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ORIGINAL RESEARCH

Comparison of Echocardiographic Changes Between Surgery and Medication Treatment in Patients With Primary Aldosteronism

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BACKGROUND: Primary aldosteronism can cause cardiac dysfunction, including left ventricular hypertrophy, left ventricular diastolic dysfunction, and left atrial enlargement. A few studies have compared the cardioprotective effects between surgery and medication for primary aldosteronism, although most have not adjusted for baseline disease status. In this study, we investigated the difference in cardiovascular outcomes between surgery and medication treatment for primary aldosteronism after adjusting for baseline clinical characteristics, including aldosterone level and pretreatment echocardiographic information.

METHODS AND RESULTS: We retrospectively analyzed 220 patients diagnosed with primary aldosteronism who underwent adrenalectomy (n=144) or medication treatment (n=76) between 2009 and 2019. Echocardiographic changes were evaluated pretreatment and 1 year posttreatment. The surgery group had lower potassium, lower plasma renin activity, and higher plasma aldosterone concentration than the medication group, indicating a severe primary aldosteronism phenotype in the former. The decrease in left ventricular mass index after treatment was significantly greater in the surgery group than in the medication group (P=0.047). However, this relationship was not noted after multivariable regression analysis (standard β=−0.08, P=0.17). Additionally, decreased parameter values related to left ventricular diastolic dysfunction and left atrial enlargement were not different between the groups. Pretreatment echocardiographic values were most associated with changes in all echocardiographic parameters. The findings were consistent in the propensity score-matched analysis.

CONCLUSIONS: This study's findings suggest that there is no difference in cardioprotective efficacy between surgical and medication treatment under similar disease severity; however, it should be considered that several study participants with severe hyperaldosteronism were managed surgically.

Key Words: adrenalectomy ■ cardiac function ■ hypertrophy ■ left ventricular ■ mineralocorticoid receptor antagonist ■ primary aldosteronism

Primary aldosteronism (PA) is characterized by the autonomous production of aldosterone from the adrenal gland. It is the leading cause of secondary hypertension, accounting for ≈3% to 13% of patients with hypertension.[1] PA can cause multiple organ damage, including cardiovascular disease.[1] Past animal and clinical observational studies have shown that excess aldosterone induces cardiac inflammation, myocardial fibrosis, and left ventricular (LV) hypertrophy (LVH); thus, patients with PA have higher prevalence rates of LVH than those with essential hypertension.[2,3] LVH is the leading cause of LV diastolic dysfunction (LVDD) and is a strong predictor of cardiovascular events, including heart failure.[4] Left atrial enlargement (LAE) is also a characteristic cardiac change in PA and a predictor of cardiovascular events.[5] A severe phenotype of PA is particularly observed in patients with the *KCNJ5* mutation, the most common somatic mutation,

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CLINICAL PERSPECTIVE

What Is New?

- In patients with primary aldosteronism, posttreatment changes in echocardiographic parameters were not associated with either surgery or medication but rather with the patient's pretreatment echocardiographic values.
- On excluding patients with severe hyperaldosteronism from the surgery group, there were no differences in therapeutic effects on cardiac functions between the surgery and medication groups.

What Are the Clinical Implications?

- Our results may help clinicians consider treatment strategies for patients, particularly those with mild hyperaldosteronism.
- Medication therapy might be an acceptable option for patients with mild hyperaldosteronism instead of surgery, which requires more invasive approaches, including adrenal venous sampling.

Nonstandard Abbreviations and Acronyms

AVS	adrenal venous sampling
E/E′	the ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus
LAD	left atrial dimension
LAE	left atrial enlargement
LVDD	left ventricular diastolic dysfunction
LVDd	left ventricular end-diastolic dimension
LVMI	left ventricular mass index
PA	primary aldosteronism
PAC	plasma aldosterone concentration
PSM	propensity score matching

and the mutation carriers have higher LV mass index (LVMI) than that in noncarriers.[6,7] Because patients with PA develop these multiple cardiac changes, it is important to understand the extent of improvement achieved by treatment options for PA.

Treatment for PA can be divided into 2 categories: surgery and medication treatment. The indication of surgery for PA is determined by adrenal venous sampling (AVS). Patients without surgical indications are primarily treated with mineralocorticoid receptor antagonists.[8] A few reports have evaluated the effectiveness of surgery and medication on improving cardiac function in patients with PA.[9–11] Among these reports, one has shown that both surgery and medication improved LVH,[9] whereas others have shown that surgery alone improved LVH.[10,11] Care should be taken in patients with surgical indications as they are more likely to have severe hyperaldosteronism and LVH at pretreatment status than those who qualify for medication treatment.[12] The degrees of echocardiographic changes were shown to be dependent on the baseline echocardiographic values.[13] Therefore, the difference in efficacy between surgery and medication may be influenced by the status at baseline, signifying the importance of adjusting for baseline clinical characteristics to compare the efficacy between surgery and medication. However, because of limited patient populations, such analyses have not been performed in literature. In addition, few studies have compared the impact of surgery and medication on LVH, LAE, and LVDD.

The main objective of this study was to investigate the difference in echocardiographic changes between surgery and medication treatment for PA after adjusting for baseline clinical characteristics, including aldosterone level and pretreatment echocardiographic information.

For this objective, we conducted the following 3 studies: First, we evaluated the efficacy of surgery and medication treatment for PA on multiple cardiac functions. (We also evaluated the relationship between the *KCNJ5* mutation and echocardiographic changes in patients who underwent surgery.) Second, we performed multivariable regression analysis to determine whether the pre- and posttreatment changes in each echocardiographic parameter (Δecho) were significantly different between the surgery and medication groups. Lastly, we performed propensity score matching (PSM) analysis to compare the cardiovascular outcomes between surgery and medication among those with similar baseline characteristics.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Here we retrospectively analyzed patients who were diagnosed with PA, treated with surgery or medication, and evaluated by echocardiography before and 1 year after treatment between 2009 and 2019 at Yokohama Rosai Hospital (Yokohama, Japan). Eligible patients included 144 who underwent adrenalectomy and 76 who received medication. Patients whose cardiac function was not assessed after treatment were excluded. In addition, patients with a history of atrial fibrillation, ischemic heart disease, and/or advanced valvular disease, which could cause cardiac dysfunction,

were excluded.[14] In accordance with Japan Endocrine Society guidelines, the diagnosis of PA was confirmed by endocrinological examinations, such as furosemide plus upright test, saline-loading test, or captopril-loading test.[8] We reviewed various clinical parameters on all enrolled patients as baseline characteristics. Detailed measurements of plasma aldosterone concentration (PAC), plasma renin activity (PRA), and urinary aldosterone are described in Data S1.[8,15] The study was approved by the research ethics committee of Yokohama Rosai Hospital (No. 28-54). Informed consent was waived because the data were anonymous and the study was noninterventional. The study adhered to the principles of the Declaration of Helsinki.

Treatments

Of the 220 patients, 144 underwent laparoscopic adrenalectomy (76 patients underwent partial adrenalectomy[16] and 68 patients underwent total adrenalectomy). The remaining 76 patients received only mineralocorticoid receptor antagonist medication for treatment.

The laterality of the PA was diagnosed by segmental selective AVS in all patients.[16,17] A laparoscopic adrenalectomy was performed for patients who had unilateral disease (n=116) or bilateral disease (n=28) who requested surgery to ameliorate the symptoms.[16–18] In patients who underwent laparoscopic adrenalectomy, the Primary Aldosteronism Surgical Outcomes criteria[19] were used to evaluate the treatment response. The details of the criteria are described in Data S1.

Echocardiography

Echocardiography was performed using the Aplio i700TM (Canon Corporation, Tokyo, Japan) or ALOKA ARIETTA 850TM (Hitachi Corporation, Tokyo, Japan) before and 1 year after treatment based on the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines,[20,21] and multiple echocardiographic findings were evaluated. Left atrial dimension (LAD), LV end-diastolic dimension (LVDd) and end-systolic dimension, LV posterior wall thickness in diastole, and LV ejection fraction were measured with the M-mode in the parasternal long-axis view. The ratio of early (E) and late diastolic filling velocities, early wave deceleration time, early diastolic peak velocity of the septal mitral annulus (E′), and the ratio of E and E′ (E/E′) were obtained in the apical 4-chamber view. LVMI was calculated using the following equation: LVMI=LV mass (LVM)/body surface area. We focused on LVMI, LAD, and E/E′ in particular as representative parameters for LVH, LAE, and LVDD, respectively. Based on the echocardiographic findings 1 year after treatment, we defined "cured group" and "noncured group" and compared clinical variables for each echocardiographic parameter to determine the factors associated with the response to intervention. The definitions of "cured group" and "noncured group" are provided in Data S1.[20,21]

Sequencing of the *KCNJ5* Gene

Of 144 patients who underwent adrenalectomy, 85 were examined for the *KCNJ5* mutation from their adrenal gland specimens as previously described.[6] We evaluated the relationship between the *KCNJ5* mutation and echocardiographic changes in patients who underwent surgery.

