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RAPID COMMUNICATION

Have Main Types of Primary Aldosteronism Different Phenotype?

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Summary

Primary aldosteronism (PA) is the most common cause of endocrine hypertension with a high frequency of cardiovascular complications. We found in our previous study higher occurrence of metabolic disturbances in patients with idiopathic hyperaldosteronism (IHA) compared to subjects with aldosterone-producing adenoma (APA). The aim of our present study is to evaluate potential differences in the frequency of end-organ damage (arterial stiffness and microalbuminuria) between two main types of PA. The diagnosis of the particular form of PA was based on adrenal venous sampling and/or histopathological examination. We analyzed clinical and laboratory data from 72 patients with PA (36 with IHA, 36 with APA). The arterial stiffness was expressed as the carotid-femoral pulse wave velocity (PWV) and the renal damage as urinary albumin excretion levels (UAE). Patients with IHA had significantly ($p<0.03$) higher prevalence of metabolic syndrome (17 % in APA, 35 % in IHA), higher triglycerides (1.37±0.71 mmol/l in APA, 1.85±0.87 mmol/l in IHA), lower HDL cholesterol (1.25±0.28 mmol/l in APA, 1.06±0.25 mmol/l in IHA), higher PWV (7.91±1.61 m/s in APA, 8.99±1.77 m/s in IHA) and higher UAE (12.93±2.21 mg/l in APA, 28.09±6.66 mg/l in IHA). It seems that patients with IHA may have a slightly different phenotype compared to APA.

Key words

Primary aldosteronism • Aldosterone producing adenoma • Idiopathic hyperaldosteronism • Pulse wave velocity • Metabolic profile

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The prevalence of primary aldosteronism (PA) characterized by autonomous overproduction of aldosterone is in the non-selected hypertensive population around 11 % (Rossi *et al.* 2006a) and in a preselected population of patients with severe hypertension 19 % (Štrauch *et al.* 2003). The main forms of PA are idiopathic aldosteronism (IHA) caused by bilateral adrenal hyperplasia and unilateral aldosterone producing adenoma (APA). Other forms of PA are less common, and include unilateral hyperplasia and rare familial aldosteronism type I and II. Recent data show that patients with PA have a significantly higher rate of cardiovascular risk than patients with essential hypertension (EH) (Catena *et al.* 2008). There is a higher rate of left ventricular hypertrophy (Rossi *et al.* 1996), stroke, atrial fibrillation, myocardial infarction (Milliez *et al.* 2005), higher urinary albumin excretion (Rossi *et al.* 2006b), increased intima-media thickness of the common carotid artery (Holaj and Widimský 2008) and higher prevalence of metabolic syndrome (Fallo *et al.* 2006, 2008, Ronconi *et al.* 2010) in patients with PA. It was also reported that patients with PA have higher aortic wall stiffness measured by PWV compared to patients with EH (Strauch *et al.* 2006, Bernini *et al.* 2008). Specific treatment with adrenalectomy might reverse these changes (Strauch *et al.* 2008).

There are only few data regarding potential clinical differences between the two main types of primary aldosteronism. McAreavey published in 1983, that there is a similarity of idiopathic aldosteronism and essential hypertension and both these types of hypertension may differ from aldosterone producing

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adenoma (McAreavey *et al.* 1983). Young and Blumenfeld later showed differences between the two types of primary aldosteronism; patients with APA have more severe hypertension, more frequent hypokalemia, higher plasma aldosterone levels and are younger than those with IHA (Young and Klee 1988, Blumenfeld *et al.* 1994). In our last study we found differences in the prevalence of the metabolic syndrome and in lipid levels between APA and IHA. Patients with IHA have a higher prevalence of metabolic syndrome, higher levels of triglycerides and higher prevalence of hyperlipidemia than patients with APA (Šomlóová *et al.* 2010). We hypothesized that patients with IHA may have compared to APA higher frequency of end-organ damage due to metabolic disturbances. It has been previously demonstrated that arterial stiffness increases with blood pressure levels, age, obesity, DM (Aoun *et al.* 2001, Mitchell *et al.* 2007), atherosclerosis (van Popele *et al.* 2001), end-stage renal disease (London *et al.* 1990) and lipid disorders (Wilkinson *et al.* 2002). Microalbuminuria levels may reflect metabolic and vascular abnormalities.

