ORIGINAL RESEARCH

Left Ventricular Dysfunction in Patients With Primary Aldosteronism: A Propensity Score–Matching Follow-Up Study With Tissue Doppler Imaging

Yi-Yao Chang, MD; Che-Wei Liao, MD, MMS; Cheng-Hsuan Tsai, MD; Ching-Way Chen, MD; Chien-Ting Pan, MD; Zheng-Wei Chen, MD; Ya-Li Chen, BS; Lung-Chun Lin, MD, PhD; Yi-Ru Chang, MS; Vin-Cent Wu, MD, PhD; Kwan-Dun Wu, MD, PhD; Chi-Sheng Hung, MD, PhD; Yen-Hung Lin, MD, PhD; on behalf of the TAIPAI Study Group*

***Background*—**Primary aldosteronism is the most common cause of secondary hypertension and is associated with left ventricular hypertrophy. However, whether aldosterone excess is responsible for left ventricular (LV) diastolic dysfunction is unknown.

***Methods and Results*—**We prospectively enrolled 129 patients with aldosterone-producing adenoma and 120 patients with essential hypertension, and analyzed their clinical, biochemical, and echocardiographic data, including tissue Doppler images. The patients with aldosterone-producing adenoma were reevaluated 1 year after adrenalectomy. After propensity score matching, there were 105 patients in each group. The patients with aldosterone-producing adenoma had worse diastolic function than the patients with essential hypertension, as reflected by lower e′ ($P<0.001$) and higher E/e′ ($P=0.003$). Multivariate analysis showed that LV diastolic function was significantly correlated with age ($P<0.001$), sex ($P<0.001$), body mass index ($P=0.002$), systolic blood pressure ($P=0.004$), creatinine ($P=0.008$), and log-transformed aldosterone-renin ratio ($P=0.003$). After adrenalectomy, the patients with aldosterone-producing adenoma had significant improvements in LV diastolic function as reflected by an increase in e′ ($P=0.003$) and decrease in E/e′ ($P=0.002$). The change in E/e′ was independently correlated with baseline E/e′ ($P<0.001$) and change in LV mass index ($P=0.006$).

***Conclusions*—**The patients with primary aldosteronism had worse LV diastolic function than the patients with essential hypertension after propensity score matching, and this could be reversed after adrenalectomy, suggesting that aldosterone excess may induce LV diastolic dysfunction. **(*J Am Heart Assoc*. 2019;8:e013263. DOI: 10.1161/JAHA.119.013263.)**

Key Words: adrenalectomy • aldosterone • diastolic function • primary aldosteronism • propensity score matching

Primary aldosteronism (PA) is one of the most common causes of secondary hypertension[1] and affects 5% to 15% of patients with hypertension.[2] Excess aldosterone results in various cardiac structure changes and damage. In animal studies, aldosterone infusion with a high-sodium diet has been shown to cause left ventricular hypertrophy (LVH), interstitial fibrosis, and scarring in both left and right ventricles.[3] Clinical studies have shown that patients with PA have more distinct left ventricular (LV) mass and cardiac fibrosis than patients with essential hypertension (EH).[4–9] Patients with PA have also been reported to have higher prevalence rates of myocardial infarction, atrial fibrillation, and heart failure compared with EH patients.[9–12]

Worse LV diastolic function as assessed by measuring mitral inflow velocity-derived parameters via Doppler echocardiography has been reported in patients with PA compared with patients with EH.[4] However, these parameters can be influenced by fluid status.[13] In contrast, tissue Doppler imaging (TDI) of the mitral annulus can be used to measure early diastolic

From the Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan (Y.-Y.C.); Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan (Y.-Y.C.); Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan (Y.-Y.C., C.-H.T., C.-T.P., Y.-L.C., L.-C.L., Y.-R.C., V.-C.W., K.-D.W., C.-S.H., Y.-H.L.); Center of General Education, Chihlee University of Technology, New Taipei City, Taiwan (Y.-Y.C.); Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan (C.-W.L.); Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan (C.-W.C., Z.-W.C.).

*A complete list of the TAIPAI Study Group members can be found in the Appendix at the end of the article.

Correspondence to: Yen-Hung Lin, MD, PhD, or Chi-Sheng Hung, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan. E-mails: austinr34@gmail.com; petrehcs@gmail.com

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Clinical Perspective

What Is New?

- The first study using propensity score matching analysis for diastolic function between patients with primary aldosteronism (PA) and patients with essential hypertension, and with 1-year follow-up after adrenalectomy in patients with PA.
- Changes in diastolic function (ΔE/e′) after adrenalectomy in patients with PA was correlated with baseline E/e′ and changes in left ventricular mass index.

What Are the Clinical Implications?

- The patients with PA had worse diastolic function than the patients with essential hypertension.
- Diastolic dysfunction in the patients with PA improved after adrenalectomy.

peak velocity of the myocardium (e′), which represents early diastolic relaxation. TDI-derived parameters are considered to be less preload dependent than mitral inflow velocity parameters,[14] and they have been used to evaluate diastolic dysfunction in patients with PA in recent studies.[15,16]

Nevertheless, the sample sizes in the studies that have investigated diastolic function in patients with PA have been relatively small. Furthermore, the blood pressure was significantly different between patients with PA and patients with EH in previous studies, which may be a major confounding factor in the analysis of diastolic function. Moreover, for patients with unilateral aldosterone-producing adenoma (APA), although adrenalectomy can improve blood pressure control and reverse LV mass[4,17] and myocardial fibrosis,[18] it is unknown whether diastolic dysfunction can be reversed after adrenalectomy.[17,19–21] Therefore, we conducted this prospective study to investigate diastolic function in patients with APA and changes after adrenalectomy via TDI studies.