Statistical Analysis

Data were presented as median (25th–75th percentile). For group comparisons, the Wilcoxon rank-sum test was performed for continuous variables, and Fisher's exact test was performed for categorical variables. The Wilcoxon signed-rank test was used for comparisons before and after treatment. Spearman's correlation coefficient was calculated to evaluate the relationship between the continuous variables. Multivariable regression analysis was performed to determine whether the pre- and posttreatment changes in each echocardiographic parameter were significantly different between the surgery and medication groups. The different clinical parameters of both groups and the baseline echocardiographic findings were included in the model, with a P value of <0.05.

Additionally, PSM analysis was conducted to evaluate the difference in cardiovascular outcomes between surgical and medical interventions in patients with similar baseline characteristics. Propensity scores were calculated using a nonparsimonious multivariable logistic regression model including clinical parameters that differed between the treatment groups (P<0.05), along with age and sex. In our PSM analysis, we used a 1:1 matching ratio with a caliper of 0.20×. The study models included only urinary aldosterone levels owing to the high correlation with PRA and PAC and the smaller likelihood of bias than these measurements.[22] In all statistical analyses, statistical significance was set at P<0.05. The JMP 12 software (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

RESULTS

Baseline Characteristics of Patients

The baseline characteristics of the patients are presented in Table 1. Patients in the surgery group had lower body mass index, a longer duration of hypertension, and more antihypertensive medications than those in the medication group. In both groups, we found lower systolic blood pressures and higher doses of antihypertensive agents after admission compared with those at the first attendance. Laboratory tests

Table 1. Baseline Characteristics of Patients in the Surgery and Medication Groups

Variable	Surgery (n=144)	Medication (n=76)	*P* value*	SD†
Age, y	51 (44–58)	50 (42–56)	0.32	0.13
Male, n (%)	75 (52.1)	37 (48.7)	0.67	0.07
BMI, kg/m^2	24.0 (21.4–26.8)	24.7 (22.8–27.9)	0.048	0.29
Systolic BP at first attendance, mm Hg	144 (134–161)	147 (136–161)	0.83	0.03
Diastolic BP at first attendance, mm Hg	86 (82–96)	91.5 (82.8–99.3)	0.14	0.21
DDD of antihypertensive agents at first attendance	1.0 (0.5–2.0)	1.0 (0.5–1.5)	0.44	0.24
Systolic BP after hospitalization, mm Hg	136 (125–147)	130 (123–142)	0.06	0.25
Diastolic BP after hospitalization, mm Hg	85 (78–92)	85 (77–92)	0.82	0.03
DDD of antihypertensive agents at hospitalization	2.0 (1.0–2.5)	1.5 (1.0–2.0)	<0.01	0.43
Number of antihypertensive agents at hospitalization	1 (1–2)	1 (1–1)	<0.01	0.48
Duration of hypertension, y	8 (3–15)	3 (1–7)	<0.01	0.42
Family history of hypertension, n (%)	102 (70.8)	58 (76.3)	0.41	0.12
Smoking history, n (%)	54 (37.5)	31 (40.8)	0.70	0.07
Habitual drinking, n (%)	46 (31.9)	26 (34.2)	0.72	0.05
Diabetes, n (%)	8 (5.6)	5 (6.6)	0.37	0.04
Dyslipidemia, n (%)	24 (16.7)	12 (15.8)	1.00	0.02
History of stroke, n (%)	9 (6.3)	4 (5.3)	1.00	0.04
eGFR, mL/min per 1.73 m^2	82.3 (69.3–96.2)	80.5 (69.1–95.1)	0.51	0.15
Potassium, mmol/L	3.2 (3.0–3.7)	3.8 (3.6–4.0)	<0.001	1.21
PRA, ng/mL per h	0.24 (0.15–0.43)	0.35 (0.23–0.52)	0.003	0.16
PAC, ng/dL	30.8 (16.6–46.1)	14.5 (11.6–18.0)	<0.001	0.79
Urinary aldosterone, μg/d	21.4 (10.3–34.5)	9.8 (7.1–12.8)	<0.001	0.92
Urinary cortisol, μg/d	43.0 (31.0–64.0)	40.5 (28.0–54.0)	0.06	0.30
Urinary sodium, mEq/d	151.6 (121.6–182.0)	126.5 (105.0–183.1)	0.06	0.28
Echocardiographic parameters				
E/A	1.04 (0.81–1.34)	1.10 (0.81–1.33)	0.58	0.10
DT, ms	0.20 (0.17–0.22)	0.20 (0.18–0.22)	0.70	0.09
E′, cm/s	7.75 (6.1–8.93)	7.5 (6.4–8.8)	0.82	0.04
E/E′	9.1 (7.6–9.9)	9.0 (7.9–10.2)	0.98	0.003
LVMI, g/m^2	92.0 (77.7–114.6)	90.0 (75.9–105.8)	0.12	0.26
LAD, mm	35.6 (32.4–38.5)	35.6 (31.0–38.4)	0.39	0.12
LVEF (%)	69.9 (66.3–73.8)	70.3 (67.5–74.0)	0.48	0.10
LVDd, mm	48.2 (45.3–51.9)	49.1 (45.7–51.4)	0.71	0.01
LVDs, mm	29.2 (26.2–32.3)	29.2 (27.2–31.2)	0.87	0.05
LVPWd, mm	7.9 (6.9–9.0)	7.5 (6.9–8.8)	0.12	0.21

Data are given as median (interquartile range) or n (%).

BMI indicates body mass index; BP, blood pressure; DDD, daily defined dose; DT, early wave deceleration time; E′, early diastolic peak velocity of the septal mitral annulus; E/A, ratio of early and late diastolic filling velocities; E/E′, ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SD, standardized difference.

**P* values for differences between the surgery and medication groups.

†Standardized differences between the surgery and medication groups.

further showed that patients in the surgery group had low potassium levels, low PRA, high PAC, and high urinary aldosterone levels, indicating a severe phenotype of PA. Pretreatment echocardiographic findings showed no significant difference between the surgery and medication groups, but LVMI tended to be higher in the surgery group.

Clinical and Echocardiographic Parameters Before and After Treatment

Comparisons before and after treatment are shown in Table 2. The estimated glomerular filtration rate decreased, and potassium levels and PRA increased significantly in both groups. Meanwhile, PAC decreased in

Table 2. Clinical and Echocardiographic Parameters Before and After Surgical or Medical Interventions

