Obstructive sleep apnea syndrome as a cause of secondary arterial hypertension: a case report

Petr Štverka[a], Miroslav Homza[a], Vilém Novák[b]

[a] *Cardiovascular Department, University Hospital Ostrava, Ostrava*
[b] *Center for Sleep and Wakefulness Disorders, Sleep Laboratory, Department of Pediatric Neurology, University Hospital Ostrava, Ostrava*

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SOUHRN

Somnologie je přírodní věda o spánku. Jako jeden z mladých lékařských oborů zažívá v posledních deseti letech nebývalý rozvoj. Je multidisciplinárním oborem s nutnou mezioborovou spoluprací. Syndrom spánkové apnoe je onemocněním, kterým spánková medicína proniká i do kardiologie. Výsledkem patofyziologických procesů je mimo jiné hyperaktivace sympatického nervového systému s celou řadou důsledků pro kardiovaskulární systém. Z pohledu kardiologa je proto klíčové na syndrom obstrukční spánkové apnoe pomyslet.
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ABSTRACT

Sleep medicine is a young discipline that has experienced unprecedented development in the last ten years. It is a multidisciplinary field that necessitates cooperation with other medical disciplines. Sleep apnea is a condition in which sleep medicine impacts cardiology. The pathophysiology of obstructive sleep apnea includes, inter alia hyperactivation of the sympathetic nervous system (SNS) with a number of implications for the cardiovascular system. This case report reveals the importance of considering obstructive sleep apnea syndrome in relation to resistant hypertension.

Introduction

Sleep apnea syndrome is defined as the cessation of or pause in breathing (apneic or hypopnoic) during sleep, lasting for at least 10 seconds and repeated more than 5 times an hour of sleep. It is generally divided into obstructive, central and mixed forms. Obstructive sleep apnea (OSA) is characterized by persistence of the breathing effort, the central form by the complete absence of breathing and the mixed form a combination of OSA and central forms, beginning as a central form without breathing effort.[1] Most relevant to cardiology is obstructive sleep apnea (OSA), which includes about 90% of patients with apnea syndrome, central sleep apnea (CSA) about 10%.

The OSA syndrome is considered to be an independent risk factor for cardiovascular morbidity and mortality. The most clinically pertinent is the impact of OSA on blood pressure (BP) and the development of secondary hypertension. A linear relationship between OSA severity and degree of arterial hypertension has been demonstrated in large population studies. The basis is the pathophysiology underlying OSA in particular hyperactivation of the sympathetic nervous system (SNS), along with changes in the humoral control of the organism. The cause is severe fragmentation of the sleep microarchitecture which disrupts regeneration of the autonomic system of homeostasis.[2]

In addition to secondary hypertension, there is a higher prevalence of coronary heart disease (CHD), atrial fibrillation, heart failure, pulmonary hypertension and metabolic syndrome in general, including associated comorbidities.[3] A general awareness of these facts is still relatively low in the medical community including cardiology. The latter needs to consider the role of sleep disorders like sleep apnea in the pathogenesis of specific cardiovascular conditions. Around 85% of patients with clinically significant and potentially treatable obstructive sleep apnea have never been diagnosed.[1]

Address: MUDr. Petr Štverka, Cardiovascular Department, University Hospital Ostrava, 17. listopadu 1790/5, 708 52 Ostrava-Poruba, e-mail: petrstverka@seznam.cz
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Case study

