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 adrenectomy 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
levels may reflect metabolic and vascular abnormalities. The diagnosis of PA 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 sphygmmomanometer (Dinamap, Critikon, Tampa, FL, USA). PWV was assessed 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 sphygmmomanometer (Dinamap, Critikon, Tampa, FL, USA). 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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. |
|---------------------------------------------------------------|
|                  | APA          |          | 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/m²       | 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 potassium, 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.

|                          | APA               | HIA               | 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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