Materials and Methods

The anonymized data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

In this prospective study, we enrolled 129 patients with APA who were scheduled to undergo adrenalectomy from November 2006 to July 2017 at National Taiwan University Hospital. Another 120 patients with EH were enrolled as the control group. The medical history, including demographic data and current medications, of all patients were reviewed and carefully documented. Serum biochemistry data were obtained at the initial patient evaluation. The diagnosis of EH was made by exclusion, including clinical presentation and biochemical surveys of all detectable types of secondary hypertension.

All patients received biochemical examinations and echocardiography at enrollment. For the patients with APA, we recorded biochemical and echocardiography data again 1 year after adrenalectomy. Patients who were completely off all antihypertensive drugs and had normalized blood pressure (systolic blood pressure [SBP] <140 mm Hg and diastolic blood pressure [DBP] <90 mm Hg) after adrenalectomy were defined as being "cured." All patients provided informed consent before inclusion in the study, and the study was approved by the Ethics Committee of National Taiwan University Hospital.

Laboratory Measurements

Plasma aldosterone concentration (PAC) was evaluated using a commercial radioimmune assay kit (Aldosterone Maia Kit; Adaltis Italia, Bologna, Italy). Plasma renin activity (PRA) was evaluated using the generation of angiotensin I in vitro with a commercial radioimmune assay kit (DiaSorin, Stillwater, Minnesota).

Diagnostic Criteria for APA

The diagnosis of APA was confirmed according to the "modified 4-corner criteria" after adrenalectomy,[22,23] which were (1) evidence of autonomous excess aldosterone production based on an aldosterone-renin ratio (ARR) >35, TAIPAI (Taiwan Primary Aldosteronism Investigation) score >60%[24]; and seated post-saline loading PAC >16 ng/dL or urine aldosterone >12 μg/24 h[25]; (2) adenoma evidenced with a computed tomography scan; (3) lateralization of aldosterone secretion by adrenal venous sampling or by dexamethasone suppression NP-59 single-photon emission computed tomography[26]; (4) histopathological evidence of adenoma after adrenalectomy, and subsequently either a cure pattern of hypertension without antihypertensive agents or improvement in hypertension with biochemical cure.

The probability of PA (TAIPAI score) was equal to:

$$\text{TAIPAI score} = 1/1 + e^{-\beta};$$

where

$$\beta = (\text{PAC}\,[\text{ng/dL}] \times [0.063]) + \text{PRA}\,[\text{ng/mL per hour}] \times [-0.205]) + ([\text{ARR} \times 0.001] + \text{BMI}\,[\text{kg/m}^2] \times [0.067]) + (\text{Male} \times [-0.738] + \text{SK}\,[\text{mmol/L}] \times [-1.512]) + (\text{eGFR}\,[\text{mL/min per } 1.73\text{m}^2] \times [0.017]) + ([\text{propensity score}] \times [-0.539] + [1.851]).$$

In adrenal venous sampling, a reliable adrenal venous sample was defined as a >3-fold increase in the ratio of cortisol level in the adrenal vein to the inferior vein

cava. Lateralization of aldosterone secretion was defined as a >4-fold increase in the ratio of aldosterone/cortisol divergence between bilateral adrenal glands.[26]

Echocardiography

Echocardiography was performed using a Hewlett-Packard Sonos 5500 (Hewlett-Packard, Palo Alto, California) or Philips IE33 system (Royal Dutch Philips Electronics, Bothell, Washington). Measurements were performed according to the American Society of Echocardiography guidelines.[27] LV end-diastolic and end-systolic diameters, wall thickness, and LV ejection fraction were assessed using M-mode in the parasternal long-axis view. The LV mass was estimated by the formula reported by Devereux and Reichek,[28] and normalized by body surface area to provide the LV mass index (LVMI). LVH was defined as an LVMI $\geq$134 g/m^2 in men and $\geq$110 g/m^2 in women.[29] Transmitral flow velocity with Doppler was measured using a 3-mm sample volume at the level of the mitral valve tips in an apical 4-chamber view, and the early (E) and late (A) diastolic filling velocities, their ratio (E/A ratio), and early wave deceleration time (DT) were obtained. Mitral annular velocities were acquired by TDI in an apical 4-chamber view. A 3-mm sample volume was placed at the septal margin of the mitral valve annulus, and Doppler samples were determined at the end-expiration phase in normal respiration. At least 3 consecutive cardiac cycles were taken into consideration, and average values were used. Early diastolic peak velocity of the septal mitral annulus (e′) was obtained. The E/e′ ratio was also calculated, and reflected the LV filling pressure.[27,30]

Adrenalectomy

All patients with APA received laparoscopic adrenalectomy using the lateral transperitoneal approach by experienced laparoscopic surgeons.

Histopathologic Study

The surgical specimens were blindly evaluated by a pathologist. The histopathologic diagnosis of adenoma was confirmed by well-defined nodules clearly demarcated by a pseudo-capsule, predominantly composed of foamy clear cells.[31] Adenomas can be differentiated from nodular adrenal hyperplasia because of their well-circumscribed and solitary nature.[32]

Statistical Analysis

Propensity scores were estimated using a nonparsimonious multiple logistic regression model. The following variables of the patients with PA and EH were selected to calculate the propensity score: age, sex, body mass index (BMI), SBP, DBP, duration of hypertension, and number of antihypertensive medications. In our propensity analysis, a 1:1 matching ratio was used, and covariate balance between the matched groups was subsequently examined.