Variable	Surgery (n=144)				Medication (n=76)				*P*† between groups
	Before	After	*P* value*	Change	Before	After	*P* value*	Change	
Systolic BP, mm Hg	136 (125 to 147)	127 (118 to 139)	<0.001	−6 (−21 to 5)	130 (123 to 142)	130 (120 to 140)	0.35	−2 (−17 to 12)	0.054
Diastolic BP, mm Hg	85 (78 to 92)	83 (76 to 91)	0.17	−3 (−10 to 8)	85 (77 to 92)	82 (74 to 89)	0.09	−3 (−13 to 6)	0.55
Laboratory parameters									
eGFR, mL/min per 1.73 m^2	82.3 (69.3 to 96.2)	69.8 (58.3 to 84.2)	<0.001	−11.9 (−22.0 to −6.0)	80.5 (69.1 to 95.1)	73.0 (63.2 to 85.7)	<0.001	−6.2 (−13.4 to −2.0)	<0.01
Potassium, mmol/L	3.2 (3.0 to 3.7)	4.0 (3.9 to 4.3)	<0.001	0.7 (0.3 to 1.2)	3.8 (3.6 to 4.0)	4.1 (3.8 to 4.2)	<0.001	0.2 (0.1 to 0.5)	<0.001
PRA, ng/mL per h	0.24 (0.15 to 0.43)	0.70 (0.40 to 1.31)	<0.001	0.39 (0.05 to 1.0)	0.35 (0.23 to 0.52)	0.7 (0.4 to 1.2)	<0.001	0.32 (0.04 to 0.80)	0.31
PAC, ng/dL	30.8 (16.6 to 46.1)	8.8 (6.9 to 12.2)	<0.001	−19.3 (−37.5 to −6.6)	14.5 (11.6 to 18.0)	19.5 (15.3 to 26.7)	<0.001	4.7 (1.3 to 9.4)	<0.001
Echocardiographic parameters									
E/A	1.04 (0.81 to 1.34)	0.94 (0.75 to 1.28)	0.02	−0.07 (−0.23 to 0.14)	1.10 (0.81 to 1.33)	1.02 (0.8 to 1.32)	0.37	−0.01 (−0.20 to 0.14)	0.51
DT, ms	0.20 (0.17 to 0.22)	0.20 (0.18 to 0.24)	0.01	0.01 (−0.02 to 0.04)	0.20 (0.18 to 0.22)	0.20 (0.18 to 0.24)	0.37	0.00 (−0.02 to 0.03)	0.35
E′, cm/s	7.75 (6.1 to 8.93)	7.1 (5.9 to 8.9)	0.17	−0.5 (−1.4 to 1.1)	7.5 (6.4 to 8.8)	7.4 (6.0 to 8.8)	0.70	0.1 (−1.1 to 1.4)	0.24
E/E′	9.1 (7.6 to 9.9)	8.7 (7.1 to 9.7)	<0.01	−0.4 (−1.7 to 0.7)	9.0 (7.9 to 10.2)	8.5 (7.1 to 10.0)	0.06	−0.7 (−2.0 to 0.8)	0.98
LVMI, g/m^2	92.0 (77.7 to 114.6)	83.8 (72.1 to 97.5)	<0.001	−9.9 (−24.7 to 3.2)	90.0 (75.9 to 105.8)	84.5 (72.7 to 94.5)	<0.001	−5.8 (−12.0 to 3.0)	0.047
LAD, mm	35.6 (32.4 to 38.5)	34.5 (31.8 to 37.0)	<0.001	−1.0 (−3.5 to 0.9)	35.6 (31.0 to 38.4)	33.8 (30.5 to 38.4)	0.09	−0.2 (−3.3 to 1.4)	0.22
LVEF, %	69.9 (66.3 to 73.8)	70.6 (66.4 to 74.6)	0.26	0.5 (−4.0 to 5.3)	70.3 (67.5 to 74.0)	70.0 (66.0 to 74.5)	0.27	−0.8 (−5.7 to 3.3)	0.12
LVDd, mm	48.2 (45.3 to 51.9)	46.5 (43.4 to 50.5)	<0.001	−1.9 (−4.3 to 1.1)	49.1 (45.7 to 51.4)	47.7 (44.1 to 50.0)	<0.01	−0.9 (−3.2 to 0.9)	0.21
LVDs, mm	29.2 (26.2 to 32.3)	27.5 (25.1 to 31.0)	<0.001	−1.6 (−4.0 to 0.8)	29.2 (27.2 to 31.2)	28.9 (26.0 to 31.0)	0.21	−0.7 (−2.3 to 1.4)	0.03
LVPWd, mm	7.9 (6.9 to 9.0)	7.7 (6.9 to 8.6)	0.02	−0.2 (−1.0 to 0.5)	7.5 (6.9 to 8.8)	7.9 (7.0 to 8.3)	0.98	0.0 (−0.7 to 0.6)	0.17

Data are given as median (interquartile range).

BP indicates blood pressure; DT, early wave deceleration time; E′, early diastolic peak velocity of the septal mitral annulus; E/A, ratio of early and late diastolic filling velocities; E/E′, ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; PAC, plasma aldosterone concentration; PRA, plasma renin activity

**P* values for differences before versus after treatment.

†*P* values for differences in changes in variables between the surgery and medication groups.

the surgery group and increased in the medication group. The decreases in estimated glomerular filtration rate and PAC, as well as the increase in potassium levels, were significantly greater in the surgery group than in the medication group. Based on the echocardiographic findings, ratio of early and late diastolic filling velocities, early wave deceleration time, E/E′, LVMI, LAD, LVDd, left ventricular end-systolic dimension, and left ventricular posterior wall thickness in diastole were all significantly improved in the surgery group. In the medication group, LVMI and LVDd were significantly improved, and LAD and E/E′ showed similar trends. The decreases in LVMI and left ventricular end-systolic dimension were significantly greater in the surgery group than in the medication group (Table 2). In the surgery group, there was no difference in the Primary Aldosteronism Surgical Outcomes[19] or echocardiographic changes between patients who underwent partial and those who underwent total adrenalectomy (Table S1). Patients with bilateral PA had a higher rate of biochemical incomplete success than those with unilateral PA (Table S2, Figure S1). Pathological findings and biochemical outcome in bilateral PA are shown in Table S3. In 17 cases with aldosterone synthase cytochrome P450 staining, 14 had aldosterone-producing adenoma and 3 had multiple aldosterone-producing micronodules. In 11 cases without staining, 10 had adenoma and 1 had hyperplasia.

Factors Associated With ΔLVMI, ΔLAD, and ΔE/E′

Correlation analyses showed that the pretreatment echocardiographic parameters were most correlated with the echocardiographic changes (Table 3). Moreover, multivariable regression analysis showed that treatment methods (surgery versus medication) were not associated with echocardiographic changes (Table 4).

Clinical and Echocardiographic Parameters Before and After Surgery or Medication After PSM

After PSM, there were 50 patients in each group (Table S4). In our PSM analysis, patients with high urinary aldosterone levels were unmatched in the surgery group (Figure S2). The clinical and echocardiographic parameters before and after treatment are shown in Table 5. We found a decrease in estimated glomerular filtration rate levels and an increase in potassium and PRA levels in both groups; however, the differences between groups were not significant. With regard to the echocardiographic findings, early wave deceleration time, E/E′, LVMI, and LVDd were significantly improved in the surgery group, whereas LVMI and LVDd were significantly improved in the medication group. There were no significant between-group differences in any echocardiographic parameters (Table 5). In addition, given the incomplete balance of some covariates with a standardized difference of >0.10 in PSM analysis, we further adjusted for covariates included in PSM after matching.[23] The results were consistent: treatment methods (surgery versus medication) were not associated with echocardiographic changes (Table S5).

Table 3. Correlations Between Echocardiographic Changes and Baseline Clinical Parameters

	ΔLVMI*		ΔLAD*		ΔE/E′*	
Variable	ρ	*P* value	ρ	*P* value	ρ	*P* value
Age, y	0.04	0.59	−0.04	0.54	−0.04	0.59
BMI, kg/m^2	0.11	0.10	−0.02	0.76	−0.03	0.69
Systolic BP, mm Hg	−0.06	0.39	0.09	0.18	−0.04	0.54
Diastolic BP, mm Hg	−0.02	0.78	0.09	0.17	0.01	0.89
Duration of hypertension, y	−0.02	0.81	0.05	0.46	0.02	0.80
eGFR, mL/min per 1.73 m^2	−0.03	0.64	0.07	0.31	0.13	0.05
Potassium, mmol/L	0.22	<0.001	0.02	0.74	−0.05	0.46
PRA, ng/mL per h	0.08	0.25	0.01	0.93	−0.04	0.59
PAC, ng/dL	−0.28	<0.001	−0.07	0.30	−0.01	0.84
Urinary aldosterone, μg/d	−0.17	0.01	−0.03	0.68	0.04	0.53
LVMI, g/m^2	−0.63	<0.001	…	…	…	…
LAD, mm	…	…	−0.46	<0.001	…	…
E/E′	…	…	…	…	−0.48	<0.001

BMI indicates body mass index; BP, blood pressure; E/E′, ratio of early diastolic filling velocity to early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; HT, hypertension; LAD, left atrial dimension; LVMI, left ventricular mass index; PAC, plasma aldosterone concentration; PRA, plasma renin activity

*Pre- and post-treatment changes in each echocardiographic parameter.

Table 4. Multivariable Analyses for Echocardiographic Changes Before Propensity Score matching

Variable	ΔLVMI* ($R^{2\dagger}$=0.46, P<0.001)		ΔLAD* ($R^{2\dagger}$=0.28, P<0.001)		ΔE/E′* ($R^{2\dagger}$=0.33, P<0.001)	
	Standard β	*P* value	Standard β	*P* value	Standard β	*P* value
Treatment (surgery vs medication)	−0.07	0.23	−0.02	0.77	−0.07	0.34
BMI, kg/m^2	0.13	0.02	0.27	<0.001	0.10	0.12
Duration of hypertension, y	0.08	0.15	0.06	0.37	0.17	0.01
Number of antihypertensive agents	−0.01	0.84	0.02	0.74	−0.04	0.50
Potassium, mmol/L	0.03	0.66	−0.04	0.60	−0.04	0.57
Urinary aldosterone, μg/d	0.09	0.16	0.02	0.77	0.06	0.37
LVMI, g/m^2	−0.66	<0.001	…	…	…	…
LAD, mm	…	…	−0.59	<0.001	…	…
E/E′	…	…	…	…	−0.60	<0.001

Treatment (surgery vs. medication), the clinical parameters (BMI, duration of HT, number of antihypertensive agents, potassium, urinary aldosterone) and the baseline echocardiographic findings (LVMI, LAD, E/E') were included in the model. BMI indicates body mass index; E/E′, ratio of early diastolic filling velocity to early diastolic peak velocity of the septal mitral annulus; LAD, left atrial dimension; LVMI, left ventricular mass index.

