of TNF-α, IL-6, IL-8, CRP and adhesion molecules (intercellular adhesion molecule-1, vascular cellular adhesion molecule-1, L-selectin, P-selectin) (38-41), which are markers of systemic inflammation with proatherogenic properties. In rodents, experiments show that intermittent hypoxia increases endothelins-1, (42), causes up-regulation of the sympathetic nervous system and RAAS (43), which stimulates endothelial dysfunction directly or indirectly by hypertension.

### Определения на термините

<table>
<thead>
<tr>
<th>Термин</th>
<th>Определение</th>
</tr>
</thead>
<tbody>
<tr>
<td>Апнея</td>
<td>Спиране на въздушен поток за над 10 секунди</td>
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<tr>
<td>Хипопнея</td>
<td>Намаление, но не пълно спиране на въздушен поток до под 50% от нормалния, обичайно с нарушение на оксихемоглобиновата сатурация</td>
</tr>
<tr>
<td>АХИ</td>
<td>Честотата на апнея и хипопнея за час сън, мярка за тежестта на сънна апнея</td>
</tr>
<tr>
<td>ОСА и хипопнея</td>
<td>Апнея или хипопнея, резултат от частичен или пълен колапс на фаринкса по време на сън</td>
</tr>
<tr>
<td>ЦСА и хипопнея</td>
<td>Апнея или хипопнея, резултат от пълна или частична загуба на централния респираторен импулс към респираторните мускули по време на сън</td>
</tr>
<tr>
<td>Кислородна десатурация</td>
<td>Намаление на оксихемоглобиновата сатурация, най-често поради апнея или хипопнея</td>
</tr>
<tr>
<td>Синдром на сънна апнея</td>
<td>Поне 10 или 15 епизода на апнея или хипопнея на час сън, асоциирани със симптоми като хъркане, неспокоен сън, нощен задач, сътресение главоболие, дневна сънливост.</td>
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Obstructive Sleep Apnea and Obesity

OSA is often associated with obesity, confirmed by a lot of epidemiology studies. About 40 % of the obese patients have OSA and 70 % of patients with the condition are obese (47, 48). Parameters like BMI, neck circumference and visceral fat are significant predictors of OSA (49,50). Elevated abdominal fat, seen in patients with OSA and obesity, found by CT, is an independent risk factor for cardiovascular disease (51). Upper-abdominal obesity is
WORK-UP IN A PATIENT WITH EMBOLIC STROKE OF UNKNOWN SOURCE – CLINICAL CASE

OBSCTRTIVNA C³NNA APNEIA I ZATL^ST^VANJE

Obstrictivnata c³nna apneia chesto v³rvi redom s³c zat⁷st⁷vanie i tova se potv⁷r³djava ot mnogoestvo epidemiologivski proouchvani. Pri oko 40% ot zat⁷st²lite patienti se srechta obstrictivna c³nna apneia i 70% ot otst³kata s¹ tak¹ s³ndrom s³ zat⁷st²lîti (47, 48). Parametri na zat⁷st⁷vanieto kato BMI, obnikola na shînata i vischerala mastna t³kkan s¹ va³ni prediktori na OSA (49, 50). Povii²tenite niva na abdомнalna mastna t³kkan, ktoqo se otkrivat pri patienti s¹ OSA i zat⁷st²lîti pri CT is³sladvene, sa nezavisim rísok faktor za CSC zabolëvane (51). Gorno-abdомнalnoto zat⁷st²vanje s¹ sv²rzano s po-izrazena insuliinova rezistentnost i iz³lçhane na metabolitno aktivni produkti v portalnata sistema. U nas oèenkata na patienti s¹ DNVS e predstavena v èedinichi publikaci na problèma. D. Petkova publikuvava dani, kasaëchi antropométrichni karakteristiki na bûlgarski patienti s¹ dîhatalni narzheniya po vreme na c³n (1). V naciona³en plan epidemiologivski dani otnovotne c³nata i karakteristikata na patienti s¹ DNVS ne sa naliche. Predpolaga se, c² centralnoto zat⁷st²vanje provokira i vlošava OSA poradi tova, c² mastnite ot³lagenia v gornite dîhatalni p³tiça poviñava razte⁷gama²stata im (52). Poviñenieto obem na abdомнalna mastna t³kkan vodi do hi²oventila³tata po vreme na c³n i ili namala³a kislorodnata rezerva, ulenqva kislorodnata dësaturacija po vreme na zat⁷st²lîti (53). Napod³kîx vîzmëniñeto se fokusa v³rhu v³rkata OSA i produkten na mastnata t³kkan - leptin, adiponectin, ghrelin (54).

OSA може да доведе до sistemata xipertonia (93 - 100) i se sv²rzva s po-viska c³stota na miokardni infarkt i s³rdecno-s³dova smërtnost (101, 102). V prospektivno proouchvanie, publikuvano prez 2000 g. v N Engl J Med. (93), se posocva, c² e naliva v³rkata me³du naruñenata na c³n i povata na xipertonia četiri godini po-kqeso, koeto je nazevisivo od pozitnite podleñjañi faktori. Tova pokaza³a verøynto uñtie na naruñenata na c³n v posledvañata
hypertension is a sªr dead-and-©dova disease. This is because it is a risk factor for cardiovascular disease, endocrine and kidney homeostasis (7). Atrial natriuretic peptide (ANP) and brain natriuretic peptide are of primarily cardiac origin, while natriuretic peptide C is released in the vascular endothelium and central nervous system. Misa Valo et al. find elevated levels of NT-proBNP in patients with OSA and coronary artery disease before and after sleep. An overnight with CPAP reduces this level to a considerable extent. In untreated patients the respiratory effort during obstruction of the airways causes fluctuations of the intrathoracic pressure, which leads to right ventricular volume pressure and secretion of natriuretic peptides. CPAP removes the variation of intrathoracic pressure. Some studies reveal decrease of the abnormal levels of NT-proBNP and ANP after treatment with CPAP (19,26,27). Unlike them, Cifci et al study the effect of CPAP in 33 patients with OSA and do not find any difference after 6 months long treatment with CPAP (21). Colish et al report similar results – no difference in the levels of NT-proBNP and troponin in 47 patients with OSA after 12-month-long treatment with CPAP, despite the favorable change of left ventricular remodeling (28).

