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Comparison of biomarkers of endothelial dysfunction and microvascular endothelial function in patients with primary aldosteronism and essential hypertension

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Abstract

Introduction: Studies have shown that primary aldosteronism (PA) has a higher risk of cardiovascular events than essential hypertension (EH). Endothelial dysfunction is an independent predictor of cardiovascular events. Whether PA and EH differ in the endothelial dysfunction is uncertain. Our study was designed to investigate the levels of biomarkers of endothelial dysfunction (Asymmetric dimethylarginine, ADMA; E-selectin, and Plasminogen activator inhibitor-1, PAI-1) and assess the microvascular endothelial function in patients with PA and EH, respectively.

Methods: The biomarkers of endothelial dysfunction were measured by enzyme-linked immunosorbent assay (ELISA). Microvascular endothelial function was evaluated by Pulse amplitude tonometry (PAT).

Results: Thirty-one subjects with EH and 36 subjects with PA including 22 with aldosterone-producing adenoma (APA) and 14 with idiopathic hyperaldosteronism (IHA) were enrolled in our study. The ADMA levels among the three groups were different (APA 47.83 (27.50, 87.74) ng/ml vs EH 25.08 (22.44, 39.79) ng/ml vs IHA 26.00 (22.23, 33.75) ng/ml; $p = 0.04$), however, when the APA group was compared with EH and IHA group, there was no statistical significance (47.83 (27.50, 87.74) ng/ml vs 25.08 (22.44, 39.79) ng/ml for EH, $p = 0.11$; 47.83 (27.50, 87.74) ng/ml vs IHA 26.00 (33.75) ng/ml, $p = 0.07$). The results of ADMA levels are presented as Median (p25, p75). Whereas, levels of PAI-1 and E-selectin, microvascular endothelial function were not significantly different between PA and EH subjects.

Conclusions: Our study shows no significant differences between PA and EH in terms of biomarkers of endothelial dysfunction and microvascular endothelial function. The microvascular endothelial function of PA and EH patients is comparable.

Keywords

Primary aldosteronism, peripheral arterial tonometry, asymmetric dimethylarginine, E-selectin, plasminogen activator inhibitor-1

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Introduction

Primary aldosteronism (PA) is the most common cause of endocrine hypertension.[1] Recent studies have revealed that the prevalence of PA is between 3.2% and 12.7% in primary care or between 1% and 29.8% in referral centers of hypertensive patients.[2] PA is characterized by inappropriate aldosterone secretion, hypertension, hypokalemia, and suppressed plasma renin. It is most commonly caused by aldosterone-producing adenoma (APA), bilateral idiopathic hyperaldosteronism (IHA), less commonly caused by unilateral hyperplasia or primary adrenal hyperplasia

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(PAH), and the rare causes include adrenal carcinoma or inherited conditions of familial hyperaldosteronism and others.[3]

Several important studies have shown that PA patients have a higher risk of cardiovascular complications compared to patients with essential hypertension (EH), with increased incidence of coronary artery disease, heart failure, atrial-fibrillation, and stroke.[4,5] However, such an increase in cardiovascular events in PA patients may not only be ascribed to the increased blood pressure, but be a direct consequence of hypersecretion of aldosterone secretion in PA which can cause endothelial dysfunction and increased arterial stiffness independently.[6,7] Long term exposure to the high aldosterone levels may eventually result in cardiovascular damage.

Endothelial dysfunction plays a crucial role in the pathophysiology of atherosclerosis and is associated with the development of cardiovascular disease.[8] Pulse amplitude tonometry (PAT), a novel non-invasive method to measure the endothelial function of finger microcirculation, which can obtain more reliable data and has lesser interference factors than the previous measurement of endothelial function by Flow-mediated dilation (FMD).[9] Results of PAT were automatically calculated by a computerized algorithm, the reactive hyperemia index (RHI) and augmentation index (AI) were used as parameters for evaluating vascular endothelial function and arterial stiffness respectively.[10] Generally, FMD reflects the endothelial function of macro and middle-sized blood vessels, while RHI reflects microvascular endothelial function.[9] Currently, studies on microvascular endothelial function assessed by PAT in PA are sparse and have no clear conclusion.[11–13]

Asymmetric dimethylarginine (ADMA), E-selectin, and Plasminogen Activator Inhibitor 1 (PAI-1) are commonly used biomarkers reflecting endothelium function.[9] However, the role of these endothelial biomarkers in PA are not been fully reported, and PAI-1 has not been reported yet.[14,15]

Our study was designed to compare serum levels of ADMA, E-selectin, PAI-1, and microvascular endothelial function assessed by PAT in patients with PA (including APA and IHA) and EH.