*Pre- and post-treatment changes in each echocardiographic parameter.

†Coefficient of determination.

Comparison of Clinical Variables in Patients With Versus Without Cure of Echocardiographic Parameters After the Treatment

Table S6 compares the clinical variables of patients with versus without a posttreatment cure of echocardiographic parameters after treatment. Noncured patients with LVMI or E/E′ had a longer duration of hypertension than those who were cured. Posttreatment PRA was higher in the LVMI-cured group than in the noncured group. Additionally, noncured patients with LAD had a higher baseline body mass index than those who were cured. For all parameters, the baseline echocardiographic values were high in the noncured group, and there were no significant group differences in the treatment method, or pre- and posttreatment blood pressure.

Baseline Characteristics and Clinical Outcomes Between the *KCNJ5* Mutation (+) and *KCNJ5* Mutation (–) Groups

The *KCNJ5* mutation (+) group had significantly low body mass index and potassium levels and high PAC (Table S7). Pretreatment echocardiographic findings were not significantly different between the 2 groups, although LVMI tended to be higher in the mutation (+) group. We found a larger decrease in PAC and diastolic blood pressure among the *KCNJ5* mutation (+) group than in the *KCNJ5* mutation (–) group (Table S8). Of all echocardiographic parameters, we found a larger decrease in ratio of early and late diastolic filling velocities among the *KCNJ5* mutation (–) group than in the *KCNJ5* mutation (+) group (Table S8).

DISCUSSION

In this study, we evaluated multiple echocardiographic parameters before and after treatment in 144 patients treated with surgery and 76 patients treated with medication treatment, populations that were larger than those in previous studies. Our main findings are 3-fold. First, the present study showed a significant improvement in LVH in the surgery group compared with that in the medication group. Second, multivariable regression analysis showed that treatment methods (surgery versus medication) were not associated with echocardiographic changes. Lastly, PSM analysis also showed no differences in the therapeutic effects on multiple cardiac functions between the 2 groups after PSM. The results of additional multivariable analyses for echocardiographic changes after PSM are consistent.

It has been reported that the change in LVMI after treatment is dependent on the pretreatment value of LVMI, where a higher pretreatment value means a larger change, regardless of the presence of PA.[13,24–27] Our study showed that the pretreatment values of LVMI, LAD, and E/E′ were associated with their corresponding changes. Previous reports suggested that surgery may be more effective in improving cardiac function,[9–11,13] but the difference in results might be attributed to the adjustment for potential confounders, which was conducted in our study. Importantly, our results suggest the effectiveness of medication treatment not only for LVH but also for LAE and LVDD.

Our findings do not indicate equal effectiveness of surgery and medication treatment for all patients with PA. As shown in Figure S2, several patients in the surgery group had higher urinary aldosterone levels than those in the medication group, and these patients were unmatched in PSM analysis.

Table 5. Clinical and Echocardiographic Parameters Before and After Surgical or Medical Interventions After Propensity Score Matching*

Variable	Surgery (n=50)				Medication (n=50)				*P*‡ between groups
	Before	After	*P* value†	Change	Before	After	*P* value†	Change	
Systolic BP, mm Hg	134 (126 to 146)	128 (119 to 140)	0.07	−3 (−21 to 7)	133 (125 to 145)	130 (120 to 141)	0.23	−5 (−20 to 14)	0.63
Diastolic BP, mm Hg	85 (77 to 91)	85 (75 to 91)	0.64	−1 (−11 to 10)	84 (79 to 91)	83 (75 to 89)	0.19	−2 (−14 to 6)	0.52
Laboratory parameters									
eGFR, mL/min per 1.73 m^2	84.8 (73.3 to 98.3)	80.1 (68.3 to 88.8)	<0.001	−6.3 (−11.0 to −0.4)	80.5 (69.4 to 96.2)	72.7 (63.3 to 86.1)	<0.001	−7.6 (−13.9 to −2.7)	0.15
Potassium, mmol/L	3.7 (3.4 to 3.9)	3.9 (3.8 to 4.1)	<0.001	0.3 (0.1 to 0.5)	3.8 (3.5 to 3.9)	4.0 (3.7 to 4.2)	<0.001	0.3 (0.1 to 0.6)	0.93
PRA, ng/mL per h	0.30 (0.15 to 0.53)	0.50 (0.23 to 0.80)	0.004	0.08 (−0.1 to 0.47)	0.35 (0.27 to 0.53)	0.70 (0.40 to 1.20)	<0.001	0.23 (0.03 to 0.83)	0.07
PAC, ng/dL	16.1 (12.4 to 21.3)	8.8 (6.8 to 12.3)	<0.001	−6.6 (−13.0 to −3.7)	15.1 (12.7 to 18.1)	18.9 (15.6 to 26.0)	<0.001	4.1 (1.3 to 8.8)	<0.001
Echocardiographic parameters									
E/A	0.97 (0.82 to 1.24)	1.02 (0.81 to 1.25)	0.72	−0.05 (−0.19 to 0.17)	1.08 (0.78 to 1.37)	1.06 (0.79 to 1.33)	0.48	−0.04 (−0.18 to 0.15)	0.84
DT, ms	0.19 (0.17 to 0.21)	0.20 (0.17 to 0.24)	0.04	0.00 (−0.02 to 0.05)	0.20 (0.17 to 0.23)	0.20 (0.17 to 0.24)	0.82	0.00 (−0.02 to 0.03)	0.23
E′, cm/s	7.8 (6.1 to 8.7)	7.3 (5.9 to 9.6)	0.25	0.5 (−1.1 to 2.0)	7.5 (6.1 to 9.2)	7.3 (5.9 to 8.7)	0.98	0.1 (−1.2 to 1.3)	0.32
E/E′	9.3 (7.5 to 10.4)	8.7 (7.1 to 9.3)	0.01	−0.6 (−2.2 to 0.4)	8.7 (7.9 to 10.2)	9.1 (7.4 to 10.0)	0.57	0.03 (−1.7 to 1.2)	0.12
LVMI, g/m^2	82.8 (72.9 to 94.1)	80.2 (68.3 to 90.2)	0.03	−3.6 (−17.9 to 5.3)	90.0 (76.7 to 103.6)	84.3 (75.3 to 93.9)	0.01	−5.2 (−11.7 to 4.7)	0.99
LAD, mm	35.4 (32.2 to 38.4)	34.7 (32.0 to 37.1)	0.07	−0.7 (−2.9 to 1.4)	35.2 (30.6 to 37.8)	33.8 (30.6 to 38.6)	0.28	0.0 (−2.5 to 1.3)	0.70
LVEF (%)	70.3 (65.1 to 73.6)	70.1 (65.3 to 74.1)	0.89	−0.3 (−4.1 to 4.3)	70.7 (68.4 to 74.1)	70.0 (66.8 to 74.7)	0.15	−1.1 (−5.9 to 3.2)	0.37
LVDd, mm	47.4 (44.8 to 51.0)	45.5 (42.9 to 49.2)	0.04	−1.9 (−3.7 to 1.5)	49.5 (46.8 to 51.8)	47.7 (43.7 to 50.0)	<0.001	−1.6 (−4.0 to 0.0)	0.39
LVDs, mm	28.2 (25.6 to 31.1)	27.7 (25.2 to 30.1)	0.11	−0.6 (−3.1 to 1.7)	29.6 (27.3 to 31.3)	29.4 (26.0 to 31.0)	0.12	−1.1 (−2.7 to 1.1)	0.92
LVPWd, mm	7.9 (6.9 to 8.8)	7.4 (6.9 to 8.4)	0.33	−0.1 (−0.9 to 0.6)	7.4 (6.9 to 8.5)	7.9 (7.0 to 8.4)	0.34	0.1 (−0.5 to 1.0)	0.18

Data are given as median (interquartile range). BP indicates blood pressure; DT, early wave deceleration time; E′, early diastolic peak velocity of the septal mitral annulus; E/A, ratio of early and late diastolic filling velocities; E/E′, ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; HT, hypertension; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

*1:1 matching for age, sex, BMI, duration of HT, number of antihypertensive agents, potassium, and urinary aldosterone.

†*P*-values for differences before versus after treatment.

