

Research Paper

The Association between Glomerular Hyperfiltration and Left Ventricular Structure and Function in Patients with Primary Aldosteronism

Min-Tsun Liao¹, Xue-Ming Wu², Chin-Chen Chang³, Che-Wei Liao¹, Ying-Hsien Chen⁴, Ching-Chu Lu⁵, Yen-Ting Lin⁴, Yi-Yao Chang⁶, Chi-Sheng Hung⁴, Lung-Chun Lin⁴, Chao-Lun Lai¹, Lian-Yu Lin⁴, Vin-Cent Wu⁴, Yi-Lwun Ho⁴, Kwan-Dun Wu⁴, Yen-Hung Lin⁴✉, and the TAIPAI Study Group

1. Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan;
2. Department of Internal Medicine, Taoyuan General Hospital, Taoyuan, Taiwan;
3. Department of Medical Image, National Taiwan University Hospital and National Taiwan University College of Medicine. Taipei, Taiwan;
4. Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine. Taipei, Taiwan;
5. Department of Nuclear Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine. Taipei, Taiwan;
6. Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan

✉ Corresponding author: Yen-Hung Lin, MD, PhD, Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan (e-mail: austinr34@gmail.com)

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Abstract

Background: Glomerular hyperfiltration has been recently noticed as an important issue in primary aldosteronism (PA) patients. However, its effect on the cardiovascular system remains unknown.

Methods: We prospectively analyzed 47 PA patients including 11 PA patients with estimated glomerular filtration rate (eGFR) > 130 ml/min per 1.73 m² (group 1), and 36 PA patients with eGFR 90-110 ml/min per 1.73 m² (group 2). Fourteen essential hypertension (EH) patients with eGFR 90-110 ml/min per 1.73 m² were included as the control group (group 3). Echocardiography including left ventricular mass index (LVMI) measurement and tissue Doppler imaging (TDI) was performed. Predicted left ventricular mass (LVM) was calculated. Inappropriate LVM was defined as an excess of > 35% from the predicted value.

Results: The value of LVMI decreased significantly in order from groups 1 to 3 (group 1>2>3). While group 2 had a significantly higher percentage of inappropriate LVM than group 3, the percentage of inappropriate LVM were comparable in groups 1 and 2. Group 1 had a higher mitral E velocity, E/A ratio than that of group 2. In the TDI study, the E/E' ratio also decreased significantly in order from groups 1 to 3 (group 1>2>3). Group 2 had lower E' than that of group 3, although the E' of group 1 and 2 were comparable.

Conclusions: Although PA patients with glomerular hyperfiltration were associated with higher LVMI, higher mitral E velocity, higher E/E' ratio, they had comparable E' with PA patients with normal GFR. This phenomenon may be explained by higher intravascular volume in this patient group.

Key words: Primary aldosteronism; Glomerular hyperfiltration; Left ventricular hypertrophy.

Introduction

Aldosterone as a hormone is involved in the regulation of body fluids as well as the maintenance of electrolyte balance and blood pressure (BP) homeostasis [1]. Primary aldosteronism (PA) is character-

ized by the overproduction of aldosterone by the adrenal glands and is the most frequent cause of secondary hypertension [2-4]. Although the prevalence of PA was approximately 1% in patients with hyper-

tension in older studies [5, 6], an increased prevalence of about 5-13% has been found in recent studies [4, 7], resulting from more effective methods of disease identification [8]. Long-term exposure to elevated aldosterone contributes to more cardiovascular events, such as myocardial infarction, atrial fibrillation, and left ventricle hypertrophy (LVH) independent of age, gender, and BP level [9]. Recent studies have also revealed that PA patients have significantly increased left ventricular mass (LVM) [10-12], more severe degree of diastolic function impairment [13], and myocardial fibrosis myocardial fibrosis [12, 14-16]. Activation of mineralocorticoid receptors might play a role in myocardial hypertrophy and cardiac remodeling in patients with PA [17]. The myocardial fibrosis might result from interactions of aldosterone with angiotensins, endothelin, and bradykinin [18]. Despite the direct effect of aldosterone, aldosterone also induces macrophage activation and low grade inflammation, which may play an important role in cardiac fibrosis [19]. The decrease of LVM and improvement of myocardial fibrosis after adrenalectomy [11, 14, 15] suggests that the alternation of cardiac structure is reversible (at least partially) after removal of excess aldosterone stimulation.

Glomerular hyperfiltration has been recently observed as a common phenomenon in PA patients [20-23]. A recent meta-analysis study reveals relative glomerular hyperfiltration to be the hallmark in PA and the phenomenon is beyond the effect of hypertension [24]. In patients with early stage EH, glomerular hyperfiltration indicates early target organ damage, such as LVH [25]. However, whether glomerular hyperfiltration is associated with cardiac structure or functional change in patients with PA is unclear.