This case report describes a 55-year-old female, long-term hypertonic patient. She was obese (BMI 30.25), with persistent moderate bronchial asthma, chronic renal insufficiency G3a, A1 according to KDIGO classification and for 30 years she had been on antihypertensive medication which had gradually increased to a combination of up to 10 antihypertensives with non-optimal effect on blood pressure (BP) compensation. The BP values were in the range of moderate hypertension, with frequent fluctuations to severe hypertension. A suspicion of non-compliance was not confirmed from determination of antihypertensive levels. The patient did not want to be included in the renal denervation program. Our cardiology-hypertensive outpatient clinic at the University Hospital in Ostrava was contacted at the beginning of February 2016. First we examined the existing records and examinations to exclude secondary hypertension – US renal, doppler investigation of renal arteries and blood sampling for endocrinological analysis and urine tests were carried out at another medical facility without interrupting current medication. We found long-term high plasma renin levels with aldosterone at the upper limit of the norm in the past, potassium 3.3 mmol/L. For this reason, potassium was substituted. Other results were within the normal range. In the past there was repeated ambulatory blood pressure monitoring (ABPM) with nocturnal non-dipping and fluctuating values of night hypertension. The patient did not have confirmed secondary hypertension, which was in line with pharmacoresistant hypertension in a patient with metabolic syndrome. During the basic physical examination, we were alerted to the patient's habitus, weighing 80 kg at a height of 158 cm, BMI 30.25 corresponding to obesity of the first degree, morphologically short wide neck, externally distinct submandibular fatty deposits. This was logically followed by our query about snoring. There had been really spectacular intermittent snoring for several years, the people around being "frightened" by occasional apnea breaks while sleeping, daily fatigue, sleepiness, frequent dry mouth, headaches that she had become accustomed to. Microsleep was denied. Overall, she was mildly depressed. To the question of snoring, she was surprised; she had not had a similar question from a doctor before.

Suspicion of obstructive sleep apnea syndrome was agreed on. Before we started the classic OSA testing algorithm, we repeated some of the past examinations. We initially checked the BP using ABPM, where the BP oscillated at the interface of moderate to severe hypertension with classical night reversal dipping. The results were correlated with home blood pressure monitoring (HBPM). The patient was capable of home measurement using a validated tonometer. Endocrinological analysis of blood and urine was performed without interfering with the usual medication. Endocrinological analysis showed a mildly elevated plasma renin of 64 ng/L, plasma aldosterone at the upper limit of the norm –274 ng/L and 3.5 mmol/L of potassium including a permanent substitution of 0.5 g potassium chlorate daily. Due to suspicion of possible secondary hyperaldosteronism (see laboratory samples above), we performed Doppler renal artery control and dynamic renal scintigraphy with captopril both of which ruled out a renovascular etiology of the hypertension. Echocardiographic normal systolic function of heavily hypertrophic (interventricular septum in diastole [IVSd] 19 mm, left ventricle posterior wall in diastole [LVPWd] 18 mm) left ventricle without asynergies, restrictive type of LV filling with high filling pressures of LV, normal LA function, no significant valvulopathy.

The next step was the diagnostic algorithm for testing for the OSA syndrome. In our outpatient clinic she had filled out the Epworth's Sleepiness Scale (ESS) – with a score of 13 points (which is positive from 8 points and abo-