‡*P*-values for differences in changes in variables between the surgery and medication groups.

The results of PSM analysis suggest that a similar treatment efficacy could be achieved in patients with relatively mild hyperaldosteronism, although it is unclear whether this applies to patients with more severe hyperaldosteronism. Particularly for patients with severe hyperaldosteronism, medication alone may not provide adequate blood pressure control or may require more antihypertensive drugs, whereas surgery may reduce antihypertensive medications.[28] Therefore, surgical indication should be assessed carefully by AVS, especially in patients with severe hyperaldosteronism. Our results suggest that surgery and medication are comparable in the prevention of cardiac dysfunction in patients with relatively mild hyperaldosteronism.

Although the statistical power may be associated with the different results in each index, a noteworthy finding was the longer duration of hypertension in noncured patients with LVMI or E/E′ than in cured patients (Table S6). In addition, posttreatment PRA was higher in the LVMI-cured group than in the noncured group. Similarly, ΔLVMI was greater in the PRA ≥1 group (–11.8 [–26.3 to 0]) than in the PRA <1 group (–7.0 [–17.4 to 4.4]) (P=0.02). A longer duration of hypertension induces myocardial damage,[29] and continuous renin suppression is associated with cardiovascular risk[30,31]; thus, early treatment and PRA elevation may be important to preventing the deterioration of cardiac function.

Additionally, the presence of the *KCNJ5* mutation is important because it is the most common mutation in aldosterone-producing adenoma and is associated with a severe phenotype of PA in East Asian patients.[6,7] There is limited information on the influence of this mutation on echocardiographic changes after surgery. As shown in Table S8, more echocardiographic parameters were significantly improved after adrenalectomy in the *KCNJ5* mutation (+) group than those in the *KCNJ5* mutation (–) group. Similar finding has been reported in previous study.[7] However, the differences in the treatment effects between the 2 groups might have resulted from the differences in baseline clinical and echocardiographic parameters. Therefore, a multivariable analysis including baseline echocardiographic and aldosterone values as explanatory factors for this finding should be performed with a larger study population than that in our study.

The present study has some limitations. First, it was conducted in a single center specializing in PA and segmental selective AVS in Japan, which limits the generalizability of our findings. For example, the baseline resting systolic blood pressure levels after hospitalization were relatively low in this cohort. The difference from the blood pressure at the first attendance might have been related to the dose of antihypertensive agents and the decrease in salt intake after hospitalization. In a previous multicenter study, the Japanese population had a relatively lower blood pressure than populations in other countries.[19] This gap may be due to differences in insurance systems and accessibility to medical facilities.[32] Second, as we included patients who were evaluated by echocardiography before and 1 year after treatment, we cannot rule out the possibility of selection bias due to the exclusion of those who were transferred to their primary care clinics after starting medications. Third, there was a short follow-up period of 1 year, and long-term data were not collected. The genetic profile of unilateral aldosterone-producing adenoma often differs from that of idiopathic bilateral adrenal hyperplasia, and we cannot deny the possibility that aldosterone-producing adenoma may become uncontrollable with medication in the long term. Fourth, patients with relatively mild LVH, LVDD, and LAE levels were included. Fifth, patients with ischemic heart disease, valvular disease, or arrhythmia were excluded; therefore, the effect of treatment in these patients is unknown. Sixth, there may be other unevaluated confounding factors that could have affected our results.

CONCLUSIONS

In conclusion, surgical and medical management may each effectively and similarly improve multiple cardiac functions in patients with relatively mild hyperaldosteronism. Meanwhile, surgery should be carefully evaluated by AVS in patients with severe hyperaldosteronism because it is unclear whether surgery and medication are equally effective.

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S8
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Measurement of PAC, PRA, and urinary aldosterone

PAC, PRA, and urinary aldosterone levels were measured using radioimmunoassay kits with confirmed validity and reliability.[15] According to JES guidelines, we optimized the prescription of anti-hypertensive drugs to patients by prescribing only calcium channel blockers and/or alpha-adrenoreceptor antagonists several weeks before blood sampling to measure PAC and PRA.[8]

PASO Criteria for Biochemical and Clinical Success

The PASO criteria for the classification of biochemical success are described below.[19] Complete success was defined as a correction of hypokalemia and normalization of the aldosterone-renin ratio (ARR) or defined as a PAC from the saline loading test suppressed to <50 pg/mL (139 pmol/L) in patients with an increased ARR after surgery. Partial success was defined by the correction of hypokalemia and a raised ARR with PAC from the saline-loading test of 50–100 pg/mL (139–277 pmol/L). Absent success was defined as persistent hypokalemia and/or a persistently increased ARR with PAC from the saline loading test result of >100 pg/mL (277 pmol/mL). Hypokalemia was defined as a serum potassium level <3.6 mmol/L. We divided the patients into two groups: those with complete biochemical success and those with incomplete (partial or absent) biochemical success.

We also divided the patients into two groups according to clinical outcomes: those with clinical complete success and those with clinical incomplete success. Clinical complete success was defined as normotension without any antihypertensive drugs, while clinical incomplete success was defined as hypertension or normotension with antihypertensive drugs.[19]

Definitions of "cured group" and "non-cured group"

Based on the echocardiographic findings one year after treatment, we defined "cured group" and "non-cured group" as follows: cured: LVMI $\leq$ 115 g/m^2 in men and $\leq$ 95 g/m^2 in women, LAD $\leq$ 40 mm in men and $\leq$ 38 mm in women, and E/E′ < 10; non-cured: LVMI > 115 g/m^2 in men and > 95 g/m^2 in women, LAD > 40 mm in men and > 38 mm in women, and E/E′ $\geq$ 10.[20,21]

Table S1. Comparison of treatment effects of partial versus total adrenalectomy.

	Partial adrenalectomy (n=76)	Total adrenalectomy (n=68)	*P*†
Clinical success			0.86
Complete, n (%)	27 (35.5)	23 (33.8)	
Incomplete, n (%)	49 (64.5)	45 (66.2)	
Biochemical success*			0.43
Complete, n (%)	59 (79.7)	49 (73.1)	
Incomplete, n (%)	15 (20.3)	18 (26.9)	
ΔLVMI	-10.17 (-25.02– -0.55)	-9.5 (-23.4–5.51)	0.27
ΔLAD	-1.8 (-3.5–0.25)	-0.75 (-3.15–1.43)	0.36
ΔE/E′	-0.45 (-2.01–0.57)	-0.33 (-1.52–0.67)	0.30

Data are given as median (interquartile range) or n (%).

E/E′, the ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; LAD, left atrial dimension; LVMI, left ventricular mass index

*Biochemical outcome could not be judged due to missing data in 3 cases.

†*P*-values for differences between the partial and total adrenalectomy groups.

Table S2. Comparison of treatment effects with unilateral versus bilateral PA.

	Partial adrenalectomy (n=76)			Total adrenalectomy (n=68)		
	Unilateral PA (n=60)	Bilateral PA (n=16)	*P*†	Unilateral PA (n=56)	Bilateral PA (n=12)	*P*†
Clinical success			0.15			1.0
Complete, n (%)	24 (40.0)	3 (18.8)		19 (33.9)	4 (33.3)	
Incomplete, n (%)	36 (60.0)	13 (81.2)		37 (66.1)	8 (66.7)	
Biochemical success*			**0.001**			0.07
Complete, n (%)	52 (88.1)	7 (46.7)		43 (78.2)	6 (50.0)	
Incomplete, n (%)	7 (11.9)	8 (53.3)		12 (21.8)	6 (50.0)	

Data are given as n (%).

PA, primary aldosteronism

*Biochemical outcome could not be judged due to missing data in 3 cases.

†*P*-values for differences between unilateral and bilateral PA.

Table S3. **Pathological findings and biochemical outcome in bilateral PA.**

Cases with CYP11B2 immunostaining (n=17)		
Pathological diagnosis	**APA (n=14)**	**MAPM (n=3)**
biochemical success complete/incomplete	**4/10**	**1/2**
Cases without CYP11B2 immunostaining (n = 11)		
Pathological diagnosis	**cortical adenoma(n=10)**	**cortical hyperplasia (n=1)**
biochemical success complete/incomplete*	**7/2**	**1/0**

APA, aldosterone-producing adenoma; CYP11B2, aldosterone synthase cytochrome P450; MAPM, multiple aldosterone-producing micronodules; PA, primary aldosteronism.

*Biochemical outcome could not be judged due to missing data in one case.

Table S4. Baseline characteristics of patients treated with surgery or medication after propensity score matching.