Materials and methods

Subjects

We collected 22 patients with APA, 14 patients with IHA, and 31 patients with EH who were finally diagnosed from the hypertensive patients consecutively. All hypertensive patients were referred to the department of endocrinology for diagnosis and treatment in the first Affiliated Hospital with Nanjing Medical University during April, 2017 to September, 2018. This study was approved by the Ethics Committee of the same hospital, and from all patients informed consent. Medical history (including oral potassium supplement and antihypertensive drugs), blood pressure, biochemical and hormone investigations, imaging studies, and microvascular endothelial (RHI-PAT) of participants were collected. All hypertensive patients were examined during hospitalization and PA patients were examined before specific treatment (surgical or medical). Fasting venous blood samples were withdrawn and collected on the second day of admission to examine the biochemical index and hormone levels and for further detection of biomarkers of endothelium dysfunction. Subjects with incomplete data or other causes of secondary hypertension were ruled out. EH was diagnosed according to the following criteria: patients with systolic blood pressure ($\geqslant$140 mmHg) and/or diastolic blood pressure ($\geqslant$90 mmHg) confirmed by three different occasions or have been taking medicine for hypertension; other secondary hypertension (such as pheochromocytoma and Cushing syndrome) should be excluded. The diagnosis of PA was according to the report of the guidelines "The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline" in 2016.[16] Plasma aldosterone concentration-to-plasma renin activity (ARR) was recommended to screen patients with PA, prior to testing, hypokalemia should be corrected to normal range and the antihypertensive drugs which can interfere with aldosterone and renin measurements should be discontinued or substituted with other agents (Verapamil slow-release or/and Prazosin hydrochloride). Saline infusion and captopril challenge test are mostly used in our center to definitely confirm or exclude the diagnosis of PA when patients with ARR $>$ 30 (ng/dl/ng/ml/h). Generally, two kinds of diagnostic tests are carried out, as long as one meets the diagnostic criteria of PA, that is, diagnostic PA. Saline infusion test, post-infusion plasma aldosterone levels $>$10 ng/dl are a sign of very probable PA. Captopril challenge test, the plasma aldosterone is normally suppressed by captopril ($>$30%), while patients with PA can remains elevated and PRA remains suppressed. Then, CT and adrenal venous sampling (AVS) were used to distinguish between APA and IHA. The unstimulated sequential bilateral AVS was used in our center, the selectivity index and lateralization index cut-offs used for adrenal vein sampling are all 2:1.

Measurement of endothelial function by PAT

PAT was used to assess the endothelial function by measuring the pulse amplitude of one finger on each hand at rest and after induced reactive hyperemia (Endo-PAT2000, Itamar Medical, Caesarea, Israel). It includes three steps: baseline, occlusion, and hyperemia. Firstly, it generates an inflation pressure on each of the fingers which was set to 10 mmHg below the subject's diastolic blood pressure or at

least 70 mmHg. After baseline pulse amplitude was recorded from both fingers for 5 min and 45 s, the arterial flow was occluded for 5 min by a cuff placed on a proximal forearm with occlusion pressure higher than systolic blood pressure (SBP). Following cuff release, pulse amplitude was recorded for up to 5 min. During the process the pulse amplitude was recorded form both fingers, the pulse amplitude recordings are digitized and analyzed by an automated proprietary algorithm. Reactive hyperemia index (RHI) reflects microvascular endothelial function and augmentation index (AI) reflects arterial stiffness. In 2004, Mayo clinic found that the PAT-RHI index of 1.67 for the diagnosis of endothelial dysfunction, with a sensitivity of 82% and a specificity of 77%.[17]

