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RATIONAL ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

Abstract

Background. The relationship between obstructive sleep apnea (OSA) and hypertension is well known. In numerous studies, obstructive sleep apnea was found to be an independent predictor of the development of resistant hypertension (RH), and the severity of apnea directly correlated with the severity of RH with the exception of such confounders as age, obesity, and gender. **The objective** of this publication is to present a new strategy and modern approaches of drug and non-pharmacological therapy of resistant hypertension in patients with OSA with the possibility of their implementation in real clinical practice. **Conclusion.** Currently, for a practitioner, the therapy of the patient with OSA and RH is a serious clinical task. A new rational therapeutic strategy for the treatment of such patients includes a combination of three-component drug therapy and non-pharmacological continuous positive air pressure therapy (CPAP therapy). A reasonable duration of CPAP therapy should exceed 12 weeks. The proposed strategy for the treatment of patients with OSA + RH has the highest efficiency in achieving target blood pressure levels and significantly reduces the risks of fatal cardiovascular events.

Keywords: *antihypertensive therapy, obstructive sleep apnea, resistant hypertension, CPAP therapy.*

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AHT — antihypertensive therapy, CAs — calcium antagonists, CCBs — calcium channel blockers, ARBs — angiotensin II receptor blockers, AHI — apnea-hypopnea index, ACEIs — angiotensin-converting enzyme inhibitors, OSA — obstructive sleep apnea, ARF — acute respiratory failure, RAAS — renin-angiotensin-aldosterone system, RH — resistant hypertension, RCTs — randomized clinical trials, SNS — sympathetic nervous system.

Introduction

There is now a clinical definition of obstructive sleep apnea (OSA), which was achieved through consensus among pulmonologists, cardiologists and sleep medicine professionals.

Obstructive sleep apnea (OSA) is a heterogeneous parasomnia (sleep-related) disorder characterized by pharyngeal collapses (respiratory pauses longer than 10 sec) during sleep period with preserved respiratory efforts, frequent nocturnal desaturations (reduced arterial oxygen saturation) and daytime signs (excessive sleepiness, hypertension, cardiac arrhythmias, insulin resistance, metabolic disorders) varying in time and intensity and associated with the severity of the disease (Figure 1) [1]. The severity of the disease is described by the total number of events of pharyngeal narrowness (hypopnea) and occlusion (apnea) per 1 hour of sleep-state monitoring (Apnea-Hypopnea Index, AHI). AHI higher than 5 events/hour corresponds to the onset of the disease. AHI of 5 to 15 events/hour corresponds to mild disease, AHI of 15 to 30 events/hour — to moderate disease, and AHI over 30 events/hour — to severe disease [2].

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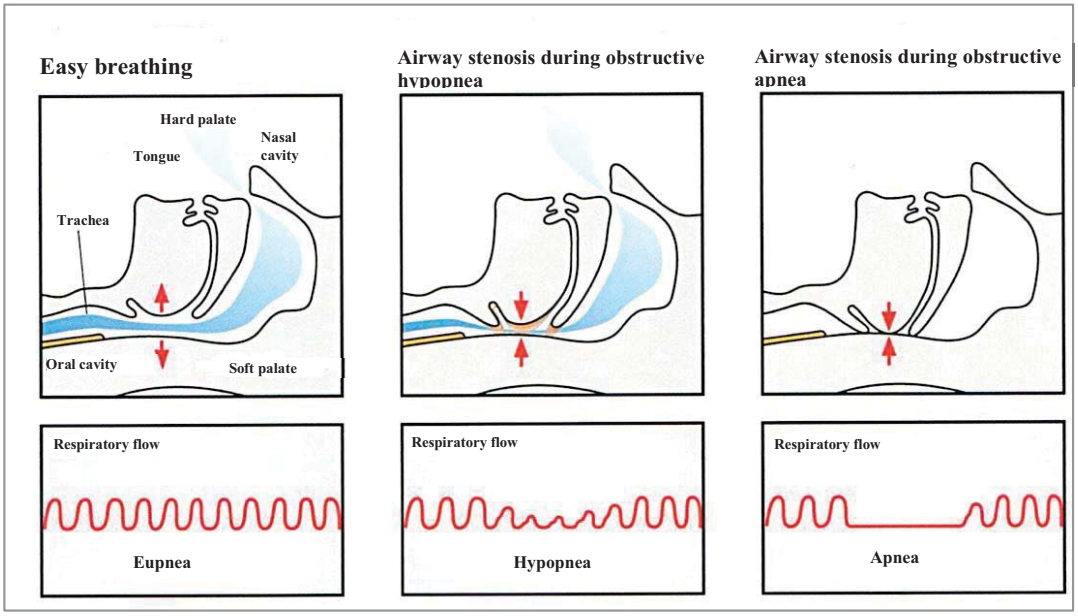