A study, conducted by Barcello et al. finds that treatment with CPAP is followed by increase of the levels of hs-Troponin T, i.e. CPAP prompts cardiac stress (29). Other studies do find higher levels of NT-proBNP in patients with OSA (16, 18-20). NT-proBNP is a separate risk factor in patients with coronary heart disease (22). Patients with stable angina demonstrate close relationship between serum concentrations of NT-proBNP, the severity of coronary disease and the induced myocardial ischemia (23, 24). CPAP is a first line therapy in moderate to severe OSA. It induces correction of the left ventricular ejection fraction in patients with OSA and results of chronic hypoxemia (25). In Bulgaria, D. Petkova et al examine levels of NT-proBNP in patients with OSA (1,2). V. Dimitrova et al examine levels of NT-proBNP in patients with chronic hypoxemia and pulmonary vascular pathology (4,5), and patients with OSA (12). Querejeta Roca et al., on the other hand, find higher levels of hs-Troponin T independently related to the severity of OSA in middle-aged and advanced aged individuals, but without coronary disease or heart failure, making the conclusion that subclinical myocardial damage has a role in the link between OSA and heart failure (16). A disadvantage of this study is that hs-Troponin T was not examined long with polysomnography and therefore there is no definite link between hs-Troponin T and the right ventricle. Unlike the aforementioned study, Einvik et al. find an independent connection between the severity of OSA and the higher levels of hs-Troponin T (17). The discrepancies may be due to biological reasons as well as due to different sensitivity and accuracy of analyses.
WORK-UP IN A PATIENT WITH EMBOLIC STROKE OF UNKNOWN SOURCE – CLINICAL CASE

OSA AND ATRIAL FIBRILLATION

Sleep Heart Health Study reports 4-fold higher incidence of atrial fibrillation in OSA. The risk of atrial fibrillation increases with the severity of OSA. Besides, OSA is more common in patients with atrial fibrillation, than in the rest of the population. The question is if OSA adds additional predictive value to the CHA2DS2VASC score. The risk for brain stroke is 1.62 times higher in patient with OSA and score 0, but OSA in patients with a higher score does not raise the risk for stroke.

The prospective study, conducted by Gami AS et al., demonstrates a strong correlation between the two conditions (OR 2.19, 95% CI 1.40-3.42, p = 0.0006). AF and OSA have similar risk factors like advanced age, obesity, hypertension, heart failure and heart diseases. OSA has a causative relationship with intermittent hypoxia, impaired autonomic nervous system, oxidative stress and endothelial dysfunction, which are part of the pathophysiology of AF. OSA raises the proinflammatory markers like CRP, interleukine-6 and TNF-α. The periods of obstruction in OSA cause negative intrathoracic pressure, which in turn causes dilation of the atra, atrial fibrosis and remodeling of the pulmonary vessels.

The association between OSA and endocrine-metabolic and cardiovascular alterations shows, that beyond local abnormalities, OSA I a systemic disease. During the hypoxemia-re-oxygenation cycles, oxidative stress and secretion of proinflammatory markers, a vicious circle is formed, stimulating a general state of inflammation.

CENTRAL SLEEP APNEA

CSA is seen in 30-50 % of the patients with heart failure. Clinically CSA presents with sleeplessness, fatigue and/or daily sleepiness, but the latter symptom is often absent. Clinicians often omit CSA as its symptoms are typical for heart failure as well. Thus the possibility for treating it is missed and this independently worsens the prognosis of HF. The risk factors for CSA in patients with HF are male gender, advanced HF, low ejection fraction, sleeplessness, circulatory delay and cerebrovascular abnormalities. OSA increases the risk for stroke. One study, conducted by Gami AS et al. (2016), demonstrated a significant correlation between the two conditions (OR 2.19, 95% CI 1.40-3.42, p = 0.0006).

The association between OSA and endocrine-metabolic and cardiovascular alterations shows, that beyond local abnormalities, OSA I a systemic disease. During the hypoxemia-re-oxygenation cycles, oxidative stress and secretion of proinflammatory markers, a vicious circle is formed, stimulating a general state of inflammation.
OSA AND PRESENCDNT MURMUS

Sleep Heart Health Study documented for 4-yearly period, when compared with 2006. Risk Measurement for Sleep Apnea syndrome (OSA), the demographic data showed that patients with OSA (OR = 3.42, 95% CI 1.40-3.42, p = 0.0006). Onset of OSA and other factors contributed to the development of COPD, which also plays a role in obstructive sleep apnea syndrome (OSA).

Prospective monitoring of patients with obstructive sleep apnea syndrome (OSA) showed increased levels of brain natriuretic peptide (BNP) and troponin-I in patients with OSA. Inflammatory markers such as CRP, interleukin-6 and TNF-α contribute to the pathophysiology of OSA. OSA increases the risk of cardiovascular disease, which is the hallmark of OSA and contributes to the development of heart failure.

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