ORIGINAL ARTICLE

Effect of eplerenone on the severity of obstructive sleep apnea and arterial stiffness in patients with resistant arterial hypertension

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KEY WORDS

arterial stiffness, eplerenone, obstructive sleep apnea, resistant hypertension

ABSTRACT

INTRODUCTION Obstructive sleep apnea (OSA) is considered to be one of the major causes of resistant arterial hypertension (RAH). Apnea episodes cause hypoxia, which triggers the activation of the renin–angiotensin–aldosterone system. This leads to water retention and swelling in the neck region, exacerbating OSA symptoms. It is assumed that the use of eplerenone may reduce the swelling and thus alleviate the severity of OSA.

OBJECTIVES We aimed to prospectively assess the impact of eplerenone on the severity of OSA and arterial stiffness in patients with RAH.

PATIENTS AND METHODS The study included 31 patients with RAH and OSA. The exclusion criteria were as follows: secondary hypertension, myocardial infarction, stroke 6 months prior to the study, congestive heart failure, chronic kidney failure, alcohol or drug addiction, and active cancer. In all patients, the following tests were performed: blood pressure (BP) measurement (traditionally and using ambulatory BP measuring [ABPM]), applanation tonometry, polysomnography, and the apnea–hypopnea index (AHI) calculation. The tests were done before and after 3 months of eplerenone therapy. Patients received 50 mg of oral eplerenone daily, along with other hypertensive drugs.

RESULTS The mean age of participants was 57.76 ±6.16 years. After 3 months of eplerenone therapy, we observed a significant reduction in the AHI, neck circumference, BP, aortic pulse wave, and arterial wall stiffness. There were significant correlations between the AHI and mean BP measured by ABPM and between the AHI and arterial stiffness parameters.

CONCLUSIONS Our results provide evidence for the clinical significance of eplerenone, not only as an antihypertensive medication but also as a drug that may reduce the severity of OSA and arterial stiffness in patients with RAH and OSA.

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INTRODUCTION In patients with resistant arterial hypertension (RAH), it is impossible to achieve the target values of blood pressure (BP), despite the use of 3 antihypertensive agents (including a diuretic) at maximum doses. Patients with RAH are at high and very high cardiovascular risk, and their treatment constitutes a major clinical and therapeutic challenge.[1] The prevalence of RAH is difficult to estimate, and data from clinical studies are often divergent.[2] According to the NHANES and de le Sierra studies,[3,4] RAH is observed in 10% to 15% of patients treated with antihypertensive drugs.

One of the most common causes of RAH is obstructive sleep apnea (OSA). Arterial hypertension is observed in 37% to 56% of patients with OSA, and OSA occurs in 70% to 85% of patients with RAH.[2,5] Logan et al[2,6] reported that the prevalence of OSA in patients with RAH is 83% (65% in women and 96% in men). Similar results were

obtained by Gonçalves et al,[7] who confirmed that 71% of the 63 patients with RAH had OSA (86% of men and 64% of women).

OSA is characterized by recurrent episodes of ceased or reduced flow through the airway, with the respiratory effort retained. The main criterion of diagnosing OSA in polysomnography is the apnea–hypopnea index (AHI), which is an indicator of the number of apnea and hypopnea episodes per hour. OSA can be diagnosed if the AHI exceeds 5 and such symptoms as excessive daytime sleepiness, insomnia, awakenings at night, morning headaches, nocturnal dyspnea, and cognitive dysfunction are present.[8] The severity of OSA is based mainly on the value of the AHI. OSA is mild when the AHI ranges from 5 to 15; moderate, when it ranges from 16 to 30; and severe, when it exceeds 30.[8]

Several studies have indicated that higher plasma levels of aldosterone, although still within the normal physiological range, predispose to the development of RAH. Aldosterone has an adverse effect on the cardiovascular system because it causes water and sodium retention. This leads to an increase in intravascular volume, which results in resistance to antihypertensive agents. Numerous studies have shown that adding spironolactone to a multidrug antihypertensive therapy in patients with RAH significantly improves BP control.[9-11]

The studies of Gonzaga et al[12] and Gaddam et al[13] suggested that an elevated level of aldosterone may be responsible for the development of RAH in patients with OSA, and that treatment with spironolactone reduces the severity of OSA in those patients. However, in the available publications, there are no reports on a beneficial effect of eplerenone on the severity of OSA in patients with RAH. To confirm this hypothesis in our study, eplerenone at a dose of 50 mg/d was added to a standard antihypertensive therapy. This drug belongs to a group of diuretics that save potassium. It is characterized by the specificity of action and a low risk of side effects. Blocking the action of aldosterone causes a decrease in BP mainly by reducing fluid retention. In patients with OSA, this probably results in a reduction of fluid accumulation in the neck. This, in turn, contributes to lowering the resistance in the upper respiratory tract and improves the severity of OSA.