Figure 1. *The mechanism of development of sleep apnea-hypopnea with a decrease in oropharynx muscle tone during sleep (adapted from Bradley T.D., Floras J.S. Sleep apnea and heart failure: Part I: obstructive sleep apnea. Circulation. 2003; 107: 1671–8)*

The relationship between OSA, risk factors for vascular diseases, metabolic disorders and vascular diseases was described in major prospective clinical studies [3, 4]. Moreover, it was found that sleep apnea was an independent predictor of the development of hypertension, and OSA severity correlated to the blood pressure (BP) level when adjusted for age, obesity and gender [5]. Logan et al. (2001) first verified resistant hypertension (RH) in patients with obesity and apnea. Currently, OSA is considered to be the most common cause of resistant hypertension (RH), in which changes in lifestyle and rational combination therapy using adequate doses of at least three antihypertensive drugs, including diuretic, fail to achieve the target BP [6, 7].

According to the current randomized clinical trials (RCT), the percentage of patients with OSA among all patients with RH reaches 64 % (Figure 2) [8].

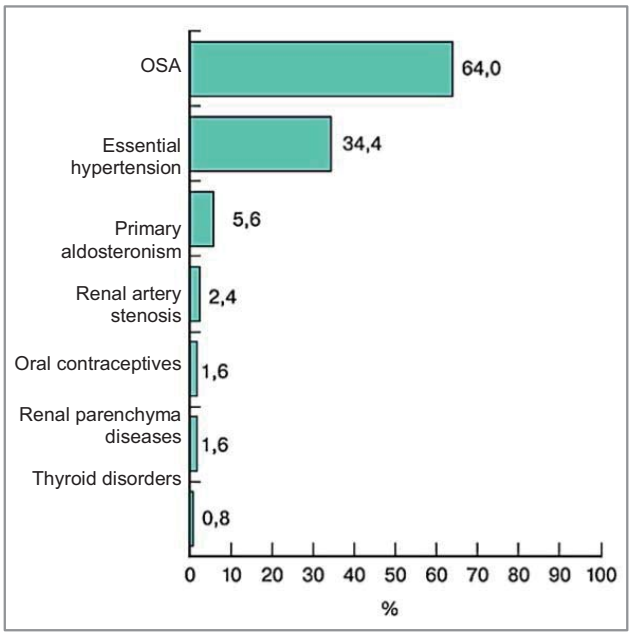

Figure 2. *Basic clinical conditions associated with the development of RH (adapted from Pedrosa R.P. et al. Hypertension. 2011 Nov; 58 (5): 811–7)*

1. RH development mechanisms in patients with OSA

It has been found that sleep fragmentation as a result of frequent nocturnal arousals in OSA patients has an active impact on blood pressure through the activation of the sympathoadrenal system, renin-angiotensin-aldosterone system (RAAS) and neurohumoral regulation as a whole [9].

Hypoxemic stimuli, hypercapnic reactions, hypoxemia/reoxygenation cycles triggered by apnea episodes significantly increase the activity of the sympathetic nervous system (SNS). Chronic stimulation of SNS is directly associated with the development and worsening of hypertension in OSA patients, thus forming resistance to antihypertensive therapy [10–12].