Variable	After PSM*			
	Surgery (n=50)	Medication (n=50)	*P*†	SD‡
Age (years)	51 (44–59)	50 (41–55)	0.37	0.17
Male, n (%)	20 (40.0)	23 (46.0)	0.69	0.12
BMI (kg/m^2)	24.6 (21.9–27.1)	24.7 (21.8–28.0)	0.52	0.16
Systolic BP (mmHg)	134 (126–146)	133 (125–145)	0.90	0.05
Diastolic BP (mmHg)	85 (77–91)	84 (79–91)	0.59	0.14
Duration of HT (years)	4 (1–11)	4 (2–7)	0.95	0.01
Family history of HT, n (%)	39 (78.0)	41 (82.0)	0.46	0.10
Smoking history, n (%)	17 (34.0)	17 (34.0)	0.77	0.00
Habitual drinking, n (%)	14 (28.0)	14 (28.0)	1.00	0.00
Number of antihypertensive agents	1.0 (1.0–1.3)	1.0 (1.0–1.0)	0.54	0.18
Diabetes mellitus, n (%)	2 (4.0)	5 (10.0)	0.48	0.24
Dyslipidemia, n (%)	12 (24.0)	10 (20.0)	0.81	0.10
History of stroke, n (%)	2 (4.0)	4 (8.0)	0.68	0.17
eGFR (mL/min/1.73 m^2)	84.8 (73.3–98.3)	80.5 (69.4–96.2)	0.32	0.17
Potassium (mmol/L)	3.7 (3.4–3.9)	3.8(3.5–3.9)	0.57	0.13
PRA (ng/mL/h)	0.30 (0.15–0.53)	0.35 (0.27–0.53)	0.07	0.27
PAC (ng/dL)	16.1 (12.4–21.3)	15.1 (12.7–18.1)	0.47	0.34
Urinary aldosterone (μg/d)	9.1 (7.0–11.9)	10.4 (8.1–13.4)	0.27	0.18
Urinary cortisol (μg/d)	40.5 (29.8–61.4)	43.8 (28.6–54.6)	0.77	0.16
Urinary sodium (mEq/d)	134.6 (110.5–167.2)	129.3 (105.7–175.4)	0.57	0.11
Echocardiographic parameters				
E/A	0.97 (0.82–1.24)	1.08 (0.78–1.37)	0.51	0.17
DT (ms)	0.19 (0.17–0.21)	0.20 (0.1–0.23)	0.44	0.21
E′ (cm/s)	7.8 (6.1–8.7)	7.5 (6.1–9.2)	0.85	0.02
E/E′	9.3 (7.5–10.4)	8.7 (7.9–10.2)	0.56	0.14
LVMI (g/m^2)	82.8 (72.9–94.1)	90.0 (76.7–103.6)	0.18	0.18
LAD (mm)	35.4 (32.2–38.4)	35.2 (30.6–37.8)	0.55	0.12
LVEF (%)	70.3 (65.1–73.6)	70.7 (68.4–74.1)	0.27	0.25

LVDd (mm)	47.4 (44.8–51.0)	49.5 (46.8–51.8)	**0.04**	0.44
LVDs (mm)	28.2 (25.6–31.1)	29.6 (27.3–31.3)	0.35	0.18
LVPWd (mm)	7.9 (6.9–8.8)	7.4 (6.9–8.5)	0.56	0.16

Data are given as median (interquartile range) or n (%).

BMI, body mass index; BP, blood pressure; DT, early wave deceleration time; E′, early diastolic peak velocity of the septal mitral annulus; E/A, ratio of early and late diastolic filling velocities; E/E′, ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; HT, hypertension; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PSM, propensity score matching; SD, standardized difference

*1:1 matching for age, sex, BMI, duration of HT, number of antihypertensive agents, potassium, and urinary aldosterone.

†*P*-values for differences between the surgery and medication groups.

‡Standardized differences between the surgery and medication groups.

Table S5. Multivariable analyses for echocardiogram changes after propensity score matching.

Variable	ΔLVMI*		ΔLAD*		ΔE/E`*	
	standard β	*P*	standard β	*P*	standard β	*P*
Treatment (surgery vs. medication)	-0.02	0.93	-0.01	0.95	-0.02	0.90
Age	-0.03	0.73	-0.02	0.86	-0.10	0.27
Sex (male vs. female)	0.37	0.05	-0.31	0.14	0.07	0.72
BMI (kg/m^2)	0.13	0.19	0.22	0.06	0.01	0.92
Duration of HT (years)	0.11	0.25	0.03	0.78	0.05	0.60
Number of antihypertensive agents	-0.14	0.15	0.15	0.19	0.15	0.13
Potassium (mmol/L)	0.04	0.67	0.04	0.71	0.00	0.96
Urinary aldosterone (μg/day)	-0.06	0.49	0.08	0.42	0.12	0.19
LVMI (g/m^2)	-0.59	**<0.001**	-		-	
LAD (mm)	-		-0.33	**<0.001**	-	
E/E`	-		-		-0.44	**<0.001**
R^2†	0.31		0.13		0.33	
P	**<0.001**		**0.007**		**<0.001**	

Treatment (surgery vs. medication), the clinical parameters that were adjusted for propensity score matching (age, sex, BMI, duration of HT, number of antihypertensive agents, potassium, urinary aldosterone) and the baseline echocardiographic findings (LVMI, LAD, E/E`) were included in the model. BMI, body mass index; E/E`, ratio of early diastolic filling velocity to early diastolic peak velocity of the septal mitral annulus; HT, hypertension; LAD, left atrial dimension; LVMI, left ventricular mass index

*Pre- and post-treatment changes in echocardiographic parameters.

†Coefficient of determination

Table S6. Comparison of clinical variables in patients with versus without cure of echocardiographic parameters after the treatment.

	LVMI			LAD			E/E′		
	Cured (n=190)	Non-cured (n=30)	*P**	Cured (n=188)	Non-cured (n=32)	*P**	Cured (n=167)	Non-cured (n=42)	*P**
At baseline									
Age (years)	50 (43–58)	52 (46–58.3)	0.32	49 (43–58)	53 (45–59)	0.21	49 (43–58)	52 (46–58)	0.09
Male, n (%)	100 (52.6)	12 (40.0)	0.24	91 (48.4)	21 (65.6)	0.09	86 (51.5)	20 (47.6)	0.73
BMI (kg/m^2)	24.5 (21.7–26.9)	23.2 (21.4–26.6)	0.26	23.9 (21.5–26.7)	26.2 (23.6–29.5)	**<0.01**	24.4 (21.7–26.9)	24.0 (21.4–27.2)	0.90
Systolic BP (mmHg)	133 (125–147)	139 (125–146)	0.52	134 (125–146)	134 (126–148)	0.86	134 (125–146)	133 (125–148)	0.89
Diastolic BP (mmHg)	85 (78–92)	84.5 (78.8–88.3)	0.74	85 (78–92)	84 (76–96)	0.63	84 (78–92)	85 (78–94)	0.68
Duration of HT (years)	5.0 (2.0–12.0)	10.0 (5.3–16.5)	**0.01**	5 (2–12)	6 (3–15)	0.32	4 (2–11)	10 (5–18)	**<0.001**
Smoking history, n (%)	73 (38.6)	12 (40.0)	1.00	72 (38.3)	13 (40.6)	0.85	60 (35.9)	19 (46.3)	0.28
Habitual drinking, n (%)	60 (31.7)	12 (40.0)	0.41	60 (31.9)	12 (37.5)	0.55	57 (34.1)	14 (33.3)	1.00

Number of antihypertensive agents	1 (1–2)	1 (1–2)	0.22	1 (1–2)	1 (1–2)	0.11	1 (1–2)	1 (1–2)	0.40
Diabetes mellitus, n (%)	10 (5.3)	3 (10.7)	0.22	10 (5.3)	3 (9.4)	0.41	7 (4.2)	5 (12.0)	0.07
Dyslipidemia, n (%)	31 (16.4)	5 (19.2)	0.78	25 (13.7)	11 (34.4)	**0.01**	26 (16.1)	8 (19.1)	0.65
History of stroke, n (%)	9 (4.7)	4 (13.3)	0.08	11 (5.9)	2 (6.3)	1.00	8 (4.8)	5 (12.0)	0.14
eGFR (mL/min/1.73 m^2)	81.3 (69.6–95.0)	83.7 (67.3–103.4)	0.93	82.5 (69.3–96.4)	77.1 (69.1–91.8)	0.12	81.0 (68.9–95.7)	83.6 (68.7–97.1)	0.90
Potassium (mmol/L)	3.5 (3.1–3.9)	3.4 (3.1–3.6)	**0.048**	3.5 (3.1–3.8)	3.6 (3.1–3.8)	0.94	3.5 (3.1–3.8)	3.4 (3.0–3.7)	0.13
PRA (ng/mL/h)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.07	0.3 (0.1–0.5)	0.3 (0.1–0.4)	0.89	0.3 (0.1–0.5)	0.2 (0.1–0.4)	0.34
PAC (ng/dL)	18.5 (13.1–37.1)	27.6 (16.0–57.0)	**0.04**	18.0 (12.4–36.3)	17.3 (13.9–29.1)	0.87	17.4 (12.2–35.7)	22.3 (12.9–36.0)	0.40
Urinary aldosterone (μg/d)	13.8 (8.5–25.8)	16.7 (10.9–34.1)	0.09	13.5 (8.2–29.2)	16.4 (10.6–23.0)	0.42	12.9 (8.4–25.4)	20.1 (11.3–36.1)	**0.01**

