Impaired aldosterone response to the saline infusion test in patients with resistant hypertension and obstructive sleep apnea

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Summary

Background In this cross-sectional study, we sought associations among severity of obstructive sleep apnea (OSA), renin-angiotensin-aldosterone system and blood pressure patterns in patients with resistant hypertension.

Material and methods In 65 patients with resistant hypertension we measured the apnea-hypopnea index (AHI) by a portable sleep recorded system and aldosterone and plasma renin activity (PRA) in response to saline infusion test. We also collected data on cardiovascular events, dyslipidemia, chronic kidney disease, and diabetes and performed 24-hour blood pressure monitoring (ABPM).

Results Baseline PRA, aldosterone and aldosterone-to-renin ratio were within normal range but aldosterone level in response to saline infusion was increased above normal upper limit. In ABPM, 68% of patients had an altered pattern of blood pressure (non-dipping or reverse dipping). AHI was inversely correlated with PRA and positively with weight, BMI, plasma aldosterone, aldosterone to renin ratio, and aldosterone after saline load but not with blood pressure. Patients with severe OSA (AHI > 30) in comparison to those with mild OSA (AHI 5–15) had significantly higher PRA and aldosterone (baseline and after saline load) but comparable values of blood pressure. We did not find significant impact of OSA severity on the frequency of abnormal blood pressure patterns. Frequencies of diabetes, abnormal lipid profiles, ischemic heart disease, myocardial infarction, and stroke increased with increases in severity of OSA.

Conclusions Despite of normal basal PRA and aldosterone concentration, patients with resistant hypertension and OSA had impaired response to saline load and a rate of this impairment depended on the severity of OSA.

key words: obstructive sleep apnea; resistant hypertension; saline infusion test; aldosterone

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Background

Hypertension is a key risk factor in the development of cardiovascular diseases and one of the leading causes of death worldwide [1, 2]. In Poland, hypertension affects approximately 10.5 million of inhabitants. Recently, the NATPOL 2011 survey demonstrated the decline in number of deaths due to cardiovascular disease since 1990, what is undoubtedly associated with improvements in lifestyle as well as diagnosis and management of hypertension [3–5].

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder characterized by pauses in breathing and shallow or infrequent breathing during sleep leading to a reduction in arterial blood oxygenation [6]. According to current guidelines, diagnosis of the condition should be confirmed by the assessment of indicators that are linked to the quantity of apneic

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events per hour of sleep, such as Respiratory Disturbance Index (RDI) or Apnea-Hypopnea Index (AHI) [7, 8]. High mortality in patients with OSA is associated with severity of the disease as well as comorbid obesity and cardiovascular events, and traffic accidents [8, 9].

Epidemiological association of OSA and hypertension is well established. Majority of observational studies demonstrated robust correlations between AHI and blood pressure, either at baseline or over long-term follow-up [10, 11]. It has been demonstrated that in patients with OSA the physiological nocturnal decrease of blood pressure is frequently altered leading to non-dipping and reverse dipping hypertension, which are known as independent predictors of cardiovascular risk and increased mortality [10, 12].

Pathophysiological links of OSA and hypertension are complex and involve at least several mechanisms. OSA is frequently associated with autonomic nervous system derangements induced by hypercapnia and hypoxemia, which results in elevated catecholamine levels [10, 13]. In addition, OSA correlates with markers of low-grade chronic inflammation, such as high sensitivity C-reactive protein, tumor necrosis factor-α, or interleukins [14]. Other studies suggested in OSA-induced hypertension a possible role of hemodynamic alternations in response to stress, endothelial dysfunction [10], nocturnal fluid redistribution [15], and up-regulation of the renin-angiotensin-aldosterone system [16]. However, the role of the latter mechanism has not yet been fully elucidated. Some earlier studies suggest that plasma aldosterone level in patients with resistant hypertension is closely related to severity of OSA [16], especially if dietary sodium intake is increased [17]. In line with these findings, it was reported that patients with OSA showed elevated aldosterone excretion and plasma aldosterone levels with concomitant suppression of plasma renin activity (PRA) [18]. On the other hand, some studies showed no significant changes in plasma aldosterone alone [19], or aldosterone and PRA [20]. However, in these studies PRA and aldosterone were assessed only in the baseline conditions. To our best knowledge, there have been no previous reports evaluating aldosterone levels in the saline infusion test, which principle is that control of aldosterone is deteriorated and not suppressed in response to excessive salt and water load.