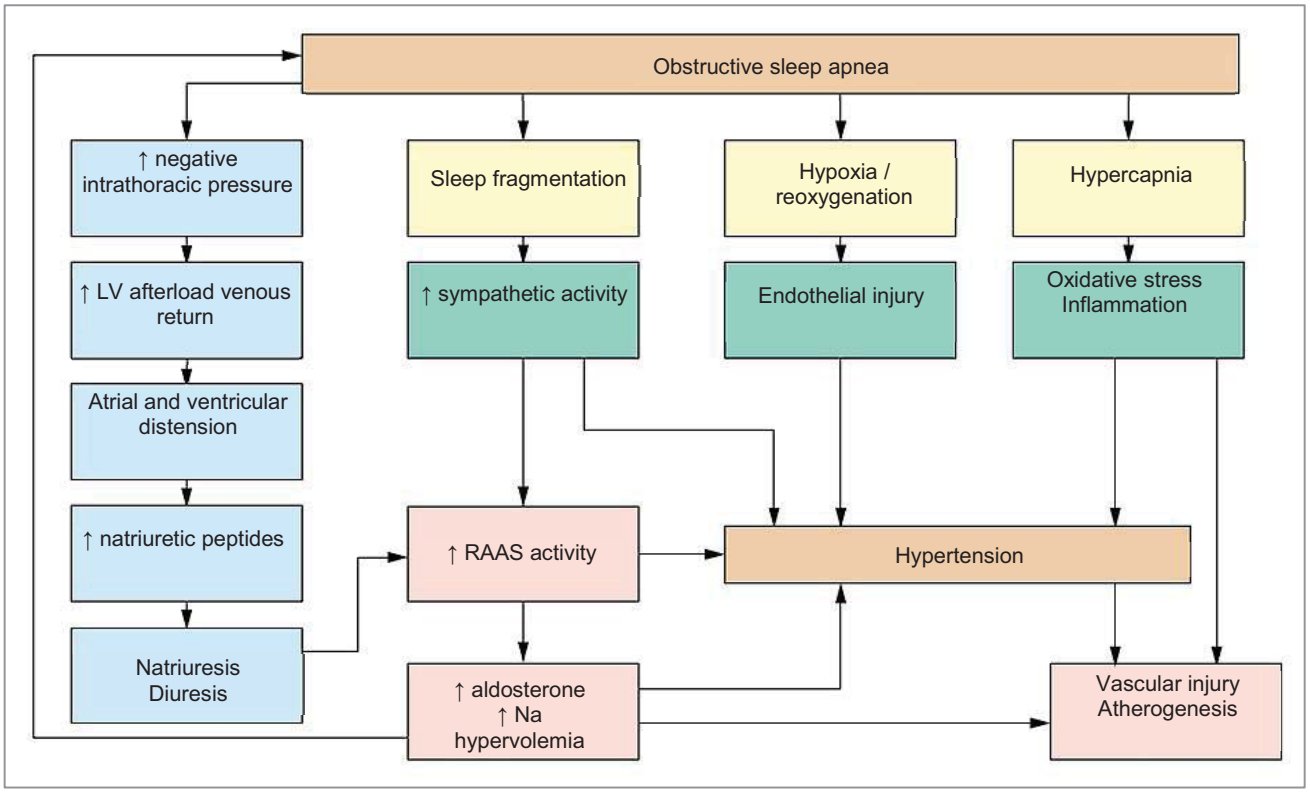

Figure 3. *Diagram of the main pathogenetic links of RH development in patients with OSA (adapted from Malyavin A.G., Babak S.L., Adasheva T.V. et al., Diagnostics and Management of Patients with Resistant Arterial Hypertension and Obstructive Sleep Apnea (Clinical Recommendations). Therapy. 2018; 1 (19): 4–42)*

The major pathogenetic elements of the SNS imbalance in OSA patients include:

1. **Reduced stroke volume** in apnea events due to the increase in negative intrathoracic pressure. The result is carotid sinus zone activation, which activates the vasomotor center and increases sympathetic impulses. As a result, baroreflex zone damage occurs, including due to the impact of hypoxia/reoxygenation cycles. Reduced baroreflex sensitivity to hypotension is the most common phenomenon observed in OSA patients, which is effectively resolved by continuous positive air pressure therapy (CPAP-therapy) [13, 14].
2. **Hypoxia and hypercapnia** that stimulate medulla oblongata and peripheral aortic and sinocarotid chemoreceptors. Activated chemoreceptors stimulate the vasomotor center, which, in turn, increases sympathetic activity and reduces parasympathetic activity (as a result, BP and HR increase). It has been found that the activity of chemoreceptors was of key importance in the development of systemic hypertension in OSA patients [15].
3. **Termination of stretching of pulmonary receptors** during inspiration and, as a consequence, inhibition of the central sympathetic activity (pulmonary baroreflex).
4. **Cortical arousals (sleep fragmentation)** and the resulting increase in sympathetic activity and reduction in vagal tone/
5. **Vibration effect of regular snoring** leads to the direct damage of carotid arteries and impairs the baroreflex function and chemoreceptor stimulation, which promotes structural failures and accelerates atherosclerotic vascular disease [16].