FMD and PAT are useful non-invasive methods to assess the endothelial function, both of them are strongly related to cardiovascular risk factors and cardiovascular events.[18] However, FMD measurement has several interference factors, it is highly dependent on operator expertise and was susceptible to neurologic and environmental factors, while PAT may be a better alternative technique for it.[9]

Measurement of ADMA, E-selectin and PAI-1 concentrations

Fasting venous blood samples were collected on the second day of admission and centrifuged for serum, then stored at −80°C until assay, centrifuged again before analysis. The concentrations of ADMA, E-selectin, and PAI-1 were detected by enzyme-linked immunosorbent assay (ELISA) (Human ADMA/E-selectin/PAI-1 ELISA Kit, CUSABIO, WuHan, China). The analytical sensitivity for ADMA/E-selectin/PAI-1 was 1.95, 0.078, and 2.201 ng/ml, respectively. Intra-assay and inter-assay CV for ADMA/E-selectin/PAI-1 were all $<8\%$ and 10%, respectively. (All samples were obtained with patient's consent).

Other indicators

Homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin resistance with the following formula: HOMA-IR = Fasting blood glucose (FBG) (mmol/l) × Fasting insulin (FINS) (μU/ml)/22.50.

Left ventricular mass index (LVMI) was used to evaluate left ventricular hypertrophy (LVH), doppler echocardiography was performed to measure the left ventricular end-diastolic dimension (LVDd), interventricular septal thickness (IVST), and posterior wall thickness (PWT), and calculated the average value measured three times. Left ventricular mass (LVM) was estimated according to the Devereux correction formula. LVMI was calculated by dividing the LVM by the body surface area (BSA). LVH diagnosis was based on left ventricular mass index (LVMI), male $>125\ g/m^2$ and female $>120\ g/m^2$.

Statistical analysis

The SPSS 20.0 software was used for statistical analysis. Data distribution normality was tested with Kolmogorov–Smirnov test. Results are presented as mean ± SD or median for continuous variables and as percentages for categorical variables. Student's *t*-test or Mann–Whitney *U* test was used to compare continuous variables for two groups, and ANOVA with the SNK post hoc test or Kruskal–Wallis *H* test was used for the three groups. Categorical variables were analyzed by chi square test. The relationship between the two parameters was investigated by Spearman correlation. A value of $p<0.05$ was considered to indicate statistical significance.

Results

The clinical and biological characteristics of the 22 subjects with APA, 14 subjects with IHA and 31 subjects with EH are summarized in Table 1. There were no significant differences in Sex, Age, BMI, Duration of hypertension, SBP, DBP among the three groups. The concentrations of serum potassium were significantly lower in patients with PA than in patients with EH, especially in APA subgroup. The percentage of hypokalemia were significantly higher in patients with PA compared to patients with EH, especially in APA subgroup. PRA was significantly lower and ARR was significantly higher in PA group, while no difference between APA and IHA. No significant differences in aldosterone, left ventricular mass index (LVMI), lipoprotein-associated phospholipase A2 (LP-PLA2), serum creatinine, and other resting parameters between PA and EH was shown in our study.

The ADMA levels among the three groups were different (APA 47.83 (27.50, 87.74) ng/ml vs EH 25.08 (22.44, 39.79) ng/ml vs IHA 26.00 (22.23, 33.75) ng/ml; $p=0.04$), however, when the APA group was compared with the EH group and the IHA group, there was no statistical significance (47.83 (27.50, 87.74) ng/ml vs 25.08 (22.44, 39.79) ng/ml for EH, $p=0.11$; 47.83 (27.50, 87.74) ng/ml vs IHA 26.00 (33.75) ng/ml, $p=0.07$). With further analysis there was no significant difference in ADMA levels between PA and EH (30.13 (23.97, 58.28) ng/ml vs 25.08 (22.44, 39.79) ng/ml, $p=0.14$). No significant differences were found for the levels of PAI-1 and E-selectin among the three groups (Table 2). Microvascular endothelial function and arterial stiffness in patients with EH, APA, and IHA are shown in Table 3. We did not find any significant differences in RHI, AI and other parameters among the three subgroups.