Therefore, in this study, we sought associations among severity of OSA, plasma aldosterone (both baseline and after saline infusion), PRA, and altered patterns of blood pressure in patients with resistant hypertension.

Material and methods

Study population

The study was carried out among patients with established diagnosis of resistant hypertension treated at university-affiliated Department of Hypertension and Internal Medicine in Szczecin. Overall, we included consecutive 65 hypertensive patients (19 females, 46 males) who were referred to our unit for evaluation for possible OSA due to typical symptoms (unexplained daytime sleepiness, restless sleep, loud snoring, morning headaches etc.). Of them, 18 patients (28.6%) received angiotensin converting enzyme inhibitors (ACEI), 37 (56.9%) angiotensin II receptor blockers, 39 (60%) beta blockers, 42 (64.6%) calcium channel blockers (CCB), 49 (75.4%) diuretics, and 21 (32.8%) other antihypertensive medications. We excluded patients with prior diagnosis of primary hyperaldosteronism and those who were treated with spironolactone. Based on past medical history and medical records, we collected data on past cardiovascular events, dyslipidemia, chronic kidney disease, and type 2 diabetes.

Measurements

In all cases we measured height and weight and calculated body mass index (BMI). In 53 patients we performed 24-hour blood pressure monitoring (ABPM) (Spacelabs Healthcare) and analyzed 24-hour, daytime and nocturnal systolic, diastolic, and mean blood pressure. All patients underwent evaluation for OSA using a portable sleep recorder system (Embletta Gold 2003005; Embla Systems) which computes the AHI. Based on AHI, we quantified severity of OSA as mild (5–15 events per hour), moderate (15–30 events per hour) and severe (above 30 events per hour), according to current guidelines [7, 8].

PRA (normal range: 0.51–2.64 ng/ml/h) and plasma aldosterone (normal range: 10–160 pg/ml) were measured using commercially available assays. From these measurements we calculated the aldosterone-to-renin ratio (ARR). Aldosterone and PRA were measured at the baseline and after intravenous infusion of 2,000 ml isotonic saline (normal range: 6–75 pg/ml). The saline infusion test is performed in our center as a routine procedure in cases with resistant hypertension.

Statistical analyses

Descriptive statistics included frequency distribution for categorical variables and means, standard deviation, and range for continuous variables. Differences among groups were evaluated by non-parametric methods (Mann-Whitney U test and Kolmogorov-Smirnov test) for continuous variables and by

Chi square test for dichotomous variables. Logistic regression was used to evaluate the relationship between severity of OSA and 24-hour ABPM values adjusted for age and BMI. Linear Spearman's rank correlation coefficients were used to determine the associations between AHI, blood pressure, PRA, and aldosterone. P values <0.05 (two-sided) were considered significant. All analyses were carried out in Statistica (Statsoft, Poland).

Results

As summarized in Table I, all cases were overweight or obese. Mean PRA, aldosterone and ARR were within normal range. However, mean aldosterone level in response to saline infusion was increased above normal upper limit. Mean AHI was 31.5 ± ± 24.9 per hour. As many as 72% of patients displayed abnormal lipid profiles and 19% had ischemic heart disease. More than 50% of patients had type 2 diabetes. A 24-hour ABPM revealed that 68% of patients had an altered pattern of blood pressure (dipping or reverse dipping hypertension).