All continuous variables were expressed as mean±SD. Non–normally distributed variables were expressed as median and interquartile range, including PAC, PRA, and ARR. Comparisons of continuous data between 2 groups were performed using the Student's *t* test (for normally distributed variables) or the Wilcoxon rank-sum test (for non–normally distributed variables). Comparisons of continuous data before and after adrenalectomy in the APA group were performed using paired *t* tests. The equality of 2 proportions was assessed using the Pearson chi-square test. PAC, PRA, and ARR data were log-transformed due to nonnormality as tested by the Kolmogorov–Smirnov test for further regression analysis. Univariate linear regression analysis was performed to test the relationships between diastolic function (E/e′) and clinical parameters. Significant determinants in the univariate linear regression analysis (P<0.05) were then examined using multivariate linear regression analysis with stepwise subset selection to identify the significant factors associated with diastolic function. All statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc, Chicago, Illinois). A P value of <0.05 was considered to indicate statistical significance.

Results

After performing 1:1 matching for age, sex, BMI, SBP, DBP, duration of hypertension, and number of antihypertensive medications between the APA and EH groups, there were 105 patients in each group. The demographic and baseline data of both propensity score–matched and unmatched variables are listed in Table 1. For the unmatched data, there were no significant differences in age, sex, BMI, duration of hypertension, and baseline creatinine. SBP, DBP, number of antihypertensive drugs, PAC, and ARR were significantly higher in the APA group compared with the EH group, while baseline potassium and PRA were significantly lower in the APA group. The use of α-blockers, β-blockers, and aldosterone antagonists was significantly higher in the APA group. In contrast, the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs) and direct renin inhibitor was significantly lower in the APA group. Other clinical parameters were comparable between the 2 groups.

For the matched data, there were no significant difference in age, sex, BMI, duration of hypertension, SBP, DBP, number of antihypertensive medications, and baseline creatinine. These results indicated a high degree of similarity in the distribution of baseline characters between the 2 groups. PAC

Table 1. Clinical Data of Patients

Variables	Before Propensity Score Matching			After Propensity Score Matching*		
Patient Characteristics	APA (n=129)	EH (n=120)	*P* Value	APA (n=105)	EH (n=105)	*P* Value
Age, y	50±11	52±13	0.325	52±11	51±13	0.856
Sex, male	52 (40%)	60 (50%)	0.126	44 (42%)	52 (50%)	0.270
Height, cm	162±9	163±10	0.618	163±9	163±10	0.826
Weight, kg	67±14	70±15	0.154	69±14	69±14	0.924
Body mass index, kg/m^2	25.3±4.1	26.3±4.4	0.079	25.8±4.0	25.8±3.5	0.962
Duration of hypertension, y	7.5±6.9	6.4±6.4	0.171	7.6±7.0	6.9±6.6	0.349
SBP, mm Hg	156±21	145±23	<0.001	152±20	148±23	0.174
DBP, mm Hg	93±13	88±14	0.003	91±11	89±14	0.247
Number of antihypertensive drugs	2.1±1.2	1.7±0.8	0.008	1.9±1.2	1.8±0.8	0.327
Hypertension medication type						
ACEI/ARB	49 (38%)	77 (64%)	<0.001	38 (36%)	69 (66%)	<0.001
α-blocker	27 (21%)	10 (8%)	0.005	18 (17%)	9 (9%)	0.064
β-blocker	48 (37%)	28 (23%)	0.017	39 (37%)	27 (26%)	0.075
CCB	95 (74%)	76 (63%)	0.060	74 (70%)	71 (68%)	0.656
Diuretics except aldosterone antagonist	12 (9%)	6 (5%)	0.187	9 (9%)	6 (6%)	0.424
Aldosterone antagonist	25 (19%)	2 (2%)	<0.001	20 (19%)	2 (2%)	<0.001
Vasodilator	6 (5%)	1 (1%)	0.036	5 (5%)	1 (1%)	0.099
DRI	0 (0%)	4 (3%)	0.045	0 (0%)	4 (4%)	0.045
Laboratory parameters						
Creatinine, mg/dL	0.90±0.40	0.96±0.50	0.327	0.91±0.42	0.98±0.53	0.337
Potassium, mmol/L	3.6±0.7	4.2±0.4	<0.001	3.7±0.6	4.2±0.4	<0.001
PAC,† ng/dL	45 (47)	35 (26)	<0.001	45 (42)	35 (26)	<0.001
PRA,† ng/mL per h	0.20 (0.45)	1.93 (5.89)	<0.001	0.21 (0.41)	1.92 (4.54)	<0.001
ARR†, ng/dL per ng/mL/h	308 (1766)	16 (44)	<0.001	276 (1614)	18 (41)	<0.001

Values are expressed as mean±SD, median (interquartile range), or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; APA, aldosterone-producing adenoma; ARB, angiotensin II receptor blocker; ARR, aldosterone–renin ratio; CCB, calcium channel blocker; DBP, diastolic blood pressure; DRI, direct renin inhibitor; EH, essential hypertension; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.

*1:1 matched for age, sex, body mass index, SBP, DBP, duration of hypertension, and number of antihypertension drugs between the APA and EH groups.

†Expressed as median and interquartile range.

and ARR were significantly higher in the APA group compared with the EH group. Baseline potassium and PRA were significantly lower in the APA group. The use of aldosterone antagonists was significantly higher in the APA group, while the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitor was significantly lower in the APA group.