LVMI (g/m^2)	89.2 (75.9–106.0)	118.1 (93.8–135.3)	**<0.001**	90.0 (76.7–107.3)	108.5 (82.4–127.2)	**0.01**	90.0 (76.9–107.4)	103.3 (80.8–118.2)	**0.03**
LAD (mm)	35.6 (32.0–38.4)	36.6 (32.7–39.6)	0.23	34.7 (31.5–37.8)	41.7 (38.0–44.9)	**<0.001**	35.2 (31.9–38.2)	37.0 (32.0–40.3)	0.12
E/E′	9.0 (7.6–9.9)	9.5 (8.2–11.8)	**0.02**	9.0 (7.6–9.9)	9.2 (8.2–11.2)	0.19	8.7 (7.4–9.8)	10.3 (9.1–12.1)	**<0.001**
Treatment method									
Surgery, n (%)	123 (64.7)	21 (70.0)	0.68	125 (66.5)	19 (59.4)	0.43	109 (65.3)	25 (59.5)	0.59
At follow-up									
Systolic BP (mmHg)	127 (119–139)	136 (125–145)	0.06	128 (118–139)	130 (120–137)	0.47	128 (118–139)	127 (121–138)	0.89
Diastolic BP (mmHg)	83 (74–90)	87 (78.3–93.5)	0.14	82 (74–90)	85 (80–91)	0.09	83 (74–90)	80 (75–87)	0.25
Potassium (mmol/L)	4.1 (3.9–4.2)	4.0 (3.8–4.3)	0.70	4.0 (3.9–4.2)	4.1 (3.9–4.4)	0.10	4.0 (3.9–4.2)	4.1 (4.0–4.3)	0.06
PRA (ng/mL/h)	0.7 (0.4–1.3)	0.6 (0.2–0.9)	**0.04**	0.7 (0.4–1.4)	0.6 (0.2–0.9)	0.07	0.7 (0.4–1.3)	0.7 (0.4–1.4)	0.58

Data are given as median (interquartile range). BMI, body mass index; BP, blood pressure; E/E′, the ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; HT, hypertension; LAD, left atrial dimension; LVMI, left ventricular mass index; PAC, plasma aldosterone concentration; PRA, plasma renin activity

*P-values of differences between the cured and non-cured groups.

Table S7. Baseline characteristics of patients with versus without the *KCNJ5* mutation.

	KCNJ5 (+) (n=59)	*KCNJ5* (-) (n=26)	*P**
Age (years)	48 (44–57)	55 (43–60)	0.30
Male, n (%)	24 (40.6)	16 (61.5)	0.08
BMI (kg/m^2)	22.5 (20.8–24.8)	25.2 (22.3–27.4)	**0.03**
Systolic BP (mmHg)	136 (128–150)	138 (128–147)	0.97
Diastolic BP (mmHg)	85 (79–96)	85 (75–92)	0.19
Duration of HT (years)	10 (4–16)	8 (3–15)	0.44
Family history of HT, n (%)	39 (66.1)	20 (76.9)	0.82
Number of anti-hypertensive agents	1 (1–2)	1 (1–2)	0.88
Diabetes mellitus, n (%)	1 (1.7)	2 (7.7)	0.38
Hyperlipidemia, n (%)	11 (18.6)	6 (23.0)	0.77
History of stroke, n (%)	4 (67.8)	0 (0.0)	0.31
eGFR (mL/min/1.73 m^2)	88.1 (76.1–107.5)	81.2 (69.1–91.3)	0.050
Potassium (mmol/L)	3.2 (2.9–3.4)	3.7 (3.1–3.9)	**0.02**
PRA (ng/mL/h)	0.23 (0.12–0.50)	0.27 (0.19–0.47)	0.34
PAC (ng/dL)	35.7 (24.0–54.8)	22.3 (12.6–34.3)	**<0.01**
Urinary aldosterone (μg/d)	24.9 (12.9–36.15)	14.2 (7.2–37.9)	0.12
Urinary cortisol (μg/d)	40.4 (31.8–56.0)	53.3 (31.4–65.2)	0.22
Urinary sodium (mEq/d)	144.0 (117.5–178.5)	162.0 (129.6–173.8)	0.30
Echocardiographic parameters			
E/A	1.07 (0.77–1.38)	1.03 (0.88–1.35)	0.84
DT (ms)	0.20 (0.17–0.21)	0.19 (0.17–0.22)	0.70
E′ (cm/s)	7.8 (5.9–9.6)	7.6 (6.4–8.5)	0.61
E/E′	9.2 (7.4–10.4)	8.8 (7.3–10.3)	0.92
LVMI (g/m^2)	96.0 (77.4–114.9)	85.6 (77.1–104.7)	0.21
LAD (mm)	35.2 (32.4–38.4)	36.3 (31.1–39.7)	0.9
LVEF (%)	70.9 (66.3–74.4)	69.5 (66.5–72.7)	0.51
LVDd (mm)	47.5 (44.9–52.8)	48.5 (45.6–49.9)	0.92
LVDs (mm)	28.7 (25.5–32.9)	28.4 (26.4–30.8)	0.96
LVPWd (mm)	7.9 (6.9–8.8)	7.7 (7.4–8.7)	0.83

Data are given as median (interquartile range) or n (%).

BMI, body mass index; BP, blood pressure; DT, early wave deceleration time; E′, early diastolic peak velocity of the septal mitral annulus; E/A, ratio of early to late diastolic filling velocities; E/E′, ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; HT, hypertension; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; PAC, plasma aldosterone concentration; PRA, plasma renin activity

*P-values for differences between *KCNJ5*(+) and *KCNJ5*(-) groups.

Table S8. Clinical and echocardiographic changes after surgery in patients with versus without the *KCNJ5* mutation.

	KCNJ5 (+) (n=59)				*KCNJ5* (-) (n=26)				*P*† between groups
	Before surgery	After surgery	*P**	Change	Before surgery	After surgery	*P**	Change	
Systolic BP (mmHg)	136 (128–150)	126 (117–139)	**<0.001**	-9 (-24–4)	138 (128–147)	130 (122–139)	0.15	-4 (-22–8.3)	0.41
Diastolic BP (mmHg)	85 (79–96)	83 (72–94)	**0.01**	-4 (-14–3)	85 (75–92)	86 (78.5–93)	0.40	6.5 (-10.0–14.5)	**0.04**
Laboratory parameters									
eGFR (mL/min/1.73 m^2)	88.1 (76.1–107.5)	74.51 (64.4–85.1)	**<0.001**	-14.7 (-23.7–-7.6)	81.2 (69.1–91.3)	70.0 (57.7–81.5)	**<0.001**	-9.6 (-18.8–1.2)	0.09
Potassium (mmol/L)	3.2 (2.9–3.4)	4.0 (3.9–4.2)	**<0.001**	0.7 (0.5–1.2)	3.7 (3.1–3.9)	3.9 (3.9–4.5)	**<0.001**	0.35 (0.0–1.3)	0.06
PRA (ng/mL/h)	0.23 (0.12–0.50)	0.68 (0.40–1.45)	**<0.001**	0.38 (0.07–1.23)	0.27 (0.19–0.47)	0.71 (0.43–1.05)	**<0.001**	0.25 (0.02–0.96)	0.52
PAC (ng/dL)	35.7 (24.0–54.8)	8.9 (6.9–11.3)	**<0.001**	-24.8 (-45.2–-13.4)	22.3 (12.6–34.3)	8.1 (6.2–11.3)	**<0.001**	-13.3 (-26.5–-5.3)	**0.01**
Echocardiographic parameters									
E/A	1.07 (0.77–1.38)	1.00 (0.76–1.39)	0.86	-0.01 (-0.15–0.16)	1.03 (0.88–1.35)	0.84 (0.74–1.19)	**0.01**	-0.11 (-0.34–-0.02)	**0.04**