The aim of the study was to evaluate the effect of eplerenone on the severity of OSA and on arterial stiffness in patients with RAH and OSA.

PATIENTS AND METHODS

A total of 31 patients (20 men and 11 women) with RAH and OSA were included in the study, which was conducted between 2014 and 2015 in the Department of Hypertension and the Department of Pulmonology at the Poznan University of Medical Sciences, Poznań, Poland. Permission (no. 565/14) to conduct the study was obtained from the Ethics Committee at the Poznan University of Medical Sciences. All patients gave informed consent to participate in the study. The exclusion criteria were as follows: secondary hypertension (other than primary hyperaldosteronism), myocardial infarction, stroke within 6 months before the study, congestive heart failure (New York Heart Association classes III and IV), chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2), drug or alcohol addiction, and active cancer.

Blood pressure measurement

During each visit, BP was measured in all patients, 3 times at rest in the supine position, in standard conditions, using an upper arm BP monitor (Omron 705IT, Omron Healthcare, Kyoto, Japan). Ambulatory BP monitoring (ABPM) was performed using a 24-hour ambulatory peripheral BP monitor TM2430 (A&D Medical, San Jose, California, United States). The frequency of measurements was every 15 minutes between 7:00 AM and 10:00 PM, and every 30 minutes between 10:00 PM and 7:00 AM.

Central aortic function

Central aortic BP and other parameters of the aortic pulse wave and arterial wall stiffness of the large conduit arteries were measured using pulse wave analysis with applanation tonometry (SphygmoCor PVx, Version 8.0, AtCor, Sydney, Australia) by a single observer. Brachial BP required for the algorithm of the procedure was measured noninvasively after 15 minutes of rest in the supine position, with Omron 705IT device (Omron Healthcare). For this assessment, the pulse waveform of the radial artery was recorded for 10 seconds, and a radial to aortic validated generalized transfer function was used to derive the central aortic pulse pressure waveform, from which the aortic systolic pressure (AoSP), augmentation index (AoAIx), and augmentation index estimated for a heart rate of 75 bpm (AlxHR75) were determined.[14-17]

Pulse wave velocity

For the assessment of the pulse wave velocity (PWV), the pulse wave was obtained over the right femoral artery and at the neck for the right common carotid artery. Transit time was measured as the time between the foot of the pulse wave and the R wave in a simultaneously recorded electrocardiogram. The measurements were done by a single examiner. Data were collected directly into a laptop (HP Pavilion Entertainment PC, Palo Alto, California, United States). Pulse transit time was determined as the average of consecutive beats during 10 seconds. Time delay (t) was calculated as the difference between those 2 transit times. The distance (d) travelled by the pulse wave was measured over the body surface at the distance between the 2 locations. PWV was calculated as PWV = d/t [m/sec] by the SphygmoCor device (SphygmoCor PVx, Version 8.0, AtCor) and multiplied by 0.8, according to expert consensus from 2012.[16-19]

Neck circumference measurement The neck circumference was measured in the midway of the neck, between the mid-cervical spine and mid--anterior neck, in the standing position, with a flexible nonstretchable plastic tape, and approximated to the nearest 0.1 cm.

Polysomnography The probability of OSA was established on the basis of the Epworth Sleepiness Scale.[20]

The evaluation of patients was performed in the sleep laboratory of the Department of Respiratory Medicine, Allergology and Lung Oncology of the Poznan University of Medical Sciences, using a full-night polysomnographic monitoring system (EMBLA S4000, Remlogic, Denver, Colorado, United States) with the Somnologica studio 3.3.2 software (EMBLA, Broomfield, Colorado, United States).

Standard electroencephalography monitoring (including frontal leads [F1, F2], central leads [C3, C4], occipital leads [O1, O2], and reference leads at the mastoids [M1, M2]), electromyography, and electrooculography were performed according to the American Academy of Sleep Medicine guidelines.[21] Airflow was measured using nasal and oral thermistors, as well as a nasal pressure transducer. Abdominal and thoracic movements were assessed by respiratory inductive plethysmography. Oximetry was measured using a disposable finger probe (oximeter flex sensor 8000 J, NONIN, Plymouth, Massachusetts, United States) placed on the index finger. Snoring sounds and heart rate were also recorded. Body position was monitored using a body position sensor. Apnea was defined as the cessation of airflow lasting more than 10 seconds, and hypopnea, as a discrete reduction (two-thirds) of airflow and/or abdominal ribcage movements lasting more than 10 seconds and associated with a decrease of more than 4% in oxygen saturation.[22] All studies were analyzed by trained polysomnography and sleep physicians using the criteria of Rechtschaffen and Kales, and in accordance with scoring updates provided by the American Academy of Sleep Medicine.[23]