We retrospectively studied 72 patients with primary aldosteronism classified into IHA and APA according the guidelines (Funder *et al.* 2008). Patients were divided according to the subtypes in 2 subgroups – APA (32 pts.) and IHA (32 pts.) matched by age, sex and blood pressure levels. Subjects were recruited from patients referred to our Hypertension center in order to exclude secondary hypertension between the years 2004-2011. Patients with renal failure were not included into this study, and all the patients were on a normal sodium/potassium diet with no caloric restrictions. Previous anti-hypertensive therapy was withdrawn in all patients at least two weeks (in case of spironolactone at least 4 weeks) before the investigation. To standardize the treatment and to eliminate the interference of anti-hypertensive drugs with the renin-angiotensin-aldosterone system, the anti-hypertension therapy for all patients was switched to an alpha-blocker (doxazosin) and slow-releasing calcium channel blocker (verapamil). Patients with hypokalemia have continued with oral potassium supplementation. The suspicion of PA was based on the findings of aldosterone renin ratio (ARR) >30 (ng/dl)/(ng/ml/h), plasma renin activity (PRA) <0.7 ng/ml/h and plasma aldosterone >15 ng/dl when measured after two-hour upright position. The diagnosis of PA was confirmed by the lack of aldosterone suppression (<7 ng/dl) following an intravenous saline load (2 liters of 0.9 % saline infused over 4 hours). Differential diagnosis of PA forms (IHA and APA) was supported by a computed tomography scan and by a selective adrenal venous sampling (AVS). Adrenal venous sampling was performed without ACTH stimulation as recommended elsewhere (Funder *et al.* 2008). We used AVS criteria according to previously published guidelines (Funder *et al.* 2008), selectivity was defined as adrenal vein/inferior vena cava cortisol gradient >2 and the lateralization was considered to be present when the aldosterone/cortisol ratio at one side was at least 2-times greater than that in contralateral vein. In addition, the diagnosis of APA was confirmed when successful laparoscopic adrenalectomy was associated with normalization of plasma renin activity and plasma aldosterone levels, and by histological verification. All hormonal tests were performed by radioimmunoanalysis using commercially available kits (Immunotech, Beckman Coulter Company, Prague, Czech Republic). All other biochemical parameters were analyzed using multianalyzers (Hitachi 717, Boehringer Mannheim, Germany) in the Institutional Central Laboratory. Clinical blood pressure (BP) values were obtained using a validated oscillometric sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA). Three measurements of blood pressure were obtained in the sitting position after a five minute rest period. Final office blood pressure was calculated as average from the second and third blood pressure readings. The 24-hour ambulatory blood pressure monitoring was performed during hospitalization using an oscillometric device (SpaceLabs 90207, SpaceLabs Medical, Redmond, WA, USA). PWV was measured with the applanation tonometer Sphygmocor (AtCor Medical, Australia). Subjects were studied after overnight fasting and after a 15 minute resting period, during which the patient was in a supine position in a quiet room. Aortic PWV was assessed by the time difference between pulse wave upstrokes consecutively measured at the right common carotid artery and right femoral artery, then aligned by the ECG-based trigger. The 'percentage pulse height algorithm' was used to locate the foot of the pulse waves. To define the metabolic syndrome (MS) we used the common definition for clinical diagnosis of the MS published in 2009 (Alberti *et al.* 2009). The statistical analysis was performed by STATISTICA software vers.10 (Statsoft Inc, Tulsa, OK, USA). Data are expressed depending on the normal/non-normal distribution (Shapiro-Wilks W-test) as means ± standard deviations or means ± standard errors of means. Between-group comparisons were performed by two-tailed t-test for independent samples. The Kruskal-Wallis test was used for non-normally distributed variables. Pearson's correlation analysis and multiple regression analysis (stepwise forward method) were applied to assess the relationship among PWV/microalbuminuria and clinical/laboratory parameters (variables which significantly correlated in Pearson's correlation analysis entered multiple regression analysis). P-value <0.05 was considered significant.