In echocardiography (Table 2 and Figure 1), there was no significant difference in left ventricular ejection fraction (LVEF) between the 2 groups. The APA group had a significantly higher baseline LVMI (118±29 versus 106±37 g/m^2; P=0.014) and E/e′ ratio (12.5±4.2 versus 10.8±4.2; P<0.001) compared with the EH group. In addition, e′ (6.3±1.9 versus 7.6±4.2 cm/s; P<0.001) was significantly lower in the APA group. The data of all patients before propensity score matching showed similar results (Table 2).

To determine the factors influencing preadrenalectomy diastolic function, we performed linear regression analysis using the preadrenalectomy E/e′ ratio of all matched patients as a dependent variable, and the clinical characteristics and aldosterone-related parameters as independent variables. The results of univariate analysis showed that the preadrenalectomy E/e′ ratio was significantly related to age, sex, BMI, duration of hypertension, SBP, creatinine, log PAC, log PRA, and log ARR. With E/e′ as the dependent variable, multivariate regression analysis with stepwise subset selection further identified significant associations with age, sex, BMI, SBP, creatinine, and log ARR (Table 3).

Table 2. Echocardiography Data of Patients (Before and After Matching APA Patients Versus EH Patients)

Variables	Before Propensity Score Matching			After Propensity Score Matching*		
Patient Characteristics	APA (n=129)	EH (n=120)	*P* Value	APA (n=105)	EH (n=105)	*P* Value
LVEF, %	70±6	70±7	0.779	70±6	71±7	0.863
LVMI, g/m^2	121±32	105±36	<0.001	118±29	106±37	0.014
E/A ratio	1±0.3	1±0.3	0.772	0.9±0.3	1±0.3	0.208
DT, ms	208±44	201±45	0.193	209±45	201±45	0.202
e′, cm/s	6.5±1.9	7.6±3.0	0.001	6.3±1.9	7.6±3.1	<0.001
E/e′	12.5±4.2	10.7±4.0	0.001	12.5±4.2	10.8±4.2	0.003

APA indicates aldosterone-producing adenoma; DT, early wave deceleration time; E/A, early and late diastolic velocity ratio; E/e′, early diastolic transmitral and myocardial velocity on TDI ratio; e′, early diastolic myocardial velocity on TDI; EH, essential hypertension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.
*1:1 matched for age, sex, body mass index, SBP, DBP, duration of hypertension, and number of antihypertension drugs between the APA and EH groups.

In the overall APA group (129 patients), the clinical characteristics and echocardiographic parameters were significantly better 1 year after adrenalectomy compared with the baseline parameters (Table 4), including decreases in SBP, DBP, number of antihypertensive medications, PAC, ARR, and LVMI, and increases in creatinine and PRA. Eighty-eight (68.2%) APA patients were cured 1 year after adrenalectomy.

In echocardiography (Figure 2), there were no significant differences between baseline and postadrenalectomy LVEF, E/A ratio, and E-wave deceleration time. In contrast, LVMI significantly decreased (121±32 versus 110±25; *P*<0.001), e′ significantly increased (6.5±1.9 versus 7.0±2.1; *P*=0.003), and E/e′ significantly decreased (12.5±4.2 versus 11.3±3.7; *P*=0.002). In factor analysis of changes in E/e′ (ΔE/e′=postadrenalectomy E/e′−preadrenalectomy E/e′), univariate

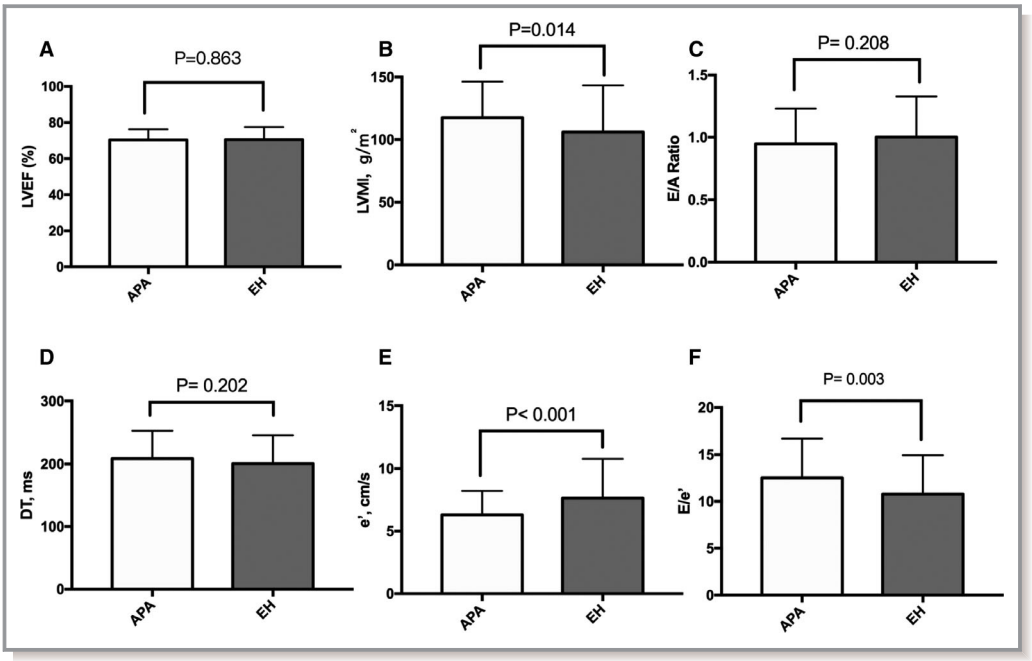

Figure 1. The echocardiographic parameters between propensity score–matched patients with aldosterone-producing adenoma and essential hypertension. **A**, No significant difference of LVEF between the 2 groups. **B**, LVMI was significantly higher in patients with APA compared with patients with EH. **C**, No difference of E/A ratio between the 2 groups. **D**, No difference of DT between the 2 groups. **E**, e′ was significantly lower in patients with APA. **F**, E/e′ was significantly higher in patients with APA. According to the above results, patients with APA had higher LVMI and diastolic dysfunction compared with the patients with EH. APA indicates aldosterone-producing adenoma; DT, early wave deceleration time; E/A, early and late diastolic velocity ratio; E/e′, early diastolic transmitral and myocardial velocity on tissue Doppler imaging ratio; e′, early diastolic myocardial velocity on tissue Doppler imaging; EH, essential hypertension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