Design of the study **First visit** The patients with previously diagnosed RAH and with suspected OSA (medical history, the Epworth Sleepiness Scale) were referred from an outpatient clinic to a hospital ward. After admission, the following laboratory and imaging tests were performed to exclude secondary causes of hypertension (other than primary hyperaldosteronism): measurement of aldosterone and plasma renin activity levels (both before and after the tilt test), measurement of creatinine, urea, eGFR, sodium, potassium, pro-B-type natriuretic peptid, thyreotropin, triiodothyronine, and thyroxine levels, 24-hour urine collection for electrolyte measurement, abdominal ultrasound, abdominal computed tomography, and Doppler ultrasound of the renal arteries. Clinical BP was measured 3 times, and ABPM and measurement of central BP arterial stiffness parameters were performed. After laboratory and imaging tests as well as after confirming RAH based on ABPM, patients were referred to the Department of Pulmonology to undergo polysomnography. Patients in whom OSA had been confirmed received 50 mg of eplerenone daily.

Second visit After 3 months, clinical BP was again measured 3 times, and ABPM and measurements of central BP arterial stiffness parameters, including polysomnography, were repeated.

Statistical analysis The normality of distribution of the analyzed variables was evaluated with the Shapiro–Wilk test and Kolmogorov–Smirnov test with the Lilliefors correction. The results of the tests showed that distributions of almost all parameters significantly differed from the normal distribution. Therefore, nonparametric methods were used in statistical analysis. The Wilcoxon signed-rank test was applied for the evaluation of the differences between the baseline values and those obtained after treatment. The *t* test was used for variables with normal distribution. Correlations between the values of the parameters were evaluated using the Spearman's rank correlation coefficient. A *P* value of less than 0.05 was considered significant. The Statistica software, version 10, was used for the analysis (www. statsoft.com; license JGNP410B316631AR-J, StatSoft, Inc., 2011, Tulsa, Oklahoma, United States).

RESULTS The mean age of patients was 57.76 ±6.16 years. They were taking on average 3.93 antihypertensive medications including diuretics (100% of patients; thiazide, 29%; loop diuretics, 61.3%; thiazide and loop diuretics, 9.7%), angiotensin-converting enzyme inhibitors (54% of patients), angiotensin II receptor antagonists (45.2% of patients), calcium antagonists (83.9% of patients), β-blockers (77.4% of patients), and α-blockers (22.6% of patients). Three months after adding eplerenone at a dose of 50 mg/d to a standard antihypertensive therapy, a slight decrease in body weight, body mass index, waist circumference, and a significant decrease in the neck size were observed (TABLE 1). There was also a significant decrease in BP measured in a standard way and using ABPM. A significant reduction in the values of arterial stiffness (PWV, AoAlx, AlxHR75) was also revealed (TABLE 2). Additionally, a significant reduction of the parameters determining the severity of OSA (AHI, apnea index, hypopnea index, Oxygen Desaturation Index, average saturation and desaturation counts) was shown (TABLE 3). During the second visit, there was a reduction in the number of patients with severe and moderate OSA (a decrease of the AHI by 10% and 13%, respectively). The distribution of mild to moderate and severe OSA as well as changes after treatment are shown in FIGURE 1. A significant positive correlation between the AHI and the parameters of ABPM, such as nighttime

TABLE 1 Characteristics of patients at subsequent visits

Parameter	Visit 1	Visit 2	*P* value
weight, kg	115.4 (96.4–123)	114 (97–122)	0.4[a]
height, cm	174.6 ±6.89	174.6 ±6.89	–
BMI, kg/m^2	36.3 (33.7–39.5)	36.2 (32.4–38.2)	0.5[a]
age, y	57.76 ±6.18	57.76 ±6.18	–
neck circumference, cm	46 (44–48)	46 (44-48)	<0.05[a]
waist circumference, cm	124 (115–131)	123 (115–130)	0.38[a]
serum potassium, mmol/l	4.2 (3.9–4.5)	4.2 (4.1–4.6)	<0.05[a]
serum creatinine, μmol/l	86.3 (77.6–104)	90.6 (80.7–96.2)	0.3[a]
eGFR, ml/min/1.73 m^2	83 (66–90)	80 (73–90)	0.4[a]

Data are presented as median ± SD or median and interquartile range.

a nonparametric test

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate

TABLE 2 Blood pressure and arterial stiffness parameters before and after eplerenone administration