AHI was inversely correlated with PRA and positively with weight, BMI, plasma aldosterone, ARR, and aldosterone after saline load (Table II). We could not find significant correlations between AHI and blood pressure values recorded in ABPM. Similarly, in the regression analyses, AHI adjusted for age and

Table I. Baseline characteristics of the study participants

Continuous variables	Mean	SD	Range
Age (years)	54.93	11.56	27–79
Height [m]	1.709	0.09	1.52–1.9
Weight [kg]	100.96	21.92	58.1–164.2
Body mass index [kg/m^2]	34.45	6.63	28.0–52.9
24-h systolic blood pressure [mmHg]	132.65	16.01	104–197
24-h diastolic blood pressure [mmHg]	77.95	10.61	59–117
24-h mean arterial pressure [mmHg]	96.35	12.2	78–143
Daytime systolic blood pressure [mmHg]	134.85	15.97	109–201
Daytime diastolic blood pressure [mmHg]	80.05	10.36	59–119
Daytime mean arterial pressure [mmHg]	98.41	12.62	68–145
Nocturnal systolic blood pressure [mmHg]	128.45	17.37	96–189
Nocturnal diastolic blood pressure [mmHg]	73.61	12.0	53–114
Nocturnal mean arterial pressure [mmHg]	91.69	14.71	54–140
Plasma renin activity [ng/ml/h]	1.59	0.86	0.54–5.48
Aldosterone [pg/ml]	166.07	58.02	66–338
Aldosterone-to-renin ratio	13.06	8.21	1.1–50.0
Aldosterone after saline infusion [pg/ml]	78.27	38.77	6.7–154.0
Plasma renin activity after saline infusion [ng/ml/min]	2.57	4.46	0.42–24.9
Apnoea-Hypopnoea Index	31.49	24.86	2.1–140.2
Categorical variables	Number	Percent	
Myocardial infarction	4	6.2	
Ischaemic heart disease	12	18.5	
Stroke	2	3.1	
Diabetes	33	50.8	
Chronic kidney disease	4	6.2	
Abnormal lipid profile	47	72.3	
Dippers	17	32.1	
Non-dippers	27	50.9	
Reverse dippers	9	17.0	

24-h ABPM was measured in 53 of 65 patients

BMI was not associated with systolic and diastolic blood pressure evaluated within the whole period of 24 hours, daytime as well as nighttime (P > 0.05 for all calculations).

Along with increases in the severity of OSA, frequencies of diabetes, abnormal lipid profiles and ischemic heart disease, and to a lesser extent, myocardial infarction and stroke also increased (Table III). Moreover, patients with a severe type of OSA (AHI above 30) in comparison to those with mild OSA (AHI from 5 to 15) had significantly higher PRA and aldosterone (either at the baseline or after saline load) but comparable values of blood pressure in ABPM (Table IV). Similarly, we did not find significant impact of OSA severity on the frequency of normal and abnormal patterns of blood pressure (Table V).

Table II. Correlations between the Apnoea–Hypopnoea Index and the measured outcomes

Variable	R	P value
Age (years)	0.09	0.462
Height [m]	0.23	0.069
Weight [kg]	0.35	0.004
Body mass index [kg/m^2]	0.27	0.024
24-hour systolic blood pressure [mmHg]	–0.13	0.292
24-hour diastolic blood pressure [mmHg]	–0.09	0.458
24-hour mean arterial pressure [mmHg]	–0.07	0.605
Daytime systolic blood pressure [mmHg]	–0.13	0.310
Daytime diastolic blood pressure [mmHg]	–0.09	0.475
Daytime mean arterial pressure [mmHg]	–0.09	0.477
Nocturnal systolic blood pressure [mmHg]	–0.11	0.374
Nocturnal diastolic blood pressure [mmHg]	–0.10	0.442
Nocturnal mean arterial pressure [mmHg]	–0.09	0.484
Plasma renin activity [ng/ml/h]	–0.46	0.001
Aldosterone [pg/ml]	0.57	0.001
Aldosterone-to-renin ratio	0.65	0.001
Aldosterone after saline infusion [pg/ml]	0.69	0.001
Plasma renin activity after saline infusion [ng/ml/h]	0.08	0.661