Table 3. Univariate and Multivariate Linear Model of E/e′ Ratio in All Matched Patients (n=210)

Variables	Univariate β-Coefficient (SD)	Adjusted R^2	*P* Value	Multivariate β-Coefficient (SD)	Adjusted R^2	*P* Value
Age, y	0.112 (0.024)	0.091	<0.001	0.101 (0.023)	0.261	<0.001
Sex, male	1.173 (0.586)	0.014	0.047	2.040 (0.561)	0.261	<0.001
Body mass index, kg/m^2	0.197 (0.077)	0.026	0.012	0.241 (0.05)	0.261	0.002
History of hypertension, y	0.167 (0.042)	0.066	<0.001			
SBP, mm Hg	0.062 (0.013)	0.092	<0.001	0.038 (0.013)	0.261	0.004
DBP, mm Hg	0.042 (0.023)	0.011	0.069			
Number of antihypertensive drugs	0.482 (0.298)	0.008	0.107			
Creatinine, mg/dL	1.312 (0.608)	0.017	0.032	1.494 (0.559)	0.261	0.008
Potassium, mmol/L	0.276 (0.514)	−0.003	0.592			
Log PAC	3.001 (1.212)	0.024	0.014			
Log PRA	−0.901 (0.320)	0.032	0.005			
Log ARR	0.984 (0.299)	0.045	0.001	0.871 (0.267)	0.261	0.003

ARR indicates aldosterone–renin ratio; DBP, diastolic blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.

regression analysis showed that ΔE/e′ was significantly correlated with BMI, duration of hypertension, baseline SBP, ΔSBP, ΔDBP, baseline E/e′, baseline LVMI, and ΔLVMI. In multivariate analysis, only baseline E/e′ and ΔLVMI were significantly correlated with ΔE/e′ (Table 5).

Table 4. Parameter Comparison in APA Patients Before and After Adrenalectomy (n=129)

Patient Characteristics	Before	After	*P* Value
SBP, mm Hg	156±22	140±20	<0.001
DBP, mm Hg	93±14	86±12	<0.001
Number of antihypertensive drugs	2.1±1.2	0.6±0.9	<0.001
Laboratory parameters			
Creatinine, mg/dL	0.89±0.33	1.04±0.72	<0.001
Potassium, mmol/L	3.6±0.7	4.3±0.5	<0.001
PAC,* ng/dL	45 (47)	30 (22)	<0.001
PRA,* ng/mL per h	0.20 (0.45)	1.53 (3.58)	<0.001
ARR*	308 (1766)	18 (38)	<0.001
Echocardiographic parameters			
LVEF, %	70±6	69±9	0.411
LVMI, g/m^2	121±32	110±25	<0.001
E/A ratio	1±0.3	1±0.3	0.838
DT, ms	208±44	218±48	0.071
e′, cm/s	6.5±1.9	7.0±2.1	0.003
E/e′	12.5±4.2	11.3±3.7	0.002

APA indicates aldosterone-producing adenoma; ARR, aldosterone–renin ratio; DBP, diastolic blood pressure; DT, early wave deceleration time; E/A, early and late diastolic velocity ratio; E/e′, early diastolic transmitral and myocardial velocity on tissue Doppler imaging ratio; e′, early diastolic myocardial velocity on tissue Doppler imaging; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.
*Expressed as median and interquartile range.

When comparing the cure and noncure (with residual hypertension) patients in APA patients after adrenalectomy, we found that there were fewer male patients in the cure group. In addition, patients in the cure group had lower BMI and serum creatinine levels compared with those in the noncure group (Table 6). In echocardiographic parameters, the baseline e′ was significantly higher, and E/e′ was nonsignificantly lower in the cure group. After adrenalectomy, patients in the cure group had higher postoperative LVEF, E/A, and e′, and lower postoperative LVMI compared with those in the noncure group. There was no significant difference in the change of these echocardiographic parameters before and after adrenalectomy between the 2 groups (Table 6).

Discussion

There are several major findings in this study. First, even with comparable blood pressure and severity of hypertension in the propensity score–matching analysis, the patients with APA had higher LVMI and diastolic dysfunction compared with the patients with EH. Second, using a large population, we found improvements in LVMI and diastolic dysfunction in the patients with APA after adrenalectomy. Third, age, sex, BMI, baseline SBP, creatinine, and log ARR were associated with baseline diastolic function. Fourth, the improvement in diastolic function after adrenalectomy was associated with baseline E/e′ and ΔLVMI.