Parameter	Visit 1	Visit 2	*P* value
SBPd, mmHg	153 (139–157)	138 (132–141)	<0.05[b]
DBPd, mmHg	90.2 ±7.36	85.84 ±4.93	<0.05[a]
MAPd, mmHg	108.56 ±7.01	103.16 ±3.99	<0.05[a]
SBPn, mmHg	134.92 ±10.47	130.01 ±5.85	<0.05[a]
DBPn, mmHg	82.0 ±10.92	79.64 ±7.57	<0.05[a]
MAPn	100 (92–108)	97 (91–102)	<0.05[b]
SBP24	147 (137–152)	136 (130–140)	<0.05[b]
DBP24	87.88 ±7.95	84.12 ±4.92	<0.05[a]
MAP24	106.72 ±6.8	101.52 ±4.09	<0.05[a]
PWV × 0.8, m/s	12.2 (11.4–13.4)	10.6 (8.8–12.1)	<0.05[b]
AoAlx, %	31 (27–37)	26 (22–31)	<0.05[b]
AlxHR75, %	28 (25–33)	20 (18–25)	<0.05[b]
clinic SBP	150.2 ±6.46	140.52 ±4.86	<0.05[a]
clinic DBP	93 (89–99)	89 (85–92)	<0.05[b]

Data are presented as median ± SD or median and interquartile range.

a parametric test, b nonparametric test

Abbreviations: AlxHR75, augmentation index at a heart rate of 75 bpm; AoAlx, augmentation index; DBP, diastolic blood pressure; DBP24, 24-hour diastolic blood pressure; DBPn, nighttime ambulatory diastolic blood pressure; DBPd, daytime ambulatory diastolic blood pressure; MAP24, 24-hour mean blood pressure; MAPd, daytime ambulatory mean blood pressure; MAPn, nighttime ambulatory mean blood pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; SBP24, 24-hour systolic blood pressure; SBPd, daytime ambulatory systolic blood pressure; SBPn, nighttime ambulatory systolic blood pressure

ambulatory SBP, nighttime ambulatory MAP (FIGURES 2 and 3) and between the AHI and parameters of arterial stiffness (PWV, AlxHR75) was observed (FIGURES 4 and 5).

DISCUSSION The nighttime use of continuous positive airway pressure (CPAP) is the basic treatment method for moderate and severe OSA. It was shown that this therapy significantly improves the quality of life of patients with OSA, causes a significant decrease in BP, and reduces the incidence of cardiovascular events. The meta-analysis of 7 randomized trials demonstrated that CPAP significantly reduced SBP (by 2.32 mmHg) and DBP (by 1.98 mmHg). The authors emphasized that CPAP leads to a greater decrease in SBP at night than during the day and that patients with RAH benefited most from the treatment.[24] Treatment of arterial hypertension in the course of OSA is difficult and should include the simultaneous use of several antihypertensive drugs with different mechanisms of action, including a diuretic and, optimally, a drug that inhibits the effect of aldosterone. Hu et al[24] suggested that drugs blocking aldosterone receptors for aldosterone not only lower BP but also reduce apnea counts at night.[24]

TABLE 3 Results of polysomnography parameters before and after eplerenone therapy

	Visit 1	Visit 2	*P* value
AHI	49.5 (20.1–63.3)	28.7 (15.7–40.3)	<0.05[b]
AI	32.2 (14.4–44.2)	15.5 (11.2–23.4)	<0.05[b]
HI	11.3 (6.7–15.6)	8.2 (5.2–14.8)	0.14[b]
ODI	39.6 (19–55.4)	27.6 (16.2–34.5)	<0.05[b]
mean saturation, %	89.69 ±3.23	93.48 ±2.28	<0.05[a]
lowest saturation, %	74 (59–84)	78 (75–87)	<0.05[b]

Data are presented as median ± SD or median and interquartile range.

a parametric test, **b** nonparametric test

Abbreviations: AHI, apnea–hypopnea index; AI, apnea index; HI, hypopnea index; ODI, Oxygen Desaturation Index

Our study aimed to assess the effect of eplerenone on the severity of OSA. We revealed a significant decrease in BP, measured both in a standard way and by ABPM, and a significant reduction in the AHI in patients with OSA and RAH 3 months after adding eplerenone to a standard antihypertensive therapy. The greatest reduction in BP was observed for daytime SBP (by 10.56 mmHg) and 24-hour SBP (by 8.92 mmHg). There was a decrease in nighttime SBP and DBP by 4.91 mmHg and 2.36 mmHg, respectively. Moreover, we observed a reduction in SBP and DBP by 9.68 mmHg and 5.08 mmHg, respectively, measured in a standard way. All results were statistically significant. After treatment with eplerenone, there was a 33% reduction in the AHI. We confirmed a significant positive correlation between the AHI and nighttime SBP, nighttime MAP, and 24-hour MAP. Our study showed that the addition of an aldosterone antagonist to a standard antihypertensive therapy is an effective therapeutic option for patients with OSA and RAH.