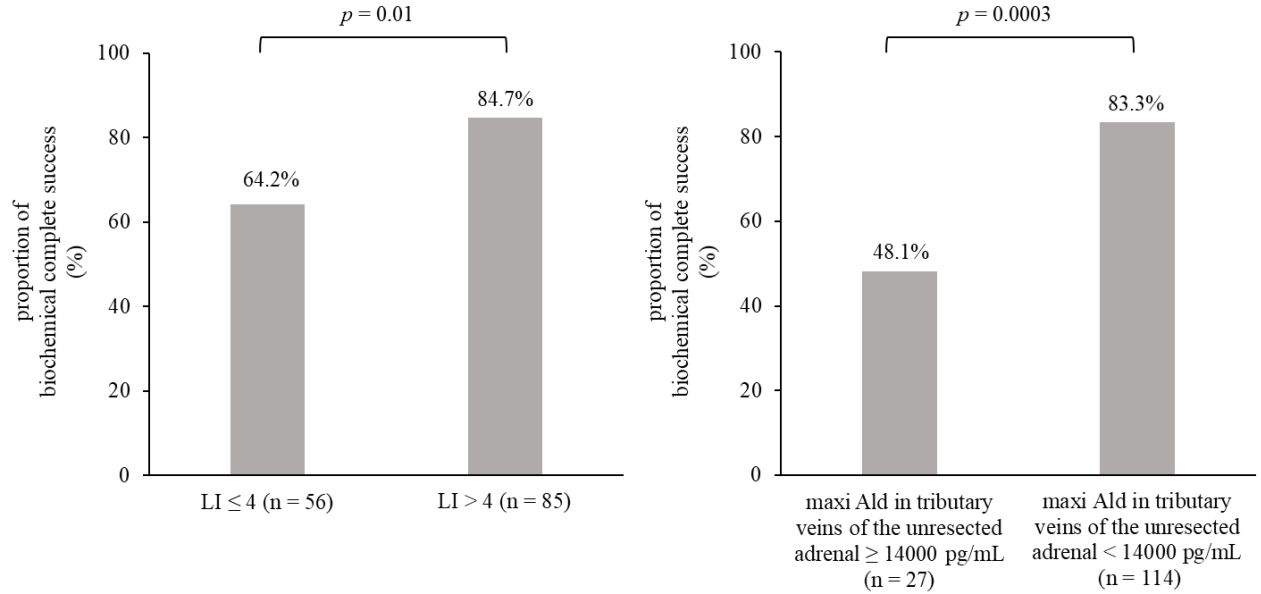
DT (ms)	0.20 (0.17–0.21)	0.20 (0.18–0.23)	0.07	0.01 (-0.01–0.04)	0.19 (0.17–0.22)	0.21 (0.19–0.25)	0.10	0.03 (-0.03–0.05)	0.40
E′ (cm/s)	7.8 (5.9–9.6)	7.2 (6.1–9.5)	0.50	0.0 (-1.4–0.8)	7.6 (6.4–8.5)	7.1 (5.6–8.9)	0.59	-0.4 (-1.2–0.9)	0.90
E/E′	9.2 (7.4–10.4)	8.6 (7.3–9.8)	**0.049**	-0.59 (-1.72–0.68)	8.8 (7.3–10.3)	8.2 (6.3–9.8)	0.47	0.09 (-2.12–1.13)	0.87
LVMI (g/m^2)	96.0 (77.4–114.9)	84.0 (71.0–100.0)	**<0.001**	-10.6 (-24.1–-1.2)	85.6 (77.1–104.7)	82.9 (74.2–92.1)	0.16	-4.7 (-22.3–8.1)	0.15
LAD (mm)	35.2 (32.4–38.4)	34.3 (31.0–36.1)	**<0.01**	-1.0 (-3.5–0.9)	36.3 (31.1–39.7)	34.7 (32.4–37.4)	**0.04**	-1.7 (-3.0–0.2)	0.83
LVEF (%)	70.9 (66.3–74.4)	70.9 (65.6–74.6)	0.98	-0.5 (-5.3–5.2)	69.5 (66.5–72.7)	70.5 (65.4–74.6)	0.80	2.1 (-3.9–3.9)	0.72
LVDd (mm)	47.5 (44.9–52.8)	46.7 (43.5–51.6)	**<0.01**	-1.4 (-4.1–1.0)	48.5 (45.6–49.9)	47.0 (43.4–48.8)	0.22	-1.5 (-4.6–3.3)	0.57
LVDs (mm)	28.7 (25.5–32.9)	27.8 (25.5–31.5)	0.052	-0.9 (-3.8–1.8)	28.4 (26.4–30.8)	27.4 (25.5–30.2)	0.12	-1.7 (-3.2–1.5)	0.91
LVPWd (mm)	7.9 (6.9–8.8)	7.4 (6.9–8.3)	**0.03**	-0.2 (-1.0–0.5)	7.7 (7.4–8.7)	7.9 (7.4–8.3)	0.75	0.0 (-1.0–0.8)	0.37

Data are given as median (interquartile range).

BP, blood pressure; DT, early wave deceleration time; E′, early diastolic peak velocity of the septal mitral annulus; E/A, ratio of early to late diastolic filling velocities; E/E′, ratio of early diastolic filling velocity and early diastolic peak velocity of the septal mitral annulus; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness in diastole; PAC, plasma aldosterone concentration; PRA, plasma renin activity

*P-values for differences before versus after treatment. †P-values for differences in changes in variables between the *KCNJ5*(+) and *KCNJ5*(-) groups.

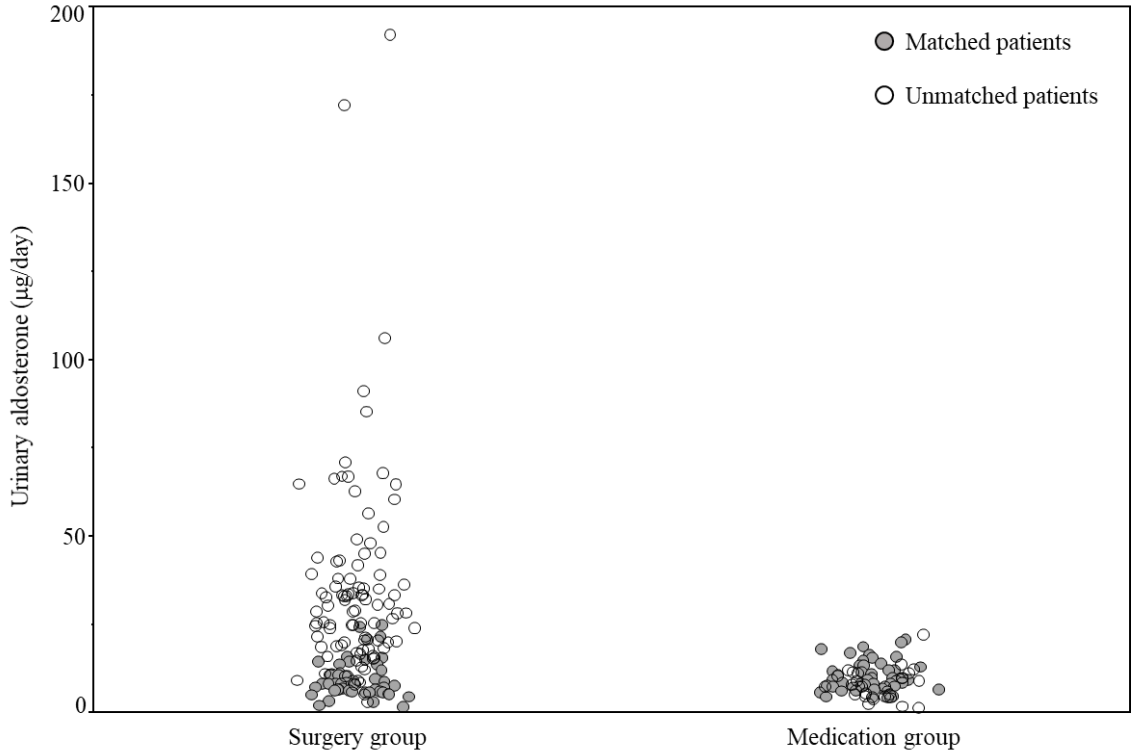
Figure S1. Comparisons of proportion of biochemical complete success between patients with low and high indices for the laterality.



LI, lateralization index; Ald, aldosterone.

Biochemical outcome could not be judged due to missing data in 3 cases of the surgery group.

Figure S2. Urinary aldosterone levels in matched and unmatched patients after propensity score matching.



Gray circles: matched patients, white circles: unmatched patients