Pharyngeal collapses are associated with the activation of RAAS. As a result, hypernatremia and fluid retention are observed in OSA patients, more often in lateral pharyngeal (parapharyngeal) segments, aggravating the severity of apnea and activating the RAAS. Assessment of the role of angiotensin II and aldosterone in patients with OSA + hypertension performed in the meta-analysis by Jin Z.N., Wei Y.X. (2016) established the direct impact of OSA on RAAS system, with drug resistance formed through activation of neurohumoral

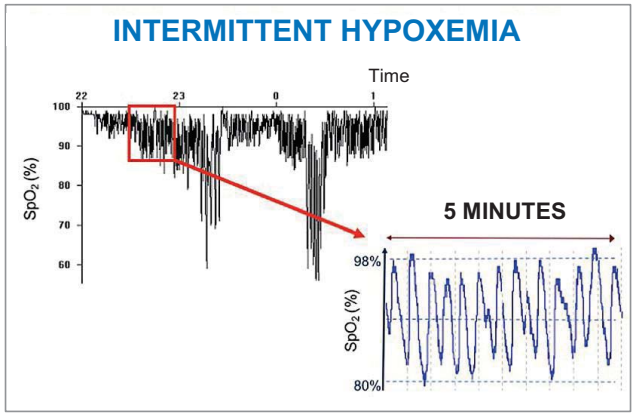

Figure 4. *An example of cyclic desaturation (rapid SpO_2 change) in a patient with severe OSA. In a short period of time (5 minutes), a sharp drop in saturation (80 %) occurs with a rapid return the parameter to a normal value (own data)*

systems. Moreover, renin in OSA patients did not significantly differ from normal values, while aldosterone correlated to both apnea severity and drug resistance intensity [14].

Recurrent hypoxia/reoxygenation cycles in OSA are similar to ischemia/reperfusion in coronary insufficiency by their ability to stimulate the formation of reactive oxygen species (ROS) and cause oxidative injury processes (Figure 4) [17].

Furthermore, hypoxia activates nuclear transcription factors, including nuclear factor kB (NF-kB), tumor necrosis factor alpha (TNF-α) and interleukin-8 (IL-8). They play the leading role in the development of endothelial injury and chronic vascular inflammation. Hypoxic stimuli promote production of endothelin, its cyclic changes in recurrent (intermittent) hypoxia at night. It is clear that the activation of oxidative stress, inflammation, endothelial dysfunction in patients with OSA + RH accelerates vascular injury processes, with increased vascular wall stiffness, early development of atherosclerosis, which substantially increases the risk of cardiovascular events [18].

2. RH diagnosis in patients with OSA

Hypertension in OSA patients has a number of clinical and functional features, which are found when taking medical history, as well as during office and 24-hour blood pressure monitoring:

1. High incidence of isolated diastolic hypertension.
2. High variability of BP with reduced cardiac rhythm variability.
3. Change in the daily profile of BP with increased number of non-dippers and night-peakers.

Increase in blood pressure in the early morning hours is well traced by the example of 24-hour BPM recording of one of our patients with OSA + RH (Figure 5).

Such results of 24-hour BPM require a practitioner to take measures to identify the causes of BP changes in the early morning hours, which can be expressed as two fundamental rules:

1. When examining RH patients, questionnaires with highly sensitive prognosis of OSA (STOP BANG, NoSAS, ESS) should be used;
2. If clinical markers of OSA are detected, apnea should be verified by polygraphy or polysomnography.