The goal of this study is to evaluate the association between glomerular hyperfiltration with left ventricular (LV) structure and function in PA patients.

Method

Patients

This prospective study enrolled 47 PA patients including 11 PA patients with glomerular hyperfiltration (eGFR > 130 ml/min per 1.73 m², group 1) and 36 PA patients with normal eGFR (90-110 ml/min per 1.73 m², group 2) who were evaluated and registered in the Taiwan Primary Aldosteronism Investigation (TAIPAI) database from October 2007 to October 2010. The database was constructed for quality assurance at one medical center (National Taiwan University Hospital, Taipei, Taiwan), one branch hospital (National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin, southern Taiwan) and two cooperative hospitals (Far-Eastern Memorial Hospital, Taipei;

Tao-Yuan General Hospital, Tao-Yuan, central Taiwan) [11, 14, 15, 26-29]. Another 14 EH patients with normal eGFR (90-110 ml/min per 1.73 m²) were enrolled as the control group (group 3). Body mass index (BMI) was calculated and eGFR was obtained using the Chinese Modification of Diet in Renal Disease (MDRD) Study equation (eGFR = 186.0 • [serum creatinine]^{-1.154} • age^{-0.203} • [0.742 if women]) [30, 31]. The definition of renal hyperfiltration and normal eGFR were described previously [32, 33]. The serum biochemistry studies were measured at the first evaluation of these patients at the National Taiwan University Hospital. All antihypertensive medications were discontinued for at least 21 days before measuring plasma aldosterone concentration (PAC) and plasma renin activity (PRA) levels. Diltiazem and/or doxazosin were administered for control of marked high blood pressure when required. Homeostasis Model Assessment- insulin resistance (HOMA-IR) index was calculated as insulin (μU/mL) × glucose (mg/dL)/405. Medical histories, including demographics and medication, were carefully recorded.

Diagnostic criteria of subtypes of PA

The diagnosis of aldosterone-producing adenoma (APA) was validated by the 'modified four-corner approach', which requires all of the following criteria to be met [12, 27, 34, 35]: (1) evidence of autonomous excess aldosterone production based on an ARR (aldosterone-renin ratio) > 35 or urine ≥ 12 μg/24 h, and a TAIPAI score more than 60% [22], as well as a post-saline loading PAC (plasma aldosterone concentration) > 10 ng/dl; (2) lateralization of aldosterone secretion at AVS (adrenal vein sampling) or during dexamethasone suppression adrenocortical scintigraphy (NP-59 SPECT/CT) [36]; (3) evidence of adenoma at computer tomography (CT) scan; and (4) pathologically proven adenoma after an adrenalectomy if operated, and cure of hypertension without anti-hypertensive agents or improved hypertension, potassium, PAC, and PRA (plasma renin activity) as previously described. Idiopathic hyperaldosteronism (IHA) was classified by the following criteria: (1) evidence of autonomous excess aldosterone production based on an ARR > 35 and TAIPAI score more than 60%; or urine ≥ 12 μg/24 h and post-saline loading PAC > 10 ng/dl; (2) non-lateralization of aldosterone secretion at AVS or during dexamethasone suppression adrenocortical scintigraphy (NP-59 SPECT/CT) [36]; (3) evidence of bilateral diffuse enlargement on CT scan; and/or (4) evidence of diffuse cell hyperplasia in the pathology studies.

Echocardiography

A Hewlett-Packard Sonos 5500 ultrasound sys-

tem equipped with a S3 transducer was used for the evaluation. Echocardiography was performed especially for the present study. Besides, all echocardiographic data were quantified by a trained cardiologist who was blinded to the clinical status and data of the patients. Echocardiography included two-dimensional, M-mode and Doppler ultrasound recordings. The left ventricular dimension, septum and posterior wall thickness, left atrial diameter and left ventricular ejection fraction (M-mode) were measured via the parasternal long-axis view according to the procedures of the American Society of Echocardiography. The left ventricular mass index (LVMI) was calculated according to the method of Devereux et al. [37]. LVH was defined as LVMI ≥ 134 gm² in men and ≥ 110 gm² in women [38]. One additional index of LV concentric geometry is end-diastolic relative wall thickness (RWT), which allows further classification of LV mass increase. RWT is defined as the ratio of posterior wall thickness to one half of left ventricular end-diastolic diameter. In patients with LVH, a RWT of more than 0.42 has been used as a threshold of concentric LVH and less than 0.42 as eccentric LVH. In patients with normal LVMI, a RWT of more than 0.42 has been used as a threshold of concentric remodeling and less than 0.42 as normal geometry [39]. LV end-diastolic and end-systolic volumes were calculated with the Teichholz method [40].