Similar results were obtained by Gaddam et al[13] in a study on patients with RAH and moderate OSA (AHI >15). Eight weeks after adding spironolactone at a dose of 25 to 50 mg/d to an antihypertensive therapy, they achieved a significant reduction in office BP (from 145/81 mmHg to 124/72 mmHg) as well as in ABPM (from 147/82 mmHg to 130/72 mmHg). They also showed a significant decrease in the AHI, from 39.8% to 22.0%.[13] It seems that in patients with OSA, aldosterone antagonists, apart from acting diuretically, act indirectly by reducing the swelling of the back of the throat and the tongue. This diminishes the size of the collapse of the upper airway during sleep and facilitates the treatment of OSA.[13]

Studies in patients with heart failure and fluid overload revealed a higher prevalence of OSA, as well as a direct relationship between the severity of OSA and the volume of fluid displaced from the lower extremities to the neck during sleep. This is because during the day, the excess of fluid accumulates in the lower limbs, and at night, while lying down, it is transferred cranially to the neck, where a narrowing of the upper airways may occur. This may predispose to OSA, especially that during sleep the tension of the throat muscles reduces. Therapy with an aldosterone antagonist, which is aimed at reducing fluid retention and redistribution, can reduce the AHI and the severity of OSA.[25,26] Similar results were obtained by Kasai et al.[27] The intensification of a diuretic therapy in patients with RAH and OSA resulted in a decrease in the AHI from 57.7 ±33.0 to 48.5 ±28.2. The authors observed an inverse correlation between the reduction in the overnight volume of fluid in the lower limbs and the decrease in the AHI ($r = -0.734$; $P < 0.001$).[27]

According to Clark et al,[28] there are 3 mechanisms explaining the effect of aldosterone antagonists on arterial BP decline in patients with normal plasma levels of aldosterone. Firstly, the aldosterone concentration in blood does not reflect its concentration in the heart, kidneys, and blood vessels. Secondly, aldosterone raises BP irrespective of the mineralocorticoid receptors. Thirdly, mineralocorticoid receptors are stimulated by hormones other than aldosterone. The authors introduced the term "mineralocorticoid receptors associated hypertension (MR associated hypertension)", or hypertension that responds well to a therapy with aldosterone antagonists. Dudenbostel and Calhoun[29] analyzed 2 hypotheses in their study, namely, whether the excess of aldosterone leads to the development of OSA, or, on the contrary, whether OSA leads to increased plasma levels of aldosterone.[29,30] Currently, there are more data to support the first hypothesis. Dudenbostel and Calhoun[29] supported the findings of Clark et al[28] that OSA aggravation is caused by fluid retention that leads to the swelling of the neck in its parapharyngeal part and increases airway resistance.

PWV is a noninvasive indicator of arterial stiffness as well as an independent stratification factor for global cardiovascular risk. Numerous factors such as hypertension, aging, smoking, hypercholesterolemia, and diabetes can alter the structural and functional properties of the vessel wall. Patients with OSA have a large number of risk factors that increase PWV, which makes it difficult to extract and evaluate the impact of only one of them on vascular lesions. Arterial stiffness measurements may be particularly useful in

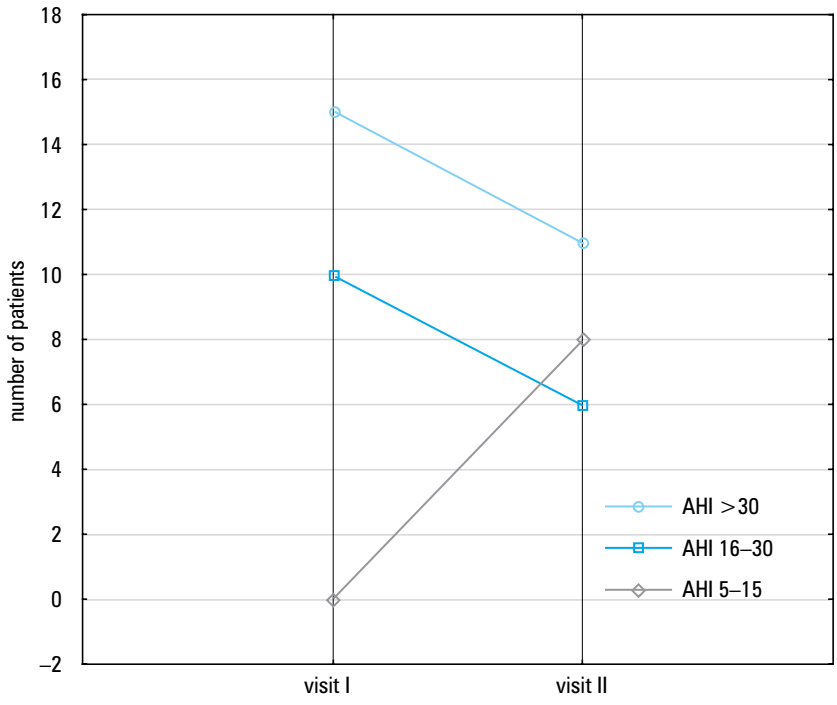

FIGURE 1 Distribution of mild to moderate and severe obstructive sleep apnea at visits 1 and 2
Abbreviations: see **TABLE 3**