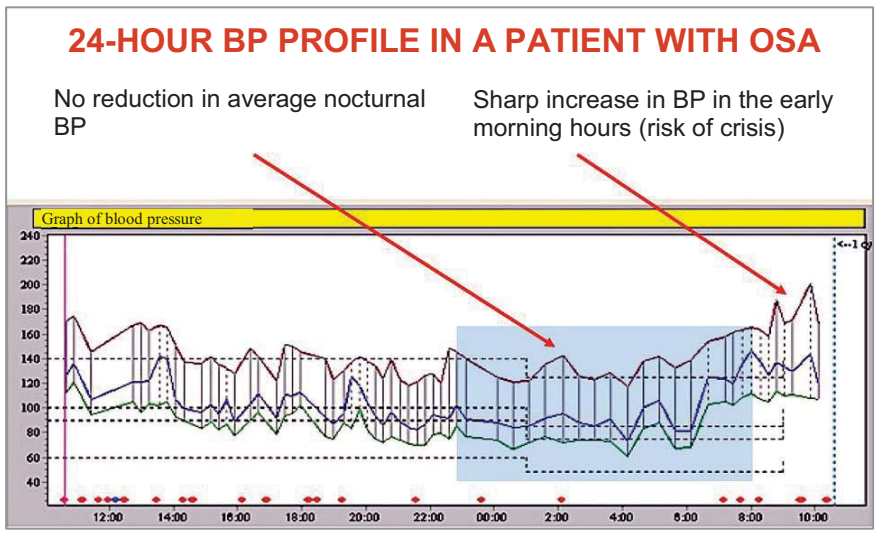

Figure 5. *An example of an increase of the blood pressure level in early morning hours in a patient with OSA + RH when performing 24-hour BPM (own data)*

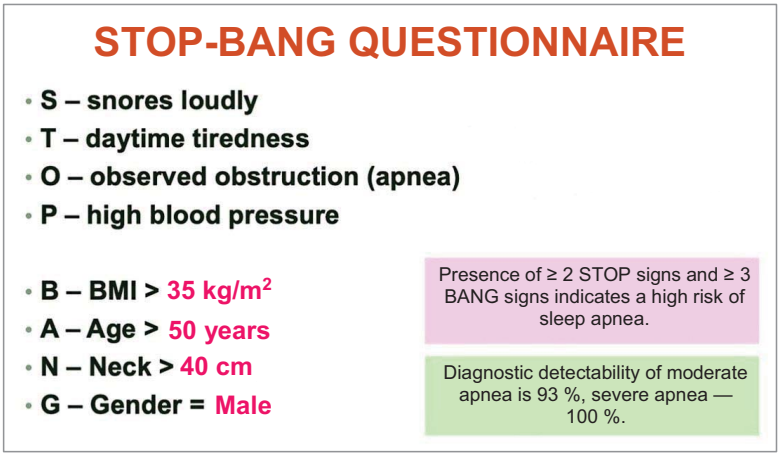

Figure 6. *STOP-BANG Questionnaire for predicting OSA (adapted from Chung F., Abdullah HR, Liao P. STOP-BANG questionnaire: a practical approach to screen for obstructive sleep apnea. Chest. 2016 Mar; 149 (3): 631–638)*