R refers to the Spearman rank correlation coefficient

Discussion

The major finding from our study is that patients with OSA and resistant hypertension had normal PRA, plasma angiotensin, and angiotensin to renin ratio but, as we report here for the first time, significantly diminished aldosterone response to saline load. Moreover, the magnitude of this response was clearly associated with the severity of OSA: patients with AHI above 30 per hour had a 2-fold higher aldosterone levels than those with mild OSA. Earlier studies evaluating baseline activity of the renin-angiotensin-aldosterone system (RAAS) in OSA yielded inconsistent results [16, 18–20]. However, the interpretation of studies, including the current study, that address this issue to resistant hypertension is often limited because treatment of this condition usually requires administration of medications (given in high doses) known to affect RAAS. ACEI and angiotensin receptor blockers increase PRA and lower aldosterone levels. Beta blockers can reduce PRA, leading to a falsely elevated angiotensin to renin ratio, whereas dihydropyridine CCB can reduce aldosterone levels, potentially leading to a falsely normal angiotensin to renin ratio in primary hyperaldosteronism. Majority of diuretics tend to induce secondary hyperaldosteronism and spironolactone, an aldosterone receptor antagonist, can raise plasma renin levels. In this study, to minimize the drug class effect on RAAS, we excluded cases treated with spironolactone.

Aside from these methodological challenges, our results suggest that RAAS in OSA may be up-regulated regardless of baseline PRA and aldosterone

Table III. Frequency distribution of lipid disorders, chronic kidney disease and main cardiovascular comorbidities in relation to the Apnoea–Hypopnoea Index

Condition	Apnoea–Hypopnoea Index		
	5–15/h (n = 18)	15–30/h (n = 16)	> 30/h (n = 31)
Myocardial infarction	0 (0%)	2 (12.5%)	2 (6.4%)
Ischaemic heart disease	2 (11.1%)	4 (25%)	6 (19.3%)
Stroke	0 (0%)	0 (0%)	2 (6.4%)
Diabetes	2 (11.1%)	7 (43.7%)	24 (77.4%)
Chronic kidney disease	1 (5.5%)	0 (0%)	3 (9.6%)
Lipid disorders	15 (83.3%)	11 (68.7%)	21 (67.7%)

Data are presented as numbers with the condition. $\chi 2$ statistics; p = 00004

Table IV. Differences in studied parameters between patients with low and high the Apnoea–Hypopnoea Index

Variable	Apnoea–Hypopnoea Index		
	5–15 (n=15)	> 30 (n = 26)	P value
Age (years)	53.27 ± 12.18	57.32 ± 10.72	0.352
Height [m]	1.67 ± 0.08	1.72 ± 0.09	0.057
Weight [kg]	93.12 ± 16.31	106.2 ± 26.7	0.093
Body mass index [kg/m^2]	33.25 ± 4.62	35.62 ± 8.26	0.431
24-hour systolic blood pressure [mmHg]	134.4 ± 14.3	131.2 ± 17.0	0.231
24-hour diastolic blood pressure [mmHg]	78.47 ± 9.13	77.43 ± 11.49	0.390
24-hour mean arterial pressure [mmHg]	96.20 ± 9.65	93.50 ± 22.21	0.361
Daytime systolic blood pressure [mmHg]	137.05 ± 14.0	133.6 ± 17.26	0.122
Daytime diastolic blood pressure [mmHg]	80.76 ± 8.78	79.50 ± 11.59	0.393
Daytime mean arterial pressure [mmHg]	98.80 ± 9.39	97.96 ± 15.12	0.784
Nocturnal systolic blood pressure [mmHg]	129.8 ± 15.54	126.4 ± 18.35	0.290
Nocturnal diastolic blood pressure [mmHg]	74.29 ± 10.12	72.80 ± 12.78	0.388
Nocturnal mean arterial pressure [mmHg]	91.80 ± 10.23	90.15 ± 17.02	0.359
Plasma renin activity [ng/ml/h]	2.11 ± 1.15	1.25 ± 0.59	0.0001
Aldosterone [pg/ml]	139.3 ± 46.5	188.83 ± 44.77	0.0001
Aldosterone-to-renin ratio	8.01 ± 6.17	17.57 ± 8.33	0.0001
Aldosterone after saline infusion [pg/ml]	47.67 ± 21.93	104.48 ± 31.35	0.0001
Plasma renin activity after saline infusion [ng/ml/h]	3.54 ± 6.59	2.62 ± 1.81	0.590
Apnoea–Hypopnoea Index	7.53 ± 8.55	51.30 ± 21.06	0.0001