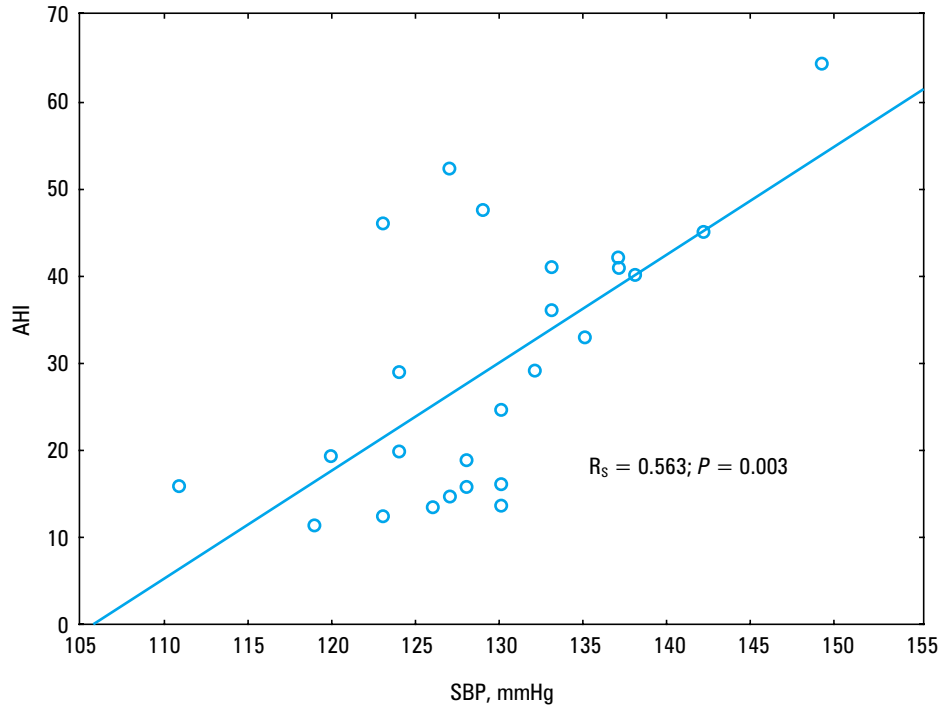

FIGURE 2 Correlations between the apnea–hypopnea index (AHI) and nighttime ambulatory systolic blood pressure (SBP)

evaluating the degree of damage to the endothelium in patients with RAH and OSA.

In the light of the current 2013 European Society of Hypertension / European Society of Cardiology (ESH/ESC) guidelines, patients suffering from RAH and having subclinical organ complications, which include increased velocity between the carotid and femoral artery PWV exceeding 10 m/s, are at high and very high cardiovascular risk.[31] Numerous recent clinical studies have provided evidence for a link between OSA and the development of subclinical organ damage.[32-37] Early detection of the damage in patients with OSA may be helpful in identifying patients who are at the highest risk of developing cardiovascular complications.

Drager et al[38,39] observed that patients with moderate to severe OSA and with a mean AHI of 52.8 ±21.0 showed a higher arterial stiffness assessed by a PWV ratio of 10.6 ±1.1 m/s.[38,39] In another study by the same author, 60 patients were divided into 4 groups: with or without OSA and with normal or elevated BP. It was shown that in comparison with the control group, patients with OSA and AH had the highest PWV (12.1 ±0.4 m/s), and a multivariate analysis showed a positive correlation between the PWV and AHI (r = 0.40; P <0.002).[40]