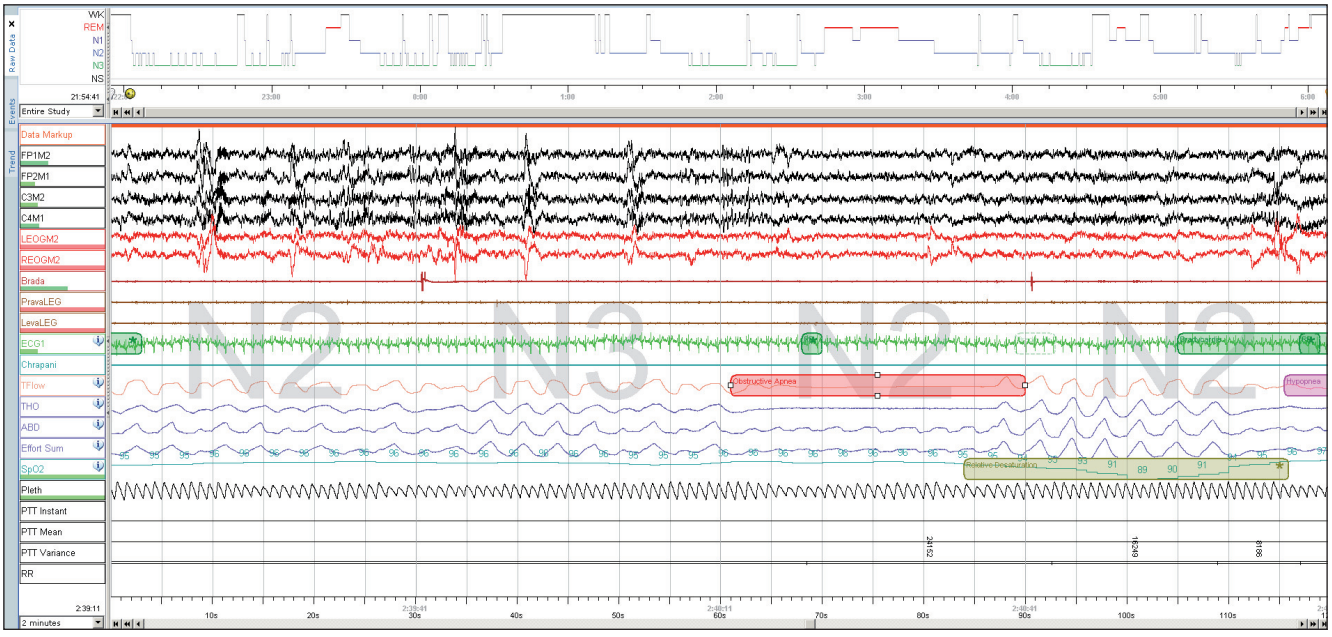

Fig. 1 – Polysomnogram. Obstructive sleep apnoe – eppisode of apnea (red box) by persistence of breathing effort. Oxygen saturation decrease with the delay (light green box).

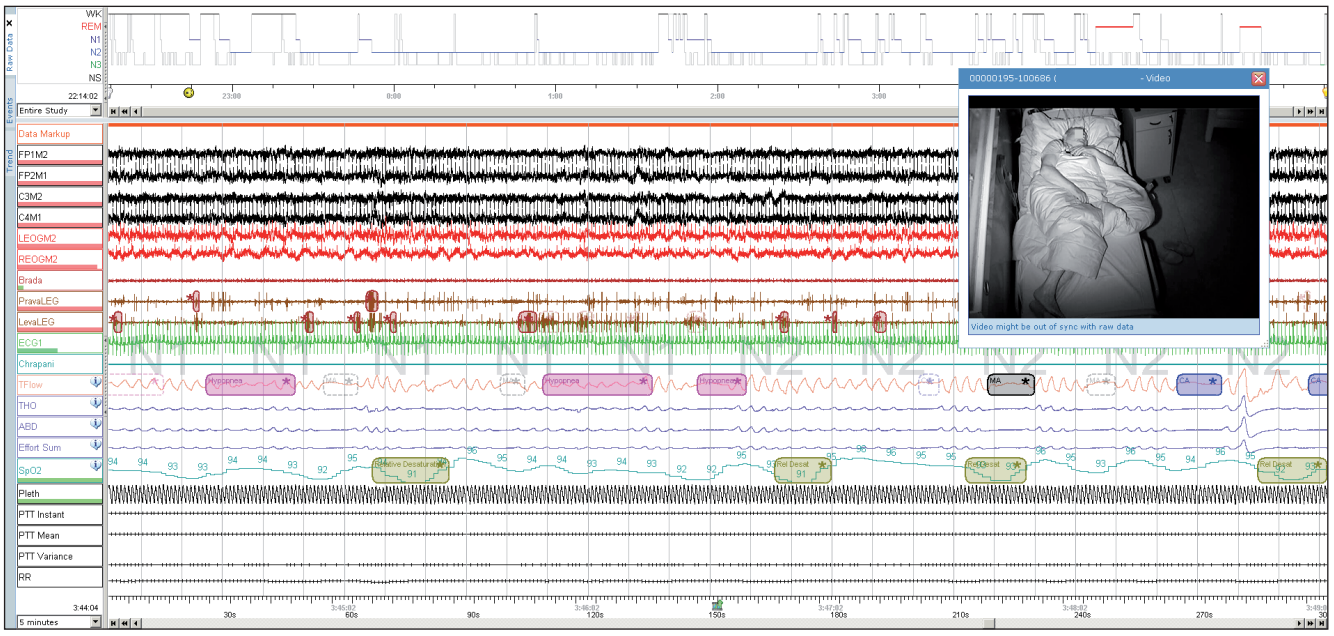

Fig. 2 – Video polysomnography. Polysomnography (multi-parametric test used in sleep medicine) with microphone and video camera recording noises, positions and movements during sleep.