The basic clinical characteristics of the studied groups are shown in Table 1. We reported no significant differences in age and duration of hypertension at the time of our investigation among the studied groups. As expected, BMI, triglycerides levels, the prevalence of the metabolic syndrome and hyperlipidemia was higher in patients with IHA. In addition, HDL cholesterol levels were lower in IHA. Aldosterone levels on the contrary were higher in patients with APA. There were no differences in the prevalence of glucose metabolism disorders and use of antidiabetic drugs among the groups. Microalbuminuria was significantly higher in patients with IHA; however, there were no intergroup differences in creatinine levels, GFR estimated with the Cockcroft formula and in age, blood pressure levels and the prevalence of diabetes. Microalbuminuria correlated with triglycerides level and with 24-hour systolic blood pressure, but after multiple regression analysis none of them remained significant predictor factor for microalbuminuria. The differences in hemodynamic parameters and arterial stiffness are summarized in Table 2. Central PWV was significantly higher in patients with IHA compared to patients with APA, while clinical blood pressure measured during the examination was comparable between the two groups. There were also no significant differences in 24-hour blood pressure monitoring. After multiple regressions analysis 24-hour systolic blood pressure and diastolic blood pressure were the main predictors of PWV. The difference in PWV remained significant after adjustments for 24-hour systolic blood pressure (SBP) and diastolic blood pressure (p=0.01 for PWV).

Table 1. Basic metabolic, biochemical and hormonal characteristics.

	n	APA	n	IHA	p
Sex (men %)	36	58.00	36	67.00	NS
Age, y	36	46.23 ± 11.41	36	48.93 ± 6.62	NS
Duration of hypertension, y	36	7.97 ± 6.51	36	10.93 ± 8.20	NS
Height, cm	36	174.50 ± 10.45	36	174.58 ± 7.66	NS
Weight, kg	36	85.76 ± 18.36	36	92.49 ± 13.33	NS
BMI, kg/m^2	36	28.17 ± 4.63	36	30.32 ± 3.59	0.031
Metabolic syndrome, %	36	17.00	36	39.00	0.035
Hyperlipidemia, %	36	42.00	36	72.00	0.009
Glucose metabolism disorders, %	36	11.00	36	25.00	NS
Serum sodium, mmol/l	36	144.03 ± 2.95	36	143.19 ± 2.63	NS
Serum pottasium, mmol/l	36	3.38 ± 0.51	36	3.63 ± 0.43	0.026
Serum creatinine, umol/l	36	78.33 ± 16.90	36	84.33 ± 20.07	NS
GFR, Cockcroft formula, ml/s	36	1.99 ± 0.53	36	2.01 ± 0.44	NS
Microalbuminuria, mg/l	18	12.93 ± 2.21	18	28.09 ± 6.66	0.038
Glucose level, mmol/l	34	4.83 ± 0.54	35	5.11 ± 0.83	NS
Total cholesterol, mmol/l	36	4.88 ± 0.96	35	4.83 ± 1.03	NS
Triglycerides, mmol/l	36	1.37 ± 0.71	35	1.85 ± 0.87	0.013
HDL cholesterol, mmol/l	36	1.25 ± 0.28	33	1.06 ± 0.25	0.003
LDL cholesterol, mmol/l	36	3.02 ± 0.84	33	2.87 ± 0.87	NS
Plasma aldosterone, ng/l	36	694.12 ± 76.67	36	453.12 ± 38.52	0.023
PRA, ug/l/h	35	0.43 ± 0.04	35	0.48 ± 0.04	NS
ARR	35	224.36 ± 38.45	35	126.11 ± 20.75	0.015

Abbreviations: APA – aldosterone producing adenoma, IHA – idiopathic hyperaldosteronism, BMI – body mass index, GFR – glomerular filtration rate, PRA – plasma renin activity, ARR – aldosterone-renin-ratio.