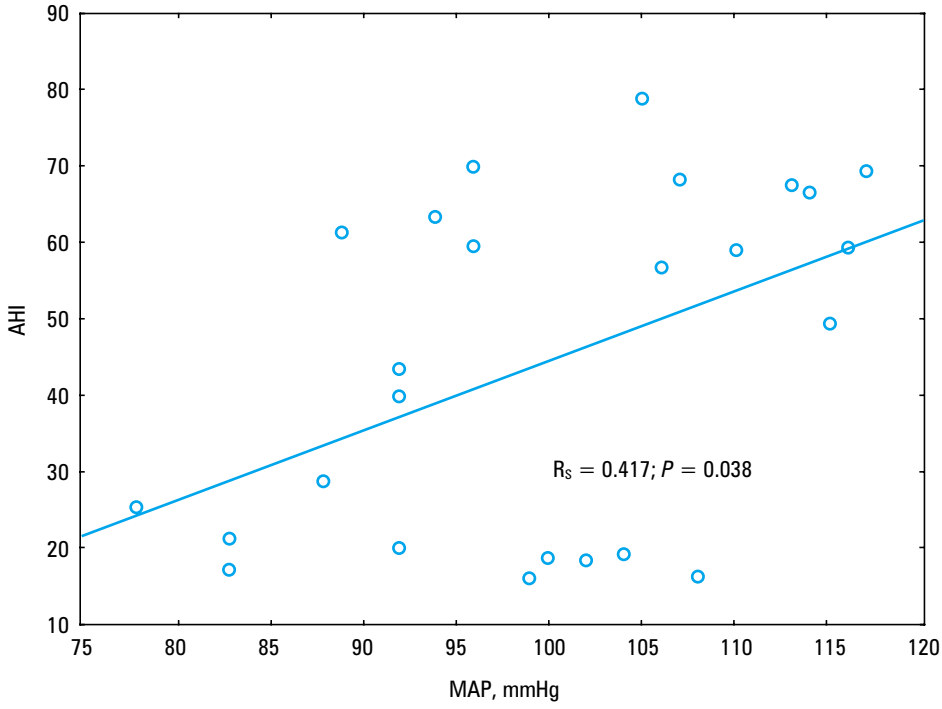

FIGURE 3 Correlations between the apnea–hypopnea index (AHI) and nighttime ambulatory mean artery pressure (MAP)

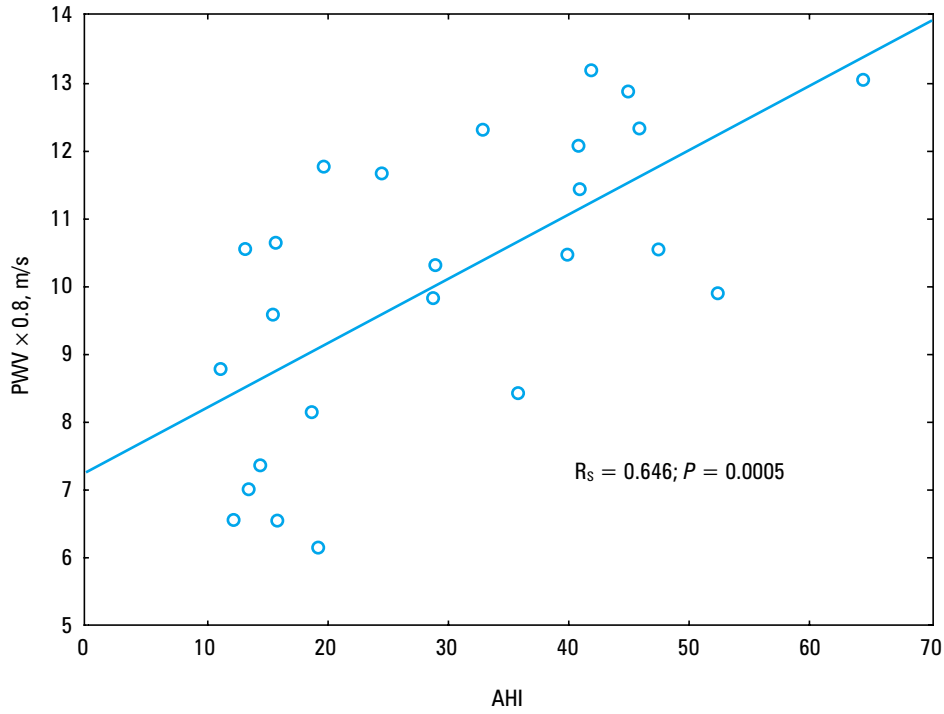

FIGURE 4 Correlations between the apnea–hypopnea index (AHI) and pulse wave velocity (PWV)

One of the strongest pieces of evidence to confirm the impact of OSA on arterial stiffness are the results of 2 randomized studies showing that CPAP treatment in patients with OSA significantly improves arterial stiffness. CPAP is currently the gold standard in OSA treatment. In the first study, after 4 weeks of CPAP treatment, there was a marked decrease in the augmentation index by 0.7% and in MAP by 2.6 ±5.4 mmHg, compared with the control group.[41] In the second study, Drager et al[38] compared 24 patients with severe OSA treated with CPAP with an untreated control group. After 4 months of using CPAP, there was a significant decrease in the intima–media thickness and PWV. The authors hypothesized that the use of CPAP in OSA treatment significantly improves parameters that are early predictors of atherosclerosis.[38]