The theoretical value of predicted LVM was estimated using an equation developed previously: predicted LVM (pLVM) = $55.37 + 66.4 \times \text{height (m}^2\text{)} + 0.64 \times \text{Stroke work (SW)} - 18.07 \times \text{gender}$ (where gender was coded as male = 1 and female = 2). Stroke work was calculated as systolic blood pressure (SBP) (in mmHg) \times stroke volume \times 0.0144 [41]. Inappropriate LVM was defined as an excess of > 35% from the predicted value [41].

Pulsed wave Doppler echocardiography for the left ventricular diastolic mitral flow was performed from the apical 4-chamber view with a 3-mm sample volume at the tip of the mitral leaflets. Transmitral flow velocity with Doppler was performed in the apical 4-chamber view, with E velocity, A velocity and mitral E-wave deceleration time being measured.

The mitral annular velocities were obtained by tissue Doppler imaging. From the apical 4-chamber view, we replaced the 3-mm sample volume at the septal and lateral margins of the mitral annulus. Doppler samples were obtained at end-expiration during normal respiration. We measured the average of early diastole (E') velocity and late diastole (A') velocity at septal and lateral mitral annulus. The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E' ratio) was also calculated. At least three cycles were

analyzed. Inter- and intraobserver studies were available according to our echocardiography lab. The intraobserver variability of mean mitral E' was 1.67% and the interobserver variability of mean mitral E' was 2.38%. [42]

Statistical analysis

Data were expressed as mean \pm SD. The t test was used to compare continuous data between the two groups. Differences between proportions were assessed with the chi-square test or Fisher exact test. Pearson's correlation test was used to analyze the association between LVMI and its determinants. Data of PRA, ARR were log-transformed due to non-normality which was tested by the Kolmogorov-Smirnov test. Significant determinants in the Pearson's correlation test ($p < 0.05$) were then tested with a multivariate linear regression test with stepwise subset selection to identify independent factors associated with LVMI or E/E'.

In the present study, the mean LVMI was 156.73 ± 26.80 g/m² in group 1 patients. In our previous study, the mean LVMI in essential hypertensive patients was 102 ± 22 g/m². [13] Assuming that the correlation between LVMI in two groups was 0, the standard deviation of difference of mean LVMI between two groups was 34.673, and the sample size in group 1 patients was 11, a two group t-test with a 0.05 two-sided significance level would have 80% power to detect the difference between two groups when the sample sizes in the EH patients (control group) was 6. We recruited 14 subjects of EH as the control group to achieve a power of more than 95%.

The variables that were included as potential association of LVMI in the multivariate linear regression test for all patients (groups 1, 2 and 3) were APA, eGFR, SBP, diastolic blood pressure (DBP), mean blood pressure (MBP), serum potassium level, usage of α -blocker and usage of β -blocker. The variables that were included as potential association of LVMI in a multivariate linear regression test for PA patients (groups 1 and 2) were eGFR, SBP, DBP, MBP, serum potassium level and usage of β -blocker. The variables that were included as potential association of E/E' ratio in the multivariate linear regression test for all patients (groups 1, 2 and 3) were age, body height, BMI, serum potassium level, usage of spironolactone, APA, eGFR, SBP, DBP and MBP. The variables that were included as potential association of E/E' ratio in a multivariate linear regression test for PA patients (groups 1 and 2) were age, body height, BMI, serum potassium level, usage of spironolactone, eGFR, SBP, MBP and usage of β -blocker. Statistical analyses were performed with SPSS version 18.0 for Windows (SPSS Inc, Chicago, IL, USA). A p value < 0.05 was consid-

ered to indicate statistical significance.

Results

Patient characteristics

Sixty-one patients were enrolled including 11 PA patients with eGFR > 130 ml/min per 1.73 m² (group 1), 36 PA patients with eGFR 90-110 ml/min per 1.73 m² (group 2) and 14 EH patients with eGFR 90-110 ml/min per 1.73 m² (group 3). The clinical data are shown in Table 1. Patients with PA (groups 1 and 2) had significantly lower serum potassium than that of patients with EH (group 3). Among the PA patients, group 1 patients had significantly lower serum potassium than group 2 patients'.

Group 1 patients had significantly lower body height (P = 0.022) than group 3 patients'. For medication usage, the percentage of PA patients (groups 1 and 2) using spironolactone was higher than that of EH patients (group 3), and the percentage of group 1 patients using α -blocker was higher than that of group 3.