PA is characterized by the excess production of aldosterone, which results in various adverse cardiac remodeling. Aldosterone has been shown to directly stimulate hypertrophy

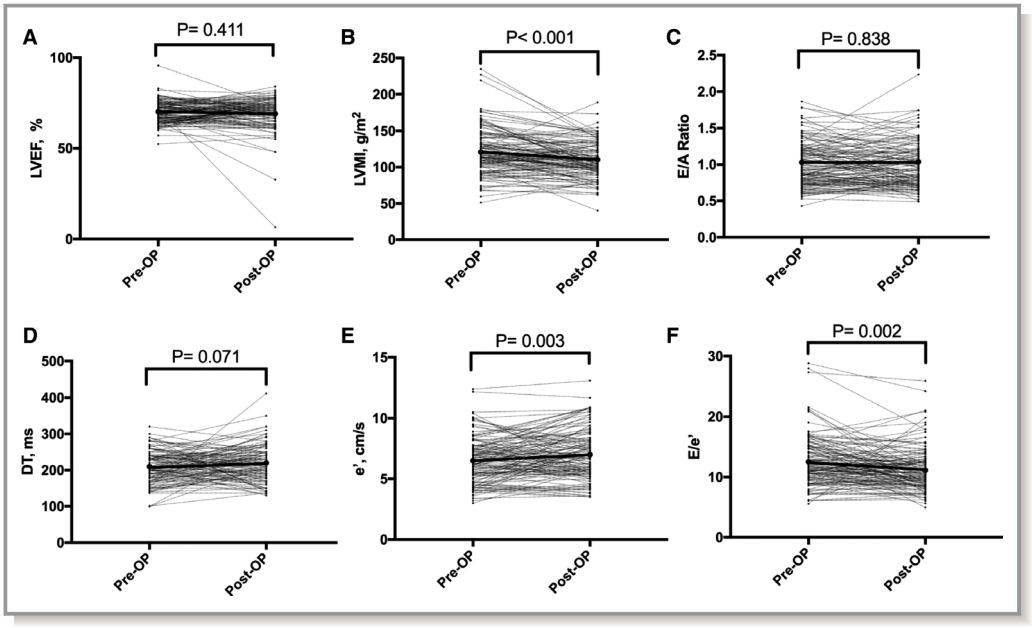

Figure 2. The echocardiographic parameters before and after adrenalectomy among all patients with aldosterone-producing adenoma. **A**, There was no significant interval change of LVEF before and after adrenalectomy. **B**, LVMI significantly decreased after adrenalectomy. **C**, There was no significant interval change of E/A ratio. **D**, There was no significant interval change of DT. **E**, e′ significantly increased after adrenalectomy. **F**, E/e′ significantly decreased after adrenalectomy. According to the above results, we found improvements in LVMI and diastolic dysfunction in the patients with APA after adrenalectomy. APA indicates aldosterone-producing adenoma; DT, early wave deceleration time; E/A, early and late diastolic velocity ratio; E/e′, early diastolic transmitral and myocardial velocity on tissue Doppler imaging ratio; e′, early diastolic myocardial velocity on tissue Doppler imaging; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; OP, adrenalectomy.

of neonatal rat ventricular cardiomyocytes by activating protein kinase C, extracellular signal-regulated kinase 1/2, and c-Jun N-terminal kinase.[33] Several animal studies have also shown that chronic increases in aldosterone accompanied by salt intake increased fibrosis in bilateral ventricles[3,34,35] and LVH.[3,35] In addition, clinical studies have reported higher rates of LVH and cardiac fibrosis independently of hemodynamic effects in PA patients compared with patients with EH.[6–8] Taken together, these results indicate that both aldosterone-induced cardiomyocyte hypertrophy and cardiac fibrosis can result in impaired LV relaxation in PA patients. In the current study, the patients with APA had lower e′ and higher E/e′ ratio, which confirmed that they had worse diastolic function compared with the patients with EH. In addition to comparing diastolic function between patients with PA and patients with EH, for patients with unilateral APA, comparing changes in diastolic function before and after adrenalectomy may further clarify the role of excess aldosterone on diastolic function. Adrenalectomy can improve blood pressure and reverse increased LVM[8,17,36] and myocardial fibrosis.[18,37] However, the reversibility of diastolic dysfunction is still under debate. In a study of 24 patients with PA who underwent adrenalectomy, diastolic function as assessed by E/A ratio and DT improved but without statistical significance.[17] In another study of adrenalectomy among 110 PA patients, diastolic function as assessed by prolongation of DT significantly improved; however, there was no significant change in atrial contribution to LV filling.[19] In the current study, diastolic function improved after adrenalectomy in the patients with APA as evidenced by a significant increase in e′ and significant decrease in E/e′ ratio, which is consistent with the conclusion that excess aldosterone contributes to diastolic dysfunction.

Accurately evaluating diastolic dysfunction by echocardiography is challenging. The effect of aldosterone on diastolic function was first proposed by Rossi et al in 1996[4] via measuring E/A integral ratio and atrial contribution to LV filling; however, both of these factors are influenced by preload.[13] In contrast to their study, our previous study showed no significant difference in early and late integral ratio between patients with PA and patients with EH.[37] This inconsistency indicates that assessing diastolic function via mitral inflow velocity-derived parameters from Doppler echocardiography is insufficient. Newer echocardiographic TDI of the mitral annulus can measure the early diastolic peak velocity of the myocardium (e′), which represents early

Table 5. Univariate and Multivariate Linear Model of ΔE/e′ Ratio Before and After Adrenalectomy in All APA Patients (n=129)