ve). The patient was sent for ear, nose and throat (ENT) examination, where a slightly elongated uvula was described, the clarity of pharynx according to Mallampati was Class II, hypertrophic root of tongue and the retrolingual space was slightly narrowed. This was followed by home respiratory polygraphy and an AHI (apnea-hypopnea index) 26.3 showed moderate sleep apnea syndrome. A polysomnography, which is the gold standard of diagnosis of the syndrome, (see Fig. 1, Fig. 2) was performed in the Sleep Laboratory. The resulting AHI 29, the upper limit of moderate sleep apnea. Average saturation throughout the measurement 94%, saturation below 90% occupying 4.38% of night time sleep.

In a multidisciplinary seminar, weight reduction was recommended, contact with the obesity center was provided without indication for surgical solution. The patient's mandibular protrusion was shifted to ventral mandibular and retrolingual area enlarged but tolerated with difficulty, and in addition, the limited examination inspection by polygraph showed no significant improvement. Through the Sleep Laboratory, the patient borrowed a continuous positive airway pressure (CPAP) device for a weekly test with pronounced effect, AHI 12.3, that is, in the range of mild sleep apnea. From 7/2016 the patient used night-time continuous pressure ventilation therapy (CPAP). In the meantime, we started her on 25 mg of spironolactone. The reasoning was the borderline elevated plasma aldosterone levels, as well as from the knowledge that hypervolemia plays an important role in the pathophysiology of hypertension in patients with OSA syndrome. The use of spironolactone has already been "allowed" at this stage but the diagnostic algorithm for endocrine hypertension has been terminated. Subsequent checking in 10/2016 showed a significant improvement in results – at regular HBPM BP values oscillated in the normotensive band, similar results on ABPM, where the average full-day BP was 129/75 with adequate night dipping. Subjectively, the patient feels much better – "finally sleeps", the headaches are gone, the usual fatigue and sleepiness are limited, AHI is 11.5. We have rationalized the antihypertensive medication, resulting in a combination of 5 antihypertensives without any centrally acting ones. BP values were similar even after a follow-up of 3 months later, sleepiness and fatigue have already gone completely and the patient is satisfied, vital and optimistic. Control endocrinological analysis after next three months (performed 6 weeks after interrupting using spironolactone) showed decreased levels of renin (55 ng/L) and plasma aldosterone (190 ng/L) and mild decrease in ARR (aldosterone-renin ratio).

Discussion

According to presented case report, obstructive sleep apnea (OSA) should be approached as a chronic disease that

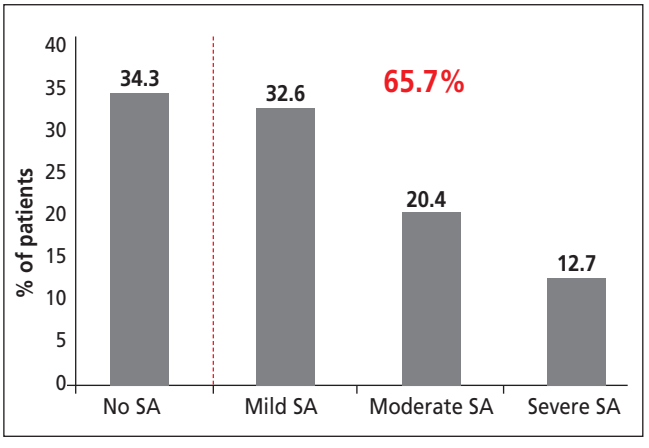

Fig. 3 – Sleep apnea prevalence in acute myocardial infarction patients. Known is the significantly higher OSA prevalence in AMI patients (SAPAMI Study, Ludka O, et al., AJC 2013).