Echocardiographic data

In echocardiographic measurement (Table 2), PA patients (groups 1 and 2) patients had significantly higher LVMI than EH patients' (group 3). Among the PA patients, group 1 patients had significantly higher LVMI than group 2 patients'. Group 2 patients had a higher percentage of inappropriate LVM than group 3 patients' (P = 0.024). The percentage of inappropriate LVM was similar for groups 1 and 2 (P = 0.740).

In a conventional Doppler analysis, group 1 patients had higher E velocity and a higher E/A ratio than those of group 2 patients. The two groups had similar A velocity and mitral E-wave deceleration times. Group 2 and group 3 had similar conventional Doppler parameters. In the TDI study, the PA patients (groups 1 and 2) had significantly higher E/E' ratio than was the case for EH patients (group 3). Among the PA patients, group 1 patients had had significantly higher E/E' ratio than was the case for group 2 patients.

In the factor analysis of LVMI in all patients, eGFR showed a significantly positive association with LVMI (P = 0.002), and serum potassium levels showed a significantly negative association with LVMI (P = 0.001). Other significant factors associated with LVMI included SBP, DBP, MBP, α -blocker, β -blocker and presence of APA (Table 3). In the multivariate analysis of LVMI in all patients, eGFR (P = 0.020), MBP (P = 0.001) and APA (P = 0.010) were independent factors associated with LVMI (Table 5).

In the factor analysis of LVMI in PA patients (groups 1 and 2), eGFR showed a significantly positive association with LVMI (P = 0.009) and serum po-

tassium levels showed a significantly negative association with LVMI (P = 0.008). Other significant factors associated with LVMI included SBP, DBP, MBP and β -blocker (Table 4). In the multivariate analysis of LVMI in PA patients (groups 1 and 2), eGFR (P = 0.055) and MBP (P = 0.003) were independent factors associated with LVMI (Table 6). And eGFR showed a significantly positive association with predicted LVM (P = 0.012), but was not correlated with inappropriate LVM (P = 0.998) (not shown in table). The prevalence of concentric remodeling was 0% in group 1, 33% in group 2 and 36% in group 3. It was significant between the group 1 and group 3. (P < 0.05, table 2) Group 1 had more concentric LVH (82% vs 45%) and less concentric remodeling (0% vs 33%) than group 2 (both P < 0.05). (Table 2)

Table 1. Baseline Characteristics of the Study Population

Clinical characteristics	Group 1	Group 2	Group 3	P value
	N=11	N=36	N = 14	
Age, y	43±12	49±13	48±16	0.454
Sex (male)	4 (36)	15 (42)	6(43)	0.978
Diabetes Mellitus	0	5 (14)	0	0.151
Prior myocardial infarction	0	0	0	-
Coronary artery disease	0	2 (6)	1	0.688
Stroke	0	5 (14)	1	0.371
Heart failure	0	0	0	-
Peripheral artery disease	0	0	0	-
Body weight, kg	65±12	67±15	65±13	0.937
Body height, cm	157±8*	162±8	165±9	0.048
Body mass index, kg/m ²	26.5±3.6	25.2±4.1	23.5±2.5	0.135
APA	9 (82)	29 (81)	0(0)	<0.001
Microalbuminuria	5 (45)	8 (22)	1 (7)	0.077
SBP, mmHg	169±23 [¶]	151±22	150±22	0.060
DBP, mmHg	97±12	93±12	91±12	0.503
MBP, mmHg	121±16	112±14	111±14	0.184
Estimate duration of hypertension, y	3.8±3.2	6.4±8.2	4.8±4.6	0.490
Laboratory variables				
Fasting glucose, mg/dL	85.6±6.9	93.9±14.7	88.9±7.9	0.116
Insulin, μ U/mL	11.7±15.3	15.8±15.9	7.8±2.7	0.290
HOMA-IR, mU/L	2.5±3.3	3.8±3.8	1.7±0.6	0.220
Creatinine, mg/dL	0.72±0.12 [§]	0.93±0.14	0.93±0.15	<0.001
Potassium, mmol/L	3.1±0.6 [□]	3.7±0.6 [△]	4.1±0.3	<0.001
PAC, ng/dL	52±34	50±32	29±15	0.072
PRA, ng/ml/hr	0.25±0.23 [¶]	1.1±2.3 [△]	9.7±9.0	<0.001
ARR	2481±4166*	1461±3171	11±13	0.121
Log PRA	-1.00±0.76 [□]	-0.051±0.86 [¶]	0.72±0.54	<0.001
Log ARR	2.63±0.92 [□]	2.13±0.98 [¶]	0.69±0.61	<0.001
Hypertension medication				
CCB	7 (64)	14 (39)	7(50)	0.380
ACEI/ARB	3 (37)	13 (36)	9(64)	0.114
Spironolactone	6 (55) [¶]	16 (44) [△]	0(0)	0.002
α -blocker	7 (64) [¶]	11 (31)	1(7)	0.013
β -blocker	3 (27)	16 (44)	5(36)	0.628