We further analyzed the correlation between biomarkers of endothelial dysfunction (ADMA, E-selectin, and PAI-1) and other relevant indicators. No correlations were found between biomarkers of endothelial dysfunction and hormonal levels (aldosterone), cardiovascular traditional

Table 1. Clinical and biological characteristics of the subjects.

Variables	EH ($n=31$)	APA ($n=22$)	IHA ($n=14$)	p
Sex, male/female	14/17	10/12	8/6	0.73
Age, year	49.29 ± 12.71	52.09 ± 10.96	52.00 ± 14.38	0.67
BMI, kg/m^2	26.13 ± 4.99	25.67 ± 3.04	25.94 ± 2.55	0.92
Waist, cm	90.27 ± 12.08	87.45 ± 7.96	89.43 ± 6.80	0.59
Duration of hypertension, year	8.00 (4.00, 12.00)	8.00 (3.00,14.25)	8.50 (2.00,11.75)	0.96
SBP, mmHg	142.9 ± 17.74	140.5 ± 16.84	152.6 ± 24.76	0.17
DBP, mmHg	86.19 ± 15.49	86.27 ± 12.14	87.57 ± 13.53	0.95
Serum potassium, mmol/l	3.91 ± 0.51	3.26 ± 0.48*	3.58 ± 0.53†‡	**<0.01**
Hypokalemic percentage, *n* (%)	6 (19.4)	15 (68.2)*	5 (35.7)	**<0.01**
Total cholesterol, mmol/l	4.88 ± 1.25	4.37 ± 1.01	4.40 ± 1.01	0.20
Triglycerides, mmol/l	1.50(1.21, 2.05)	1.32(0.91, 1.75)	1.26 (0.90, 1.46)	0.09
HDL, mmol/l	1.15 ± 0.29	1.18 ± 0.26	1.15 ± 0.22	0.92
LDL, mmol/l	3.05 ± 0.79	2.78 ± 0.85	2.76 ± 0.82	0.39
Lipoprotein a, mg/l	120.00 (86.00, 227.00)	140.50 (66.25,221.75)	211.00 (78.75,480.75)	0.28
Creatinine, µmol/l	66.60 (53.20,81.80)	67.40 (53.38,83.13)	68.35 (59.85, 88.45)	0.71
Fasting blood glucose, mmol/l	5.10 (4.66, 5.65)	5.01 (4.67, 5.47)	5.07 (4.58, 5.49)	0.90
HbA1c, %	5.60 (5.40, 5.80)	5.65 (5.23, 5.90)	5.55 (5.23, 5.98)	0.98
LP-PLA2, ng/ml	137.00 (112.00, 243.00)	178.50 (126.00,316.00)	106.00 (97.50, 201.50)	0.17
Fasting insulin, pmol/l	95.20 (49.70, 124.70)	63.25 (42.70, 84.85)	67.25 (53.63, 97.10)	0.11
C-peptide, pmol/l	878.40 (680.4, 1128.20)	852.30 (563.78, 962.88)	780.20 (679.43, 1441.50)	0.49
HOMA-IR	3.02 (1.56, 4.07)	2.07 (1.28, 2.53)	2.27 (1.60, 3.11)	0.11
LVMI, g/m^2	92.88 (80.88, 103.47)	94.51 (90.34, 101.03)	97.80 (82.17, 111.93)	0.83
Plasma renin activity, µg/l/h	2.23 (0.95, 5.54)	0.19 (0.10, 0.36)*	0.22 (0.15, 0.47)†	**<0.01**
Aldosterone, ng/l	179.60 (137.00, 212.10)	173.20 (142.98, 256.10)	173.05 (134.38,228.40)	0.86
ARR	7.95 (3.18, 18.71)	124.82 (49.65, 213.26)*	83.67 (39.95, 120.74)†	**<0.01**
Associated previous disease				
Coronary heart disease, *n* (%)	1 (3.2)	2 (9.1)	1 (7.1)	0.67
Stroke, *n* (%)	3 (9.7)	2 (9.1)	0 (0.00)	0.70
Diabetes mellitus, *n* (%)	5 (16.1)	1 (4.5)	2 (14.3)	0.49
Smoker, *n* (%)	7 (22.6)	2 (9.1)	1 (7.1)	0.36

EH: essential hypertension; APA: aldosterone-producing adenoma; IHA: idiopathic hyperaldosteronism; BMI: body mass index; y: year; SBP: systolic blood pressure; DBP: diastolic blood pressure. HDL: high-density lipoprotein; LDL: low-density lipoprotein; HBA1c: glycated hemoglobin; LP-PLA2: lipoprotein-associated phospholipase A2; HOMA-IR: homeostasis model assessment of insulin resistance; ARR: plasma aldosterone concentration-to-plasma renin activity.
*$p<0.05$ APA versus EH. †$p<0.05$ IHA versus EH. ‡$p<0.05$ IHA versus APA.