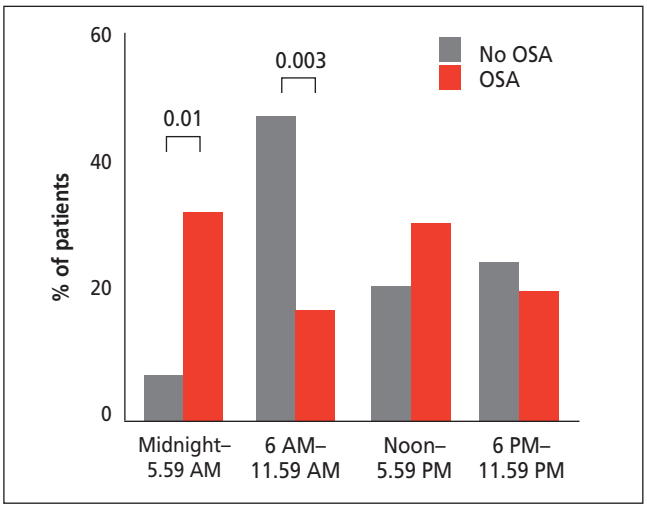

Fig. 4 – Day-night variation of acute myocardial infarction in obstructive sleep apnea. The diurnal variation in the onset of MI in OSA patients is completely different from the diurnal variation in non-OSA patients (Sert Kuniyoshi, et al., JACC, 2008).

requires long-term and multidisciplinary management and care. It is clear that the pathophysiological processes in the OSA syndrome and their consequences – sympathetic hyperactivity, decrease in parasympathetic nervous system activity, increase in heart rate with lower variability, decrease in baroreflex sensitivity, increase in blood pressure with night reversal dipping along with humoral and metabolic changes – predispose patients to the development of cardiovascular diseases.[4] In addition to hypertension, we observe a higher prevalence of atrial fibrillation, heart failure, pulmonary hypertension and CHD. Known is the significantly higher OSA prevalence in AMI patients (Ludka O, et al., AJC 2013 – see Fig. 3).[5] There is also change in the diurnal course of myocardial infarction (MI) in OSA patients – we observe up to 6 times higher risk of developing MI at night in patients with OSA, 91% of patients with MI at night and early morning (00.00–6.00 h) had obstructive sleep apnea (see Fig. 4).[6] The current trend is to see OSA as a separate, potentially modifiable risk factor for CHD.[7]

A key pathophysiological element is hyperactivation of the sympathetic nervous system. Sleep with its phases (nonREM, REM) is a key regulator of diurnal rhythms, a period of "calibration" and regeneration of autonomic systems, homeostasis of the organism. OSA syndrome leads to disruption of sleep microarchitecture, fragmentation of sleep. The result of this alteration is short-term and long-term over-activation of the SNS.[7] Three basic causes of sympathetic hyperstimulation – hypoxic hypercapnia, negative intra-thoracic pressure in the so-called Müller's maneuver and microarousal paroxysms – can be identified with some simplification.[8,9]

Obstructive sleep apnea syndrome and hypertension

OSA syndrome is one of the known causes of secondary hypertension. The pathophysiological background is SNS hyperactivity along with the extreme increase in plasma catecholamines and other vasoactive substances, activation of the renin-angiotensin-aldosterone (RAAS) system and the hypothalamus-pituitary-adrenal axis (HPA) axis. While in the general population the mean incidence of OSA in males is around 3–7% and 2–5% in women, the prevalence of the syndrome in hypertonics is 30–40% and in patients with resistant hypertension up to 83%.[10] There is higher prevalence in patients with high normal BP (20–30%). The two most well known population studies of hypertension in patients with OSA are the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study, which in line with the previous study confirmed a strong correlation between AHI and hypertension.[11] Subsequently, however, in a subanalysis in 2 470 middle-aged patients, at the time of entry into the study with no hypertension diagnosis, no linear relationship was established. The difference in results is explained by different demographic structure – subjects in the first study are younger, while in the second sub-analysis of the second study, they were middle-aged. This is a supportive argument for suspecting that younger OSA patients are more susceptible to the onset and intractability of hypertension. The linear relationship between blood pressure, weight and OSA has been demonstrated to 60 years of patient life. OSA increases the risk of developing hypertension independently of other factors (weight, BMI, sex...).[12]

This case report presents the typical patient with OSA syndrome – it means patient with drug-resistant hypertension (combination of up to 10 antihypertensives), diurnal blood pressure variability, with typical signs (anamnesis of apnea, excessive daytime sleepiness) and obesity (BMI is 30.25). The diurnal course of the blood pressure curve of our patient is specific for most of patients with OSA – we observe a disturbance of circadian rhythm in the absence of physiological nightfall of BP – so-called non-dipping to reverse dipping. The average nighttime BP is higher than the daily average. During the night, there is highly variability (repeated activations of the SNS).