Values are mean \pm SD. APA: aldosterone-producing adenoma; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PAC: plasma aldosterone concentration; PRA: plasma renin activity; ARR: aldosterone-renin ratio; CCB: calcium channel blocker; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; HOMA-IR: homeostatic model assessment-insulin resistance

*P < 0.05 between groups 1 and 3; [¶]P < 0.05 between groups 1 and 2; [§]P < 0.001 between groups 1 and 2; [□]P < 0.001 between groups 1 and 3; [△]P < 0.01 between groups 1 and 2; [△]P < 0.01 between groups 2 and 3; [¶]P < 0.01 between groups 1 and 3; [§]P < 0.001 between groups 2 and 3.

Table 2. Baseline Echocardiographic Parameters of the Study Population

Echocardiographic parameters	Group 1	Group 2	Group 3	P value
	N=11	N=36	N=14	
IVST, mm	12.09±1.51	11.75±2.26	10.64±1.60	0.145
LVPWT, mm	12.09±1.64 [□]	11.00±2.06 [□]	9.57±1.34	0.005
LVEDD, mm	47.27±4.38	45.08±4.88	46.00±4.85	0.405
LVESD, mm	28.36±3.14	28.39±4.65	27.79±5.85	0.545
Relative wall thickness	0.52±0.08	0.51±0.11 [□]	0.44±0.06	0.066
LVMI, g/m ²	156.73±26.80 ^{*□}	127.05±33.87 [□]	109.78±23.61	0.001
LVH	11/11 (100) ^{□□}	21/36 (58)	4/14(29)	0.001
Concentric LVH	9/11(82) [*]	17/36(45)	4/14(29)	0.026
Eccentric LVH	2/11(18)	4/36(11)	0/14(0)	0.343
Concentric remodeling	0/11(0) ^{*†}	12/36(33)	5/14(36)	0.053
Normal Geometry	0/11(0) [*]	3/36 (8) [□]	5/14(36)	0.019
LVM, gm	258.96±61.78 [□]	220.67±74.69	190.27±54.05	0.052
Predicted LV mass, gm	184.22±47.64	155.74±39.17	167.93±49.70	0.157
Observed/predicted LVM (%)	143.20±29.63 [*]	143.42±34.68 ^Δ	114.87±22.21	0.016
Inappropriate LVM	5/11 (45)	19/36 (53) [□]	2/14 (14)	0.044
LVEDV	104.93±22.71	94.40±23.64	98.80±24.13	0.422
LVESV	31.07±8.27	31.92±15.44	28.46±14.23	0.742
LVEF, %	69.82±5.15	66.08±8.44	71.79±9.59	0.075
E, cm/s	85.82±19.10 [†]	71.08±15.04	72.29±14.95	0.029
A, cm/s	68.64±15.15	75.17±20.29	67.21±16.78	0.325
E/A ratio	1.32±0.42 [†]	0.98±0.27	1.12±0.18	0.005
DT, sec	181.36±36.49	180.86±44.78	188.36±38.54	0.847
Tissue doppler				
Mean E', cm/s	8.05±3.31 [*]	7.78±2.05 ^Δ	10.13±1.86	0.008
Mean A', cm/s	10.65±2.07	11.49±2.43	11.03±1.81	0.522
Mean E'/E' ratio	12.57±5.72 ^{*□}	9.74±2.60 [□]	7.51±2.16	0.002

Value are mean ± SEM. IVST= interventricular septal thickness; LVPWT= left ventricular posterior wall thickness; LVEDD= left ventricular end-diastolic diameter; LVESD= left ventricular end-systolic diameter; LVMI= left ventricular mass index; LVH= left ventricular hypertrophy; LVM= left ventricular mass; LVEDV= left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume; LVEF=left ventricular ejection fraction; DT=deceleration time

[□]P < 0.01 between groups 1 and 3; ^ΔP < 0.01 between groups 2 and 3; [□]P < 0.01 between groups 1 and 2; [†]P < 0.001 between groups 1 and 3; [□]P < 0.05 between groups 2 and 3; ^{*}P < 0.05 between groups 1 and 3; [†]P < 0.05 between groups 1 and 2;

Table 3. Factors associated with LVMI (all patients, n = 61)