In our study, we observed a significant decrease in the volume of arterial stiffness parameters (PMV, AoAlx, and AlxHR75) after 3 months of treatment with eplerenone in patients with OSA and RAH. We also showed a significant positive correlation between the AHI and the above parameters. Moreover, we obtained higher PWV values than the reference values for the treatment of AH in the 2013 ESH/ESC guidelines.[31] This shows that severe OSA is associated with an increased severity of vascular damage. Assessment of PWV in patients with OSA may be a clinically

useful marker for evaluating the progression of vascular damage. This is confirmed by other authors who demonstrated higher PWV values in patients with OSA but without hypertension. PWV in these patients was similar to that of patients with hypertension but without OSA. What is more, these authors observed a further increase in PWV in patients with hypertension and concomitant OSA. A multivariate regression analysis showed that PWV was significantly correlated with SBP and AHI.[40]

Numerous studies showed a significant correlation between the AHI and PWV. Kumagai et al[34] compared patients with mild, moderate, and severe OSA and showed that PWV was the lowest in patients with mild OSA, compared with patients with moderate or severe OSA. In their multivariate regression analysis, Tomiyama et al,[32-34] demonstrated a positive correlation between the AHI and PWV, even after taking into account age, sex, and risk factors for cardiovascular disease ($r = 0.39$; $P < 0.01$).

To summarize, OSA is one of the most common causes of reversible increases in BP and a clinically important factor predisposing to the development of hypertension refractory to treatment. The results of our study emphasize the special role of aldosterone as the cause of RAH in patients with OSA. In addition, the results emphasize the benefits of adding eplerenone to an antihypertensive therapy, in terms of both reducing the severity of OSA, which can be confirmed by polysomnography, and the risk of cardiovascular complications (arterial stiffness). Therefore, it is necessary to carefully evaluate patients with RAH, particularly those with suspected OSA and obesity, and to confirm this suspicion by polysomnography and continue antihypertensive treatment with the use of aldosterone antagonists.

Contribution statement BK, SC, and LS-C contributed to the study design. AM, BK, LS-C, and TT were involved in data collection. BK, SC, ZK, KP-G, and AT contributed to data interpretation and statistical analysis. All authors edited and approved the final version of the manuscript.

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Wpływ eplerenonu na stopień ciężkości obturacyjnego bezdechu sennego oraz na parametry sztywności tętnic u pacjentów z opornym nadciśnieniem tętniczym

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eplerenon, obturacyjny bezdech senny, oporne nadciśnienie tętnicze, sztywność tętnic

STRESZCZENIE

WPROWADZENIE Obturacyjny bezdech senny (*obstructive sleep apnea* – OSA) uważany jest za jedną z głównych przyczyn rozwoju opornego nadciśnienia tętniczego (*resistant arterial hypertension* – RAH). Epizody bezdechu wywołują hipoksję, która prowadzi do pobudzenia układu renina–angiotensyna–aldosteron. Powoduje to retencję wody oraz obrzęk w okolicy szyi, przez co nasilają się objawy OSA. Uważa się, że eplerenon może zmniejszać obrzęk, a przez to stopień ciężkości OSA.

CELE Celem badania była prospektywna ocena wpływu eplerenonu na stopień ciężkości OSA oraz na sztywność tętnic u pacjentów z RAH.

PACJENCI I METODY Do badania włączono 31 pacjentów z RAH i OSA. Kryteriami wykluczenia były: wtórne nadciśnienie tętnicze, zawał mięśnia sercowego, udar mózgu do 6 miesięcy przed włączeniem do badania, zastoinowa niewydolność serca, przewlekła niewydolność nerek, uzależnienie od alkoholu lub narkotyków oraz aktywna choroba nowotworowa. U wszystkich pacjentów wykonano następujące testy: zmierzono wysokość ciśnienia tętniczego (tradycyjnie oraz za pomocą Holtera ciśnieniowego), wykonano tonometrię aplanacyjną i polisomnografię oraz oznaczono wskaźnik AHI (*apnea–hypopnea index*). Oceny dokonano przed terapią eplerenonem i po 3 miesiącach. Pacjenci otrzymywali doustnie 50 mg/d eplerenonu razem z innymi lekami hipotensyjnymi.

WYNIKI Średnia wieku uczestników wynosiła 57,76 ±6,16 roku. Po 3 miesiącach leczenia eplerenonem obserwowano istotne zmniejszenie AHI, obwodu szyi, ciśnienia krwi, prędkości fali tętna oraz sztywności tętnic. Wykazano istotne korelacje między AHI i średnimi wartościami BP mierzonymi za pomocą Holtera ciśnieniowego oraz między AHI i parametrami sztywności tętnic.

WNIOSKI Wyniki stanowią dowód na kliniczne znaczenie eplerenonu nie tylko jako leku hipotensyjnego, ale również jako preparatu, który może zmniejszyć stopień nasilenia OSA i sztywności tętnic u chorych z RAH i OSA.

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