Variables	Univariate β-Coefficient (SD)	Adjusted R^2	*P* Value	Multivariate β-Coefficient (SD)	Adjusted R^2	*P* Value
Age, y	0.005 (0.033)	−0.008	0.893			
Sex, male	0.829 (0.740)	0.002	0.265			
Body mass index, kg/m^2	−0.208 (0.089)	0.034	0.020			
History of hypertension, y	−0.122 (0.052)	0.035	0.020			
Baseline SBP, mm Hg	−0.058 (0.016)	0.085	0.001			
ΔSBP, mm Hg	0.043 (0.014)	0.065	0.003			
Baseline DBP, mm Hg	−0.048 (0.027)	0.017	0.076			
ΔDBP, mm Hg	0.059 (0.024)	0.039	0.017			
Baseline hypertension drug number	−0.579 (0.303)	0.020	0.058			
ΔNumber of antihypertensive drugs	−0.038 (0.262)	−0.008	0.884			
Baseline creatinine, mg/dL	−1.130 (0.907)	0.004	0.215			
ΔCreatinine, mg/dL	−0.530 (0.781)	−0.005	0.499			
Baseline potassium, mmol/L	0.632 (0.535)	0.003	0.240			
ΔPotassium, mmol/L	−0.809 (0.502)	0.013	0.110			
Log PAC	−1.375 (1.461)	−0.001	0.348			
ΔLog PAC	0.540 (1.084)	−0.006	0.619			
Log PRA	−0.038 (0.509)	−0.008	0.941			
ΔLog PRA	−0.713 (0.378)	0.021	0.062			
Log ARR	−0.113 (0.477)	−0.007	0.814			
ΔLog ARR	0.698 (0.357)	0.024	0.053			
Cure status	0.166 (0.787)	−0.008	0.833			
Baseline E/e′	−0.591 (0.070)	0.357	<0.001	−0.557 (0.066)	0.412	<0.001
Baseline LVMI	−0.039 (0.011)	0.082	0.001			
ΔLVMI	0.035 (0.013)	0.044	0.010	0.030 (0.011)	0.412	0.006

APA indicates aldosterone-producing adenoma; ARR, aldosterone–renin ratio; DBP, diastolic blood pressure; E/e′, early diastolic transmitral and myocardial velocity on tissue Doppler imaging ratio; LVMI, left ventricular mass index; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.

diastolic relaxation, and its derived diastolic parameters are less preload dependent.[14] The E/e′ ratio eliminates the effect of LV relaxation kinetics and age and provides a more reliable measure of LV diastolic pressure.[38] Ommen et al[30] compared various Doppler and TDI parameters with mean LV diastolic pressure by simultaneous catheterization and found that the E/e′ ratio was more strongly correlated with LV diastolic pressure than any other parameter. The E/e′ ratio has also been shown to be a strong predictor of cardiac events[39] and long-term cardiovascular mortality[40] in patients with heart failure. Accordingly, the E/e′ ratio is a valuable parameter to evaluate diastolic function, which is why we used it as the major indicator of diastolic function in this study. In this study, diastolic dysfunction was reversed after adrenalectomy in the patients with APA, as evidenced by the significant increase in e′ and significant decrease in E/e′ ratio but not the E/A ratio or DT. This discrepancy may be due to the effect of preload variation on E-wave velocity and the difficulty in distinguishing the pseudonormalization stage of diastolic dysfunction from normal diastolic function only by E/A or DT. This finding indicates that the tissue Doppler parameter E/e′ ratio is better able to detect diastolic dysfunction than the traditional E/A ratio.

Some studies have used TDI to investigate diastolic function in patients with PA. In our previous study, 27 patients with APA with significantly higher SBP and DBP than 27 patients with EH had worse diastolic function, as evidenced by a higher E/e′ compared with the patients with EH.[20] In addition, Cesari et al reported that 51 patients with PA with high blood pressure had a higher E/e′ ratio and worse diastolic function compared with 61 healthy subjects.[41] However, in both studies, the baseline characteristics including age, antihypertensive medications, and most importantly, blood pressure were not well matched between the 2 study groups, and the sample sizes were also relatively small. The severity of diastolic dysfunction is proportional to blood

Table 6. Laboratory and Echocardiographic Parameters in Cure and Noncure Groups

Patient Characteristics	Cure (n=88)	Noncure (n=41)	*P* Value
Age, y	49±11	52±11	0.153
Sex, male (%)	30 (34%)	22 (54%)	0.040
Body mass index, kg/m^2	24.7±3.9	26.6±4.1	0.014
Duration of hypertension, y	6.8±6.8	9.2±86.8	0.057
SBP, mm Hg	154±23	160±18	0.111
DBP, mm Hg	93±14	94±11	0.526
Number of antihypertensive drugs	2.0±1.2	2.2±1.2	0.336
SBP, mm Hg post OP*	134±18	151±19	<0.001
DBP, mm Hg post OP	83±11	93±13	<0.001
Number of antihypertensive drugs post OP	0±0	1.5±1.0	<0.001
ΔSBP, mm Hg	−20±25	−9±25	0.021
ΔDBP, mm Hg	−9±15	−2±14	0.006
ΔNumber of antihypertensive drugs	−2.0±1.2	−0.7±1.4	<0.001
Laboratory parameters			
Creatinine, mg/dL	0.85±0.38	1.01±0.43	0.035
Creatinine post OP, mg/dL	0.93±0.32	1.28±1.15	0.076
ΔCreatinine, mg/dL	0.12±0.21	0.24±0.78	0.346
Potassium, mmol/L	3.6±0.7	3.8±0.6	0.110
Potassium post OP, mmol/L	4.3±0.4	4.3±0.5	0.632
ΔPotassium, mmol/L	0.8±0.8	0.5±0.6	0.023
PAC,* ng/dL	45 (47)	48 (45)	0.576
PAC post OP,* ng/dL	30 (20)	30 (25)	0.787
PRA,* ng/mL per h	0.17 (0.42)	0.27 (0.58)	0.374
PRA post OP,* ng/mL per h	1.5 (3.15)	1.61 (3.9)	0.770
ARR*	320 (2156)	176 (1459)	0.511
ARR post OP*	21 (33)	18 (59)	0.987
Echocardiographic parameters			
LVEF, %	71±6	69±5	0.080
LVMI, g/m^2	121±31	122±34	0.889
E/A ratio	1.0±0.3	0.9±0.3	0.162
DT, ms	207±42	210±46	0.755
e′, cm/s	6.8±1.9	5.9±1.8	0.019
E/e′	11.9±3.0	13.8±5.8	0.064
LVEF post OP, %	71±6	67±9	0.020
LVMI post OP, g/m^2	107±26	118±23	0.020
E/A ratio post OP	1.0±0.3	0.9±0.3	0.015
DT post OP, ms	213±47	228±48	0.088
e′ post OP, cm/s	7.4±2.1	6.1±1.8	0.001
E/e′ post OP	10.8±2.9	12.4±4.5	0.065
ΔLVEF, %	0.3±7.2	−1.4±8.5	0.237
ΔLVMI, g/m^2	−14±27	−5±24	0.069
ΔE/A ratio	0.02±0.29	−0.06±0.26	0.120