	Person correlation coefficient	P value
Age, y	-0.193	0.137
Sex (male)	0.031	0.812
Body weight, kg	0.132	0.312
Body height, cm	0.116	0.372
Body mass index, kg/m ²	0.120	0.357
APA	0.382	0.003
HOMA-IR	-0.137	0.363
Presence of Diabetes Mellitus	-0.137	0.366
Presence of Microalbuminuria	0.155	0.232
eGFR, ml/min per 1.73 m ²	0.383	0.002
SBP, mmHg	0.462	<0.001
DBP, mmHg	0.394	0.002
MBP, mmHg	0.454	<0.001
Estimate duration of hypertension, y	0.085	0.516
Potassium, mmol/L	-0.422	0.001
Presence of microalbuminuria	0.155	0.232
PAC, ng/dL	0.103	0.440
Log PRA	-0.189	0.156
Log ARR	0.191	0.151
CCB	0.071	0.640
ACEI/ARB	-0.165	0.203
Spirololactone	0.077	0.555
α-blocker	0.270	0.035
β-blocker	-0.275	0.032

APA: aldosterone-producing adenoma; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PAC: plasma aldosterone concentration; PRA: plasma renin activity

Table 4. Factors associated with LVMI (PA patients, n = 47)

	Person correlation coefficient	P value
Age, y	-0.185	0.213
Sex (male)	0.130	0.383
Body weight, kg	0.077	0.606
Body height, cm	0.166	0.265
Body mass index, kg/m ²	0.023	0.878
APA	0.255	0.087
HOMA-IR	-0.250	0.141
Presence of Diabetes Mellitus	-0.190	0.202
Presence of Microalbuminuria	0.175	0.241
eGFR, ml/min per 1.73 m ²	0.376	0.009
SBP, mmHg	0.491	<0.001
DBP, mmHg	0.401	0.005
MBP, mmHg	0.473	0.001
Estimate duration of hypertension, y	0.083	0.580
Potassium, mmol/L	-0.388	0.008
PAC, ng/dL	0.010	0.946
Log PRA	0.020	0.898
Log ARR	-0.030	0.849
CCB	0.038	0.800
ACEI/ARB	-0.087	0.561
Spirololactone	-0.058	0.697
α-blocker	0.204	0.170
β-blocker	-0.444	0.002

APA: aldosterone-producing adenoma; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PAC: plasma aldosterone concentration; PRA: plasma renin activity; ARR: aldosterone-renin ratio

Table 5. Multivariate regression analysis with left ventricular mass index as the dependent variable. All patients, n = 61, model adjusted R² = 0.373

	β (95% CI)	P value	Tolerance
MBP, mmHg	0.880 (1.031; 0.629)	0.001	0.960
APA	20.279 (27.883; 12.675)	0.010	0.982
eGFR, ml/min per 1.73 m ²	0.496 (0.702; 0.290)	0.020	0.945

MBP: mean blood pressure; APA: aldosterone-producing adenoma; eGFR: estimate glomerular filtration rate; excluded variables: systolic blood pressure, diastolic blood pressure, serum potassium level, usage of α-blocker, and usage of β-blocker

Table 6. Multivariate regression analysis with left ventricular mass index as the dependent variable. PA patients, n = 47, model adjusted R² = 0.303

	β (95% CI)	P value	Tolerance
MBP, mmHg	0.958 (1.261; 0.655)	0.003	0.927
eGFR, ml/min per 1.73 m ²	0.455 (0.686; 0.224)	0.055	0.927

MBP: mean blood pressure; eGFR: estimate glomerular filtration rate; excluded variables: systolic blood pressure, diastolic blood pressure, serum potassium level, and usage of β-blocker

In the factor analysis of E/E' ratio in all patients, eGFR showed a significantly positive association with E/E' ratio (P = 0.007, not shown in the table). Other significant factors associated with E/E' ratio included PA, age, body height, BMI, SBP, serum potassium level, spironolactone, α-blocker and β-blocker. In the multivariate analysis of E/E' ratio in all patients, eGFR (P = 0.001), β-blocker (p=0.007), PA (p=0.021) and age (p=0.022) were independent factors associated with E/E' ratio (Table 7).

In the factor analysis of E/E' ratio in PA patients (groups 1 and 2), eGFR showed a significantly positive association with E/E' ratio ($P = 0.037$, not shown in the table). Other significant factors associated with E/E' ratio included body height, BMI, SBP, MBP and β -blocker. In the multivariate analysis of E/E' ratio in PA patients (groups 1 and 2), eGFR ($P = 0.003$) and β -blocker ($P = 0.001$) were independent factors associated with E/E' ratio (Table 8).