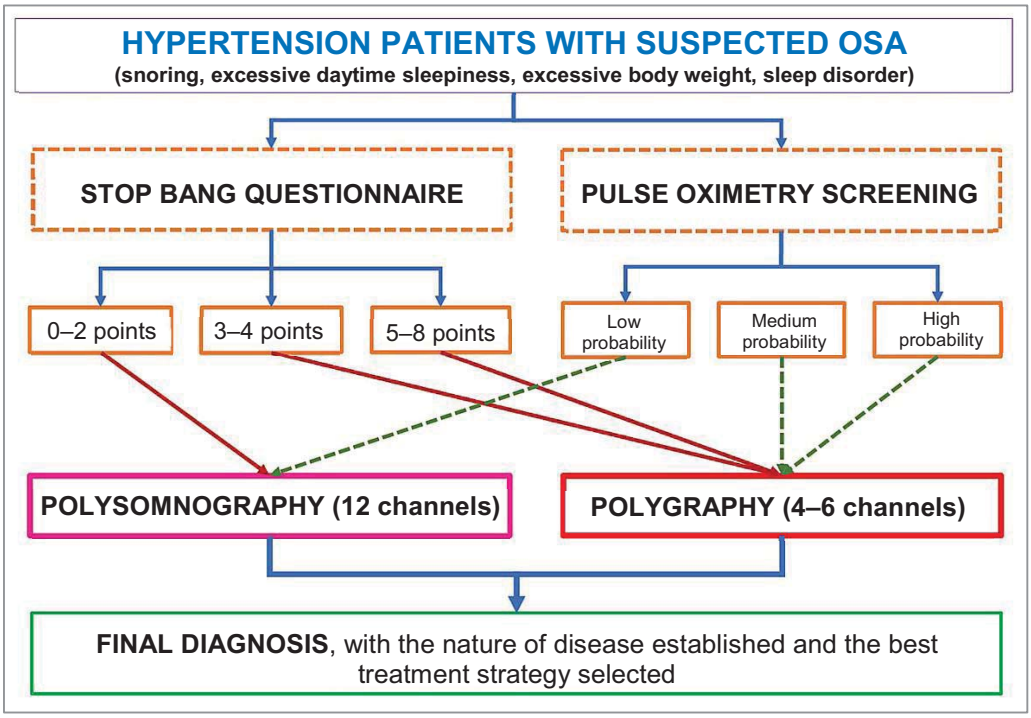

Figure 7. *Diagnostic procedure of OSA in patients with RH (adapted from Malyavin A.G., Babak S.L., Adasheva T.V. et al. Diagnostics and Management of Patients with Resistant Arterial Hypertension and Obstructive Sleep Apnea (Clinical Recommendations). Therapy. 2018; 1 (19): 4–42)*

The most reasonable and validated prediction scale for general practitioners is the STOP-BANG questionnaire (Figure 6) [19]. In fact, the use of this scale excludes the possibility of error in the subjective assessment of OSA markers by a practitioner.

In case of high risk of OSA according to the interviewing results, it is useful to perform the nocturnal polygraphy. Present-day diagnostic systems make it possible to perform respiratory monitoring on an outpatient basis, in an environment familiar to the patient, without disturbing his/her sleep process (Figure 7).

3. Therapeutic strategy for RH treatment in patients with OSA

The modern treatment strategy for RH patients with diagnosed OSA certainly includes a set of pharmacological and non-pharmacological methods:

1. Changing lifestyles (body weight loss, low-salt diet, alcohol restriction, aerobic exercise);
2. Antihypertensive therapy (AHT);
3. Non-pharmacological methods of treatment aimed at restoring upper airways patency (positioning treatment, surgical aids, intraoral applicators, CPAP-therapy).

3.1. Rational antihypertensive therapy (AHT)

Principles of rational and reasonable therapy of RH in OSA patients are based on the major pathogenetic mechanisms of the development of hypertension and clinical and functional characteristics of sleep apnea itself [20]:

1. Using drugs with the longest antihypertensive effect to control BP during night hours.
2. Adhering to chronotherapy principles, with shifting of drug administration to evening time for better BP control in patients with pathologic 24-hour profile of blood pressure (non-dippers, night-peakers).
3. Prescribing additional short- and medium-acting drugs before bedtime to prevent nocturnal shifts in blood pressure.
4. As a control of effect of antihypertensive therapy, 24-hour BPM should be used to assess the BP reduction at nighttime.
5. Using fixed combinations of antihypertensive drugs to improve adherence to the therapy.

β-blockers

Despite the lack of comprehensive data on the use of β-blockers in RH associated with OSA, the administration of this class of drugs in combination regimens is justified based on their effect on pathogenetic mechanisms of hypertension in OSA (inhibiting sympathetic activity and normalizing control over autonomic nervous system). Atenolol is the most widely studied β-blocker in patients with OSA. There are relative contraindications to the use of non-selective β-blockers (propranolol), as their negative effect on the patency of upper airways was demonstrated earlier [21].

RAAS antagonists

Data on the action of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs, sartans) are contradictory and associated with different levels of renin, angiotensin II, aldosterone in various severity of OSA. Some studies show their benefit, while others demonstrate their lesser effect or effect comparable to other drugs. However, given that the most patients with OSA + RH have significant carbohydrate and lipid metabolism disorders, RAAS blockers (ACEIs, ARBs) with the maximum organoprotective effects are the compulsory therapeutic strategy [22].

Diuretics

According to the clinical guidelines of the Russian Scientific Medical Society of Physicians concerning the management of patients with OSA + hypertension, the optimization of diuretic therapy using the combinations of thiazid/loop diuretic + spironolactone forms the basis for therapy of RH, especially associated with OSA. Significant decrease in apnea severity and BP reduction in OSA patients with uncontrolled hypertension was found when using intensive diuretic therapy with metolazone (5 mg) and spironolactone (50 mg). Moreover, there were reduced fluctuations of nocturnal fluid volumes in lower extremities, neck volume and decreased severity of apnea [23, 24].