Continued

Table 6. Continued

Patient Characteristics	Cure (n=88)	Noncure (n=41)	*P* Value
ΔDT, ms	0.01±0.06	0.02±0.06	0.255
Δe′, cm/s	0.6±2.0	0.2±1.6	0.184
ΔE/e′	−1.1±3.9	−1.3±4.7	0.844

ARR indicates aldosterone–renin ratio; DBP, diastolic blood pressure; DT, early wave deceleration time; E/A, early and late diastolic velocity ratio; E/e′, early diastolic transmitral and myocardial velocity on tissue Doppler imaging ratio; e′, early diastolic myocardial velocity on tissue Doppler imaging; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; OP, adrenalectomy; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure.
*Expressed as median and interquartile range.

pressure.[42] In the current study, we used propensity score–matching analysis to mitigate the effect of blood pressure on diastolic function between the patients with PA and patients with EH. The influence on diastolic function caused by discrepancies in the severity of hypertension, including blood pressure, number of antihypertensive drugs, and the duration of hypertension, may have been minimized using this method, thereby showing the true effect of aldosterone on cardiac diastolic function. In addition, the large sample size improves the validity of the results of this study. One recent study by Yang et al[43] showed similar findings. In their study, patients with PA had a higher E/e′ and lower e′ than patients with EH. However, the LVMI and status of LVH were comparable between the 2 groups, which is different from previous studies.[4,5,20] In addition, our study provides postoperative data that consolidate the improvements in diastolic dysfunction in the patients with APA after adrenalectomy.

Another important finding in this study is that preoperative E/e′ and ΔLVMI were associated with the reversal of diastolic dysfunction after adrenalectomy in the patients with APA. We found similar results in our previous studies, in which preoperative LVMI was independently associated with the extent of LVMI regression after adrenalectomy.[44,45] Moreover, the regression in LVMI was significantly greater in the patients with LVH before surgery, implying that more severe LVH in the patients before surgery was associated with a greater regression in LV mass after surgery. In this study, a higher E/e′ before surgery was associated with more prominent reversal of diastolic dysfunction after surgery, which may be due to the regression of LVMI. It is also possible that the decrease in LVMI after surgery was correlated with the improvement in diastolic function.

Limitations

There are several limitations to this study. First, although we used propensity score matching to overcome discrepancies in age, sex, BMI, blood pressure, hypertension duration, and number of antihypertensive drugs between the APA and EH groups, other unknown bias may have interfered with LV diastolic function not being balanced between the 2 study groups. Second, we did not enroll patients with bilateral adrenal hyperplasia in this study. Therefore, we could not assess LV diastolic function in patients with bilateral adrenal hyperplasia and the reversibility after mineralocorticoid receptor antagonist treatment. Third, we only performed follow-up echocardiography 1 year after adrenalectomy, so we could not assess the long-term effect of adrenalectomy on LV diastolic function. Fourth, we did not check somatic mutant (especially KCNJ5) data, which may be also associated with LV structure and diastolic function. Fifth, we did not have the follow-up data in patients with EH. Therefore, we do not know the change of diastolic function in patients with EH under medical treatment. Sixth, there were some difference of antihypertensive medication between the APA and EH groups, which might have a potential influence on diastolic function.

Conclusions

The patients with PA had worse LV diastolic function than the patients with EH independently of age, sex, and hemodynamic effects. The impaired LV diastolic function could be reversed by adrenalectomy.

Appendix

Membership of the TAIPAI Study Group: Che-Hsiung Wu, MD (Chi-Taz hospital, PI of Committee); Vin-Cent Wu, MD (National Taiwan University Hospital [NTUH], PI of Committee); Yen-Hung Lin, MD (NTUH, PI of Committee); Hung-Wei Chang, MD, PhD (Far Eastern Clinics, Principal Investigator [PI] of Committee); Lian-Yu Lin MD, PhD (NTUH, PI of Committee); Fu-Chang Hu, MS, ScD (Harvard Statistics, Site Investigator); Kao-Lang Liu, MD (NTUH, PI of Committee); Shuo-Meng Wang, MD (NTUH, PI of Committee); Kuo-How Huang, MD (NTUH, PI of Committee); Yung-Ming Chen, MD (NTUH, PI of Committee); Chin-Chen Chang, MD (NTUH, PI of Committee); Shih-Cheng Liao, MD (NTUH, PI of Committee); Ruoh-Fang Yen, MD, PhD (NTUH, PI of Committee); and Kwan-Dun Wu, MD, PhD (NTUH, Director of Coordinating Center).

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Disclosures

None.

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