Table 7. Multivariate regression analysis with E/E' ratio as the dependent variable. All patients, $n = 61$, model adjusted $R^2 = 0.408$

	β (95% CI)	P value	Tolerance
eGFR, ml/min per 1.73 m ²	0.081 (0.058; 0.104)	0.001	0.914
Usage of β -blocker	2.413 (1.558; 3.268)	0.007	0.908
PA	2.276 (1.320; 3.232)	0.021	0.951
Age	0.075 (0.053; 0.107)	0.022	0.910

eGFR: estimate glomerular filtration rate; PA: primary aldosteronism; excluded variables: body height, body mass index, serum potassium level, systolic blood pressure, diastolic blood pressure, mean blood pressure, presence of aldosterone-producing adenoma, and usage of spironolactone

Table 8. Multivariate regression analysis with E/E' ratio as the dependent variable. PA patients, $n = 47$, model adjusted $R^2 = 0.309$

	β (95% CI)	P value	Tolerance
eGFR, ml/min per 1.73 m ²	0.079 (0.054; 0.104)	0.003	0.952
Usage of β -blocker	3.552 (2.544; 4.560)	0.001	0.952

eGFR: estimate glomerular filtration rate; excluded variables: age, body height, body mass index, serum potassium level, usage of spironolactone, systolic blood pressure, and mean blood pressure

Discussion

The major findings of this study are as follows: (1) PA patients had a higher LVMI and worse diastolic function compared to EH patients; (2) PA patients with glomerular hyperfiltration had a higher LVMI than that of PA patients with normal eGFR, which is majorly contributed by concentric LVH and predicted LVM; (3) PA patients with glomerular hyperfiltration had higher E/E' ratio than but comparable E' to PA patients with normal eGFR, which is majorly contributed by increased E velocity. This is the first human study to demonstrate the association between glomerular hyperfiltration and other target organ damage such as cardiac structure or function change in PA patients.

EH patient had more normal LV geometry than PA patients with normal eGFR. PA patients with normal eGFR had more concentric LVH and concentric remodeling than EH patients. And PA patients with hyperfiltration had higher rate of concentric LVH not concentric remodeling than PA patients with normal eGFR. We propose that hyperfiltration had an additional effect in concentric LVH beyond PA.

It is notable that PA patients had a higher ob-

served-to-predicted LVM ratio and a higher percentage of "inappropriate" LVM than that of EH patients. This finding is the same as in Muiesan et al. [43]. However, among PA patients, although PA patients with hyperfiltration had a higher LVMI than PA patients with normal eGFR, the "inappropriate" LVM was similar between the two groups. Moreover, the observed-to-predicted LVM ratio was almost the same in these two groups, which means that the difference of LVM between the two groups contributed to the predicted LVM. The actual predicted LVM difference between the two groups was around 17%. The predicted LVM was estimated using body height, gender, BP, and stroke volume. The 4.9% higher LVEDD (left ventricular end-diastolic diameter), 11% higher LVEDV (left ventricular end-diastolic volume) and 12% higher SBP of group 1 patients over group 2 patients were the major contributing factors of this phenomenon. Combining the finding of higher LVEDD and LVEDV with the higher mitral E velocity of group 1 patients over group 2 patients, we can propose that the intravascular volume is higher in group 1 than in group 2.

The phenomenon of glomerular hyperfiltration in PA was first noted in 1996 [44]. Although the mechanisms for this are not fully understood, it may be attributed to enhanced tubular sodium reabsorption [44]. In a recent study by Fu et al., aldosterone activated mineralocorticoid receptors in macula densa cells were found to further increase nitric oxide production in the macula densa and to blunt the tubuloglomerular feedback response in rats [45]. This effect happens quickly and made possible through the rapid nongenomic pathway of aldosterone. Furthermore, although the influence of glomerular hyperfiltration in PA is still unclear clinically, in hypertensive patients, the relationship between glomerular hyperfiltration and microalbuminuria has been validated [46], and microalbuminuria may further cause cardiovascular and renal events [47]. In this investigation, glomerular hyperfiltration was found to be associated with increased LVMI, with LVH being recognized as a marker of hypertension-related target organ damage and being associated with a greater risk of cardiovascular events and death [48, 49]. This present study implies a greater cardiovascular morbidity in PA patients with glomerular hyperfiltration than that of the PA patients with normal eGFR.

In this study, we found an independent association of glomerular hyperfiltration with LVMI in PA patients. Although glomerular hyperfiltration may also be a sign of more severe hyperaldosteronism, the associations among glomerular hyperfiltration and LVMI are still significant after adjustment for BP, serum potassium levels and α -blocker usage in the

multivariate analysis. Glomerular hyperfiltration is also associated with LVH in patients with EH. At a similar age, BMI, body surface area, and BP, hypertensive patients with LVH have been observed to have a higher glomerular filtration rate and filtration fraction than those without LVH, whereas renal blood flow and renal vascular resistance measurements were not found to be significantly different [25]. However, future studies will therefore need to investigate the possible mechanisms of how glomerular hyperfiltration can cause cardiac hypertrophy in PA patients.