Continuous positive airway pressure therapy (CPAP) is the mainstay of therapy for adults with OSA. It's the most effective treatment for moderate and severe OSA. This therapy reduces the frequency of respiratory events during sleep and results in a significant reduction in the apnea-hypopnea index (AHI). However, the blood pressure lowering effect is controversial.[13] Many prospective and randomized trials have each shown discrepancies in the response of blood pressure in patients with OSA treated with CPAP. A meta-analysis of 28 studies showed an average daily systolic pressure drop in CPAP therapy of only 2.58 mmHg and a diastolic pressure of 2.01 mmHg over the control group. The results were slightly better in younger patients, with a more pronounced clinical presentation, more severe OSA and better adherence to therapy.[9] The effect occurs after at least 3 months of proper use. This analysis has similar results like other studies of Bottini, Marin and Montesi meta-analysis of 32 studies investigating the effect of CPAP treatment for obstructive sleep apnea (OSA) on systolic and diastolic blood pressure (SBP, DBP), confirming statistically significant reducing in diurnal and nocturnal SBP and DBP.[13] On the other hand, a large multicenter study conducted in Spain in 14 cent-

res that compared CPAP therapy with usual care in 725 patients with OSA showed no difference in reducing BP,[14] similarly like other multicenter study.[15] Results of these multicenter studies are very inconsistent. Where can we find the reason? Based on analysis of many studies I have found three main reasons of significant success of CPAP treatment in reducing blood pressure in our patient:

1. Level of adherence with CPAP treatment by patients with OSA.
2. Ability of CPAP therapy to influence pharmacoresistant hypertension (RH).
3. Significance of CPAP therapy as antagonistic mechanism of activated RAAS system in patient with resistant hypertension.[16]

ad 1) The question of long-term adherence with CPAP treatment and the mean duration of using ventilator in patients with obstructive sleep apnea has key importance. The lack of adherence with this therapy is the major cause of treatment failure. Because of long-term and serious health problems of our patient and significant improving after beginning CPAP treatment, her adherence was on high level. She affirmed about 6–7 hours using ventilator per night. Blood pressure decrease was significant in this case. It is known, that 25–28 hours using CPAP per week can cause 60% reducing AHI and is associated with a reduction in symptoms of sleepiness and with improved quality of life. But we have no exact facts about beneficially duration of CPAP in reducing blood pressure. It seems, that treatment for a mean of 3–4 hours per night is very insufficient to provide effect on BP reducing.[17] Barbe in his study demonstrated, that effect of CPAP is evident only in patients who use this therapy for more than 5.6 hours per night.[15]

The mean duration of CPAP treatment influences not only reduction in blood pressure, but has also significant effect on the prevention of recurrent serious cardiovascular events. Well-known are results of large multicentric SAVE study, that randomized a 2717 adults between 45 až 75 years of age and showed that the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care than among those who received usual care alone. In the group of patients with CPAP therapy there was no significant effect on the prevention of serious cardiovascular events, despite significantly reduced sleepiness and improved quality-of-life measures. Participants in the SAVE study adhered to the treatment for a mean of only 3.3 hours per night, which is consistent with CPAP use in clinical practice, but elder studies reported better cardiovascular outcomes among patients who were adherent to CPAP therapy more than 4 hours per night.[18]

ad 2) Several randomized trials show marked variability of BP response of CPAP therapy in patients with OSA and hypertension. CPAP therapy causes different decrease in ambulatory systolic, diastolic and nocturnal BP, we observe an improvement in the nocturnal blood pressure pattern, when using CPAP can eliminate intermittent hypoxemia and BP elevations during night and to restore circadian rhythm with physiological nightfall of BP. There is a big difference between the impact of OSA treatment with CPAP on patients with resistant hypertension and non-resistant hypertension. Our patient used combination of up to 10 antihypertensives including diuretics with non-optimal effect on blood pressure.