Calcium antagonists

Calcium channel blockers (CCBs), or calcium antagonists (CAs), belong to one of five classes of antihypertensive drugs recommended as first-line treatment of hypertension. This class of drugs is often included in combination regimens in resistant hypertension. However, there are several potentially negative mechanisms of action of calcium antagonists in OSA patients:

- By suppressing the hypoxic vasoconstriction of pulmonary vessels, CCBs promotes the existence of hypoxia. Such action was found first in patients with acute respiratory failure (ARF) when administering nifedipine;
- When using CCBs, fluid can accumulate in lower limbs due to vasodilation and activation of capillary filtration, especially in an upright position. During sleep (at night), it moves to the upper half of the body and lungs causing the characteristic edema of parapharyngeal tissues.

It is obvious that increasing CCBs doses is undesirable in patients with OSA + RH. They should be discontinued at the first sign of fluid accumulation in lower limbs [25].

3.2. Non-pharmacological treatment methods (CPAP-therapy)

Therapy with continuous positive airway pressure (CPAP-therapy) is recognized as one of the most effective strategies of OSA treatment (Figure 8) [26]. Special benefits from CPAP-therapy have been established for the patients with OSA + RH.

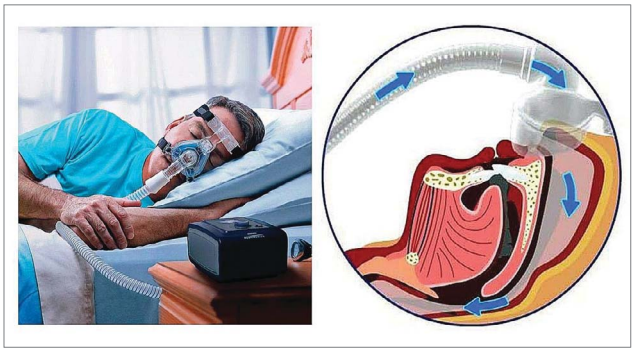

Figure 8. *Schematic representation of the CPAP therapy mechanism of action. The stabilization of pressure in upper airways during inhalation and exhalation eliminates the possibility of the development of airway occlusion (sleep apnea) in a patient at night. CPAP therapy is carried out through a nasal mask at home (adapted from Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal 1 (8225): 862-5)*

Meta-analysis of 28 RCTs has revealed considerable reduction in BP on CPAP-therapy even after excluding such factors as the severity of OSA and the existence of daytime sleepiness [27].

Of particular interest is the HIPARCO (randomized, multicenter, open-label, parallel-group) study involving OSA patients with moderate to severe RH. After 12 weeks of therapy, the combination correction (drug therapy + CPAP) led to significantly expressed reduction in BP (average daily DBP and average BP). The combination correction resulted in normalized circadian rhythm of BP: the percentage of non-dippers reduced by 10 %. There was a positive correlation between the use of CPAP-therapy and its antihypertensive effect. Linear regression analysis showed BP reduction by 1.3 mm Hg per every additional hour of CPAP-therapy [28].

Comparison of drug therapy regimens with combination correction, including CPAP-therapy, made it possible to conclude on the obvious advantage of the latter due to the normalization of blood pressure (average daily DBP and average BP), circadian rhythm, resolution of hypertension resistance and reduction of risks of fatal cardiovascular events in OSA patients with moderate to severe RH [29, 30].

Conclusion

In real clinical practice, the management of a patient with OSA and resistant hypertension represents a serious problem due to the sophisticated diagnostic algorithm. We tried to systematize and analyze the existing knowledge on the causes and consequences of hypertension resistance in OSA patients. In our opinion, only the doctor who is well experienced in causal relationships between OSA and hypertension, and possesses knowledge of the modern combination pharmacotherapy and non-pharmacological methods of sleep apnea correction, can successfully plan the treatment strategy. This is a multidisciplinary problem requiring clinicians to go beyond the scope of their profession.

The current rational therapy of patients with OSA + RH includes a combination of three-component drug therapy and non-pharmacological CPAP-therapy. To achieve a long-lasting positive effect, the duration of CPAP-therapy should exceed 12 weeks. Resolving OSA and hypertension resistance during combination therapy significantly reduces risks of fatal cardiovascular events in the group of patients concerned.

Conflict of interests

The authors declare no conflict of interests.

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