Table 2. Blood pressure levels and pulse wave velocity.

	n	APA	n	IHA	p
Systolic BP in 24 h, mm Hg	36	148.28 ± 12.79	33	148.24 ± 17.95	NS
Diastolic BP in 24 h, mm Hg	36	92.19 ± 8.40	33	90.63 ± 12.08	NS
HR in 24 h, min^{-1}	36	68.75 ± 9.22	33	68.14 ± 8.21	NS
Systolic BP, mm Hg	36	157.94 ± 20.74	36	159.92 ± 20.08	NS
Diastolic BP, mm Hg	36	91.19 ± 12.17	36	91.28 ± 12.36	NS
HR, min^{-1}	36	68.22 ± 12.73	36	65.08 ± 10.31	NS
Aortic augmentation index, %	34	25.94 ± 8.56	36	23.95 ± 8.97	NS
PWV, m/s	36	7.91 ± 1.61	36	8.99 ± 1.77	0.008

Abbreviations: APA – aldosterone producing adenoma, IHA – idiopathic hyperaldosteronism, BP – blood pressure, HR – heart rate, PWV – pulse wave velocity.

Our data indicate that between APA and IHA are not only metabolic differences but also differences in studied markers of end-organ damage. Patients with IHA have not only significantly higher prevalence of metabolic syndrome, hyperlipidemia, higher BMI, triglyceride levels, lower HDL cholesterol levels but also a significantly higher aortic stiffness measured by PWV and higher urinary albumin excretion compared to patients with APA. The precise mechanism responsible for metabolic and structural changes in patients with IHA is not clear and may involve several potential factors. Differences in arterial stiffness can be caused by dyslipidemia, higher BMI and local effect of aldosterone on the arterial wall. We found positive correlation between PWV and duration of hyperlipidemia, triglyceride levels and a negative correlation with HDL cholesterol levels; however, after a multiple regression analysis only 24-hour SBP remained a significant positive predictor factor of PWV. On the other hand arterial stiffness increases in obese patients and patients with lipid disorders (Mitchell *et al.* 2007). Proximal arterial compliance correlates with triglyceride levels, HDL cholesterol levels and with insulin levels (Neutel *et al.* 1992) and there might be a relationship between oxidative modification of LDL cholesterol and arterial distensibility (Toikka *et al.* 1999). The effect of aldosterone on the arterial wall may potentially also play a role in observed differences in PWV. Aldosterone overproduction has a negative effect on aortic stiffness (Strauch *et al.* 2006) and a successful treatment with adrenalectomy reverses this effect (Strauch *et al.* 2008). The mechanism of aldosterone-induced fibrosis of the vessel wall is still unclear, aldosterone may increase collagen I synthesis and the number of endothelin receptors (Fullerton and Funder 1994, Robert *et al.* 1994). Aldosterone has also a rapid nongenomic effect on the vessel wall mediated via activation of intracellular mineralocorticoid receptors (MR) (Funder 2006). Through MR can aldosterone directly mediate effects in target organs independent of the regulatory roles of angiotensin II (Duprez 2007) and MR receptors could be localized in endothelial and vascular smooth muscle cells (Bauersachs and Fraccarollo 2006). Extra-adrenal synthesis of aldosterone in vascular wall and a localized paracrine effect may also play a role in vascular changes (Duprez 2007). However, we have not found any correlation between aldosterone levels and arterial stiffness, but the measured plasma aldosterone levels do not necessarily reflect the local effect of aldosterone on the arterial wall. Patients with PA have higher urinary albumin excretion compared to age and BP matched patients with EH (Catena *et al.* 2008). Several factors as endothelial dysfunction or glomerular damage may play a role (Rossi *et al.* 2006b). Albuminuria could be also due to the impairment of proximal tubular reabsorption caused by hypokalemic nephropathy (Ribstein *et al.* 2005). However, in the PAPY study, there were no differences in urinary albumin excretion between patients with normokalemic and hypokalemic PA (Rossi *et al.* 2006b). In our study there was a positive correlation between microalbuminuria and the triglycerides level and also with 24-hour systolic blood pressure, but after multiple regression analysis none of them remained significant predictor factor for microalbuminuria. We have not found any difference in urinary albumin excretion between normokalemic and hypokalemic patients.

In conclusion we have shown in our study that there might be not only metabolic differences between patients with APA and IHA but also differences in the frequency of end-organ damage. It thus seems that IHA may have slightly different phenotype compared to APA.

Conflict of Interest

There is no conflict of interest.

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