HIPARCO study was designed to evaluate the effect of CPAP on BP in patients with obstructive sleep apnea and resistant hypertension. Among patients with mild to severe OSA and resistant hypertension despite optimal anti-hypertensive therapy, CPAP treatment compared with control resulted in a decrease in 24-hour mean and 24-hour diastolic blood pressure and an improvement in the nocturnal blood pressure pattern after 12 weeks of therapy. The average CPAP use was 5 ± 1.9 hours per night.[19] Iftikhar et al. performed a meta-analysis of 5 randomized clinical trials to evaluate the impact of CPAP therapy in OSA patients with RH. They demonstrated a mean decrease of 6.74 mmHg and 5.94 mmHg in ambulatory SBP and DBP and positive correlation between hours of CPAP adherence, AHI score, and duration of RH diagnosis with blood pressure response to CPAP.[20] These results suggest that the degree of BP-lowering effect in RH is greater than in hypertensive patients without RH. This is clinically significant because patients with RH are at higher risk of cardiovascular events.[21]

ad 3) In our patient, use of spironolactone had key importance in the management of therapy. A significant aspect of hypertension in the context of OSA is not only hyperactivity SNS, but also obesity with its volume component of hypertension (our patient with obesity of the first degree, BMI 30.25). Via vasoconstriction in the renal bed, the RAAS system is integral to the process.[10] In an interesting study in obese OSA patients, the CPAP-treated group experienced a decrease in systolic BP of 3 mmHg, in the weight reduction group (diet and exercise) without CPAP, a fall in pressure of 6.8 mmHg, and in the combined CPAP and weight loss group, the most significant decrease in systolic pressure by 14.1 mmHg. This confirms the importance of regime measures such as weight reduction in patients with OSA.[9] Hypervolemia is one of the essential pathophysiological connections between OSA and hypertension.[17] Increased level in serum aldosterone (common in patients with drug-resistant hypertension) is the result of RAAS activation. It leads to greater circulating blood volume, more fluid accumulation in the neck area and thus worse OSA.[21] During the night, the horizontal position of the patient means the movement of fluid is further increased in the head and neck area. In small, uncontrolled studies, the addition of 25–50 mg spirono-

lactone in OSA-resistant hypertonics, resulted in a significant reduction in AHI (after 8 weeks from 39.8 h to 22/h).[9] Increased levels of renin, aldosterone and aldosteron-renin ratio are typical for patients with RH, results of our patient were at upper level of standard norms, even a little bit higher – it confirms the integration of system RAAS in the pathophysiology of resistant hypertension of our patient. Sánchez-de-la-Torre et al. in their study demonstrated, that CPAP therapy in patients with OSA can antagonize the RAAS system, the level of decrease of plasma-renin, plasma-aldosterone and possibly ARR (aldosterone-renin ratio) is correlating with the decrease in mean BP and can help to differentiate between responders/nonresponders in terms of BP drop after CPAP treatment.[16] We couldn't confirm this fact according to early use of spironolactone, but significant effect of CPAP therapy and subsequent effective using of spironolactone is clear evidence of the role of activated RAAS system in the pathophysiology of resistant hypertension in our patient. For all of these reasons, diuretics (mostly thiazide) in combination with spironolactone can be recommended in the pharmacotherapy of hypertension in patients with OSA.

Conclusion

OSA is a condition with a high prevalence, increasing incidence and it is preventable and treatable. The long-term consequences of undiagnosed OSA, are significant increase in the risk of progression of cardiovascular and metabolic diseases. In the area of diagnostics and therapy, interdisciplinary cooperation is of key importance. In common clinical practice, it is essential for a cardiologist to think early about OSA. A typical example is an obese patient with a corresponding clinical picture, pharmacoresistent hypertension and reversible night dipping in ABPM.

Early recognized and properly treated OSA syndrome in compliant patients means significant mitigation of cardiovascular risk. Up to 85% of patients with clinically significant and treatable obstructive sleep apnea have never been diagnosed and therefore not treated.

Conflict of interest
The author is not aware of any conflicts of interest associated with this article.

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Ethical statement
The authors hereby declare that they did not violate any ethical principles when writing this article.

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