In this study, we used conventional Doppler and TDI to evaluate cardiac diastolic function. We found that PA patients with glomerular hyperfiltration (group 1) had a higher E and E/A than PA patients with normal eGFR (group 2). In the TDI analysis, group 1 patients had a higher E/E' ratio than was the case for group 2. In the current study, results of the conventional echocardiography and TDI both indicate that glomerular hyperfiltration may influence the cardiac diastolic function in PA patients. The difference in E/E' ratio was due to the elevation of E in PA patients with glomerular hyperfiltration. In addition, the E' was similar for groups 1 and 2, which implies that the higher E/E' ratio in group 1 was caused by the elevated E velocity ($P = 0.011$), with the elevated E velocity meaning early filling peak velocity, which is relative to volume status and not the LV myocardial relaxation. However, while this study was underpowered to assess a significant difference of LV internal diameter and volume between PA patients with normal eGFR and glomerular hyperfiltration, the PA patients with glomerular hyperfiltration tended to have an increased LVEDD and LVEDV. Group 2 and 3 patients had similar conventional Doppler parameters. In the TDI analysis, PA patients with normal eGFR had lower E' and higher E/E' ratio than EH patients with normal eGFR. However, it has recently been demonstrated that the E/E' ratio of transmitral flow to mitral annulus velocity is a strong and independent association of cardiac outcome [50] and TDI is superior to conventional Doppler in evaluating diastolic function [51]. In the present study, PA patients exhibited a greater degree of diastolic dysfunction than the EH patients. Also, PA patients with glomerular hyperfiltration had a higher E/E' ratio than PA patients with normal eGFR, which may also indicate a higher degree of diastolic dysfunction. The associations among glomerular hyperfiltration and E/E' ratio in PA patients are significant after adjustment for body height, BMI, SBP, MBP and β -blocker usage in the multivariate analysis. However, the higher E/E' ratio in group 1 was caused by the elevated E velocity, and not caused by the decreased E'. The actual physi-

ological meaning of the higher E/E' ratio in group 1 compared to group 2 needs further study.

There are limitations to this study. First, this is a cross-sectional correlation study and only shows the association between glomerular hyperfiltration and cardiac structure and functional change. Whether glomerular hyperfiltration is a factor influencing LVMI or only a marker to present more severe disease cannot be clearly elucidated in this study; that is, under this study design, we cannot establish a direct causal effect between glomerular hyperfiltration and LVMI. Second, this study only provides the data of glomerular hyperfiltration and LVMI, but the effect on cardiovascular mortality or morbidity cannot be known. Further long-term follow-up studies are needed to investigate the clinical impact of glomerular hyperfiltration on cardiovascular outcome. Third, the patient number is small in this study, especially in group 1, which may indicate a lack of power to demonstrate the difference between groups, such as the predicted LVM, LVEDD or LVEDV between groups 1 and 2. This study cannot provide the final evidence of association. On the other hand, the anti-hypertensive medications were not standard in this study and it may be hard to adjust the bias of different medications because of the small size. For example, usage of spironolactone in PA is able to improve the kidney damage and glomerular hyperfiltration [21, 52]. Further studies with a larger patient number are needed. Fourth, many parameters were tested in this study, which raised an issue of multiple comparison. However, all the clinically relevant parameters showed similar tendency and direction of statistical significance. The situation is unlikely due to random error. Fifth, there are several methods of calculate eGFR. All methods are designed for detection of renal dysfunction, and none is validated for evaluation of hyperfiltration. We used Chinese MDRD in this study, because it is the best method to calculate eGFR in Chinese population, even in health population [31]. However, the eGFR calculated by Chinese MDRD is still not validated in the status of hyperfiltration. Sixth, the estimation of theoretical value of predicted LVM is done with the blood pressure values recorded in the end of echocardiographic assessment in previous study [41]. The method is not confirmed by other studies. These may limit the application and accuracy of this method. Seventh, most patients were young and hypertension durations were short in this study. Age and duration of hypertension are correlated with LVM. The result of this study may not apply in an older population.

Conclusions

In conclusion, glomerular hyperfiltration in PA

patients was associated with higher LVMI, higher mitral E velocity, higher E/E' ratio, but there was a comparable E' in PA patients with normal GFR. This phenomenon may be explained by higher intravascular volume in this patient group.

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Competing Interests

The authors have declared that no competing interest exists.

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