Table 2. Serum levels of ADMA, E-selectin, and PAI-1 between EH and PA (APA, IHA) subgroups.

Variables (ng/ml)	EH ($n=31$)	APA ($n=22$)	IHA ($n=14$)	p
ADMA	25.08 (22.44, 39.79)	47.83 (27.50, 87.74)*	26.00 (22.23,33.75)	**0.04**
E-selectin	2.31 (1.11, 4.32)	2.77 (1.69, 4.40)	3.33 (1.48, 4.27)	0.64
PAI-1	37.63 (10.57,116.19)	73.42 (11.60, 122.64)	46.85 (7.25, 135.52)	0.79

EH: essential hypertension; APA: aldosterone-producing adenoma; IHA: idiopathic hyperaldosteronism; AMDA: asymmetric dimethylarginine, E-selectin, PAI-1: Plasminogen activator inhibitor-1.
*$p<0.05$ APA versus EH.

Table 3. Microvascular endothelial function and arterial stiffness in patients with EH, APA, and IHA.

Variables	EH ($n=31$)	APA ($n=22$)	IHA ($n=14$)	p
RHI	1.86 (1.52, 2.14)	1.65 (1.47, 2.02)	1.72 (1.62, 2.07)	0.56
RHI abnormality percentage, *n* (%)	19 (61.3)	10 (45.5)	10 (71.4)	0.27
AI, %	4.00 (−11.00, 13.00)	11.00 (1.25, 17.50)	7.50 (1.75, 25.50)	0.28

EH: essential hypertension; APA: aldosterone-producing adenoma; IHA: idiopathic hyperaldosteronism; RHI: reactive hyperemia index; AI: augmentation index.

risk factors (glucose, dyslipidemia, age) as well as vascular stiffness with PAT-RHI (data not shown).

Discussion

Patients with PA were associated with higher cardiovascular complications than those with EH with comparable blood pressure level,[4] which may be related to the endothelial dysfunction induced by aldosterone.[19,20] Endothelial dysfunction was involved and usually considered as the trigger in the development of atherosclerosis and cardiovascular disease.[8] PAT-measured parameters and biomarkers related to endothelial dysfunction were used in our study to explore the endothelial functions in PA.

Previous studies have reported a significant decrease of FMD in PA compared with EH,[21,22] and the difference was more significant in APA subjects.[23] Till now, only two reports investigating RHI in PA were found and the conclusions were inconsistent.[11,12] Kishimoto et al.[11] have demonstrated that Log RHI was lower in APA and IHA patients than EH patients, while Chang et al.[12] reported no significant difference in RHI between PA and EH. Our study was consistent with Chang's[12] even divided PA into APA and IHA subgroups, we did not find any significant difference in RHI among the three groups. Previous studies have suggested that RHI may not be related to FMD,[24] in the way that FMD reflects macro and middle blood vessels function but RHI reflects microvascular endothelial function. It may implicate that FMD and RHI reflected endothelial function in different vascular beds. Therefore, no significant difference in RHI between PA and EH patients even among the three groups in our study might revealed that PA subjects may have comparable peripheral microvascular endothelial function with EH. Previous studies have shown that patients with PA had decreases FMD than EH and especially in APA subgroup.[21,23] In our study, we did not compare the FMD between PA and EH groups, whether PA patients had more severe macro and middle endothelial dysfunction but comparable microvascular endothelial function compared with EH patients, and the increased cardiovascular events in PA patients were mainly associated with macro and middle endothelial dysfunction, which still need further research.