Table V. Blood pressure patterns in relation to the severity of obstructive sleep apnoea

Blood pressure pattern	Apnoea–Hypopnoea Index		
	5–15 (n = 18)	15–30 (n = 16)	> 30 (n = 30)
Dipping	6 (33%)	7 (44%)	16 (53%)
Non-dipping	11 (61%)	6 (38%)	10 (33%)
Reverse dipping	1 (6%)	3 (18%)	5 (16%)

$\chi 2$ statistics; p = 0.24

levels, the more that we found moderate to strong correlations between AHI and aldosterone (baseline and after suppression with saline), and ARR. These findings may be clinically relevant because aldosterone seems to play pathophysiological role in the relation between hypertension and OSA [16, 21–23].

It was demonstrated that aldosterone excess contributed to greater severity of OSA [21, 24]. In fact, the association between OSA and RAAS is even more complex because it may be influenced by other factors, such as coexisting obesity, excessive fat accumulation in depots outside of the subcutaneous tissue, or insulin resistance. Early studies showed higher aldosterone concentration in obese subjects than in their normal weight counterparts what might predispose them to the development of resistant hypertension [25]. Recently, Buglioni *et al.* found that aldosterone analyzed as a continuous variable was associated with hypertension, obesity, metabolic syndrome, high triglycerides, and chronic kidney diseases [26]. They suggested that aldosterone, even within the normal range, may be a biomarker of cardiorenal and metabolic disease. Accordingly, higher levels of aldosterone are present in obese and insulin-resistant patients as well as rodent models, leading to inflammation and oxidative stress and contributing to impaired insulin signaling, decreasing glucose transport and vascular dysfunction, and as a consequence – to the development of cardiovascular disease [27–30].

Reinforcing this suggestion, aldosterone has been shown to inhibit insulin effects in the vasculature inducing vascular insulin resistance [31]. On the other

hand, the positive associations between aldosterone concentrations with plasma glucose, insulin, C-peptides, and indices of insulin resistance and beta cell destruction has also been reported in a population of patients with essential hypertension [32], whereas surgical treatment or treatment with aldosterone antagonists in subjects with hyperaldosteronism rapidly and persistently restored sensitivity to insulin [33]. However, causal relationships between RAAS, obesity and glucose tolerance have not been yet elucidated [34]. In our study we found high rates of obesity and type 2 diabetes. Therefore, we cannot exclude that at the time of evaluation the associations between severity of OSA and RAAS components measured in this study were not triggered or magnified by coexisting excess body weight, insulin resistance, or resistant hypertension.

In our sample we also found high rates of cardiovascular events. This finding confirms a widely accepted view that a cluster of metabolic abnormalities, including obesity, hypertension, diabetes, abnormal lipid profiles, and OSA is a key risk factor for cardiovascular disease.

In conclusion, despite of normal basal PRA and aldosterone concentration, patients with resistant hypertension and OSA had impaired response to saline load and a rate of this impairment depended on the severity of OSA.

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