The decreased nitric oxide (NO) bioavailability caused by the disorder of NO synthesis may be involved in endothelial injury.[14] ADMA is an endogenous inhibitor of nitric oxide synthase (NOS), which was first identified by Ogawa et al.[25,26] Many studies have revealed that ADMA is a risk factor for endothelial dysfunction and was associated with cardiovascular and renal disease.[27,28] Patients with EH was reported had higher ADMA concentrations than normotensive healthy controls,[29] and ADMA was strongly negatively correlated with Acetylcholine (Ach) -stimulated forearm blood flow which represents the endothelial function.[30] So far, only one study on the ADMA levels in PA patients was reported and showed that concentrations of ADMA were higher in PA patients than in healthy controls but no difference between patients with PA and EH.[14] In our study, concentrations of ADMA among the three groups were different, especially in APA group, however, when the APA group was compared with the EH group and the IHA group, there was no statistical significance, which may be related to the small numbers of patients included in our study. Therefore, it cannot be ruled out the presence of endothelial dysfunction in APA compared to EH and IHA, further research is needed. Selectin is an adhesion molecule, also known as endothelial-leukocyte adhesion molecule 1 (ELAM-1). It was primarily expressed in activated endothelial cells induced by inflammatory mediators, few expressed in resting endothelial cells.[31] Therefore, E-selectin is an indicator of endothelial activation. E-selectin seems to play a key role in the development of atherosclerosis and coronary heart disease (CHD) by mediating rolling and initial adhesion of leukocytes to endothelium.[32,33] It has been reported that elevated E-selectin levels in many diseases, such as heart failure,[34] acute myocardial infarction (AMI) and unstable angina,[35] essential hypertension[36] and type 2 diabetes.[37] The concentrations of E-selectin between patients with PA and patients with EH was not significant different in our study. To date, only another similar study reported a similar result.[15] In addition, we further divided the PA into IHA and APA subgroups, and also no difference was found, which may reveal that the endothelial activation was similar between PA and EH.

PAI-1 is a serine protease inhibitor, a major inhibitor of tissue and urokinase type plasminogen activators. The elevated concentrations of PAI-1 may lead to multiple inflammatory factors and excessive matrix deposition via suppress plasma fibrinolytic activity, which was responsible for tissue fibrosis.[38] It also revealed that overexpression of PAI-1 was associated with atherosclerotic plaque development,[39] and participating in the development of thrombotic cerebrovascular diseases, myocardial infarction, and many cardiovascular diseases.[40–42] Study have shown that aldosterone, glucose, insulin, and dyslipidemia may increase the synthesis and production of PAI-1,[43] and the increased PAI-1 mRNA induced by aldosterone may participate in the development of myocardial fibrosis.[44] Until now, there was no relationship between serum ADMA levels and aldosterone concentration or ARR, though aldosterone may increase the synthesis and production of PAI-1. In our study, no significant difference in PAI-1 concentrations between groups was found, and there was no correlation between PAI-1 and aldosterone. The comparable levels of PAI-1 maybe due to the same levels of aldosterone, glucose, lipoprotein among the three groups in our study. To our knowledge, this is the first

study to explore the serum PAI-1 levels in PA, and the role of PAI-1 in the development of cardiovascular disease in PA remains unclear, further research is still needed.

In our study, the levels of aldosterone in PA was comparable with EH, this was different from the previous study that aldosterone levels in PA was higher than in EH, especially in patients with APA, which may be due to the renin was mainly decreased, but aldosterone was not significantly higher in our PA patients and the small numbers of subjects, the use of antihypertensive drugs may also affect aldosterone levels.

Limitations and strength of the study

Our study was a cross-sectional study, and the sample size is too small, additional samples and further cohort investigation are needed. In addition, the differences between our results and others are likely because of the differences in subjects chosen and study design. And, it is the first study to explore PAI-1 levels in PA and evaluated the endothelium dysfunction parameters within different PA subtypes.

Conclusion

Our study shows no significant differences between patients with PA and EH in terms of biomarkers of endothelial dysfunction and microvascular endothelial function. The microvascular endothelial function of PA and EH patients is comparable. In future studies more focus can be placed on central hemodynamics of conduit vessels in order to clarify the effects of PA on macrovessels.

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