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Persistent cardiac organ damage in surgically and medically treated primary aldosteronism

Arleen Aune[a,b], Eva Gerdts[a,b], Marina Kokorina[b], Ester Kringeland[a,b], Helga Midtbø[a,b], Kristian Løvís[c], and Marianne A. Grytaas[c]

Objective: We compared persistent cardiac organ damage in patients treated surgically or medically for primary aldosteronism.

Methods: Eighty-four patients (age 57 ± 11 years, 27% women) with primary aldosteronism underwent echocardiography at time of diagnosis and after one year of treatment (49% adrenalectomy, 51% medical treatment). Persistent cardiac organ damage was defined as presence of left ventricle (LV) hypertrophy, low LV midwall shortening, global longitudinal strain and/or enlarged left atrium both at baseline and at follow-up.

Results: At one year, a significant regression of LV hypertrophy was observed in surgically (44 vs. 22%, $P = 0.039$), but not in medically treated patients (60 vs. 51%, $P = 0.206$). The prevalence of enlarged left atrium was reduced in both groups (both $P < 0.001$), whereas systolic myocardial function remained unchanged. In multivariable logistic regression analysis, medical treatment [odds ratio (OR) 4.88 (95% confidence interval (CI) 1.26–18.88)] was a strong predictor of persistent LV hypertrophy independent of higher BMI [OR 1.20 (95% CI 1.04–1.38)] and presence of diabetes [OR 6.48 (95% CI 1.20–34.83), all $P < 0.05$]. Persistently low midwall shortening was associated with suppressed plasma renin after one year [OR 6.11 (95% CI 1.39–26.7)] and lower renal function [OR 0.96 (95% CI 0.94–0.99), both $P < 0.05$]. The strongest predictor of persistently low global longitudinal strain was higher HbA_{1c} [OR 2.37 (95% CI 1.12–5.02), $P = 0.024$].

Conclusion: Persistent cardiac organ damage was more common in the medical treatment group and associated with incomplete aldosterone blockade, impaired renal function and presence of metabolic comorbidities.

Graphical abstract: http://links.lww.com/HJH/B925.

Keywords: cardiac organ damage, global longitudinal strain, hypertension, left ventricle hypertrophy, midwall shortening, obesity, primary aldosteronism

Abbreviations: ARR, aldosterone–renin ratio; DDD, defined daily dose; *E/e'*, peak early transmitral filling velocity to the average of septal and lateral early diastolic annular plane velocity; GLS, global longitudinal strain; MRA, mineralocorticoid receptor antagonist; PASO, primary aldosteronism surgical outcome; SIT, saline infusion testing

INTRODUCTION

Primary aldosteronism is the most common cause of secondary hypertension [1], and is associated with increased cardiovascular risk independent of the effect of blood pressure (BP) [2]. Unilateral forms of primary aldosteronism are effectively treated with surgical adrenalectomy, whereas medical treatment including mineralocorticoid receptor antagonist (MRA) is recommended in bilateral forms and in patients with unilateral forms unsuited for surgery [3].

Cardiac organ damage is well documented as a precursor of clinical cardiovascular events in essential hypertension [4–7]. In primary aldosteronism, this has in particular been demonstrated for left ventricular (LV) hypertrophy, which is highly prevalent [8–10]. However, although most studies on primary aldosteronism have focused exclusively on LV hypertrophy, some studies have shown that also left atrial enlargement, a risk factor for atrial fibrillation and stroke, and LV myocardial dysfunction, a precursor of heart failure, are common types of cardiac organ damage in primary aldosteronism [8–10]. An essential goal of specific treatment in primary aldosteronism is to prevent cardiovascular complications, and thus regression of cardiac organ damage is crucial [11].

However, it is still debated whether surgery and medical treatment are equally effective in reducing cardiac organ damage. Rossi *et al.* [12] found a significant decrease in LV mass index in surgically treated, but not in medically treated patients, with no difference in the changes observed at one-year and long-term follow-up. In contrast, a meta-analysis including a total of 335 patients found both treatments equally effective in reducing LV mass index [13]. Further-more, during long-term follow-up, a higher incidence of atrial fibrillation in medically than in surgically treated patients with

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[a]Department of Clinical Science, University of Bergen, [b]Department of Heart Disease and [c]Department of Medicine, Haukeland University Hospital, Bergen, Norway

Correspondence to Arleen Aune, MD, Department of Heart Disease, Haukeland University Hospital, Postboks 1400, 5021 Bergen, Norway. Tel: +47 45666067; e-mail: arleen.aune@uib.no

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primary aldosteronism was reported [14]. In the present study, we explored factors associated with persistent cardiac organ damage of different types in relation to surgical and medical treatment of primary aldosteronism.

MATERIALS AND METHODS

Study population

We recruited 109 consecutive patients diagnosed with primary aldosteronism at the endocrinology outpatient clinic at Haukeland University Hospital between 2013 and 2016 [10]. Twenty-five patients underwent follow-up visits at hospitals outside our health region, leaving a total of 84 patients in this prospective follow-up study.

Primary aldosteronism was confirmed by recumbent saline infusion testing (SIT), and subtype differentiation was done by cosyntropin-stimulated adrenal vein sampling in all patients, as previously described, and in accordance with current guidelines [3,10]. Interfering antihypertensive medication was withdrawn and replaced by noninterfering medication (primarily doxazosin and/or verapamil) 2–4 weeks prior to diagnostic work up at baseline. Almost one-third of the patients, equally distributed between treatment groups, had been treated with MRA prior to study inclusion, with a median treatment duration of 7 months. Patients with hypokalemia received oral potassium supplementation. Out of 42 patients diagnosed with unilateral primary aldosteronism, 41 underwent adrenalectomy, whereas one patient refused surgery and was offered medical treatment. The remaining 42 patients were diagnosed with bilateral primary aldosteronism. In the surgical treatment group 66% had adenoma and 34% had hyperplasia confirmed by biopsy. All participants provided written informed consent, and the study was approved by the Regional Ethics Committee (REK 2013-742).

Cardiovascular risk assessment

Attended clinic BP was measured in triplicates in the seated position after at least 5 min of rest, using a calibrated aneroid sphygmomanometer, in accordance with current guidelines [15]. Clinic BP was taken as the average of the two last measurements. Antihypertensive treatment is reported as number of antihypertensive drugs and as defined dailydose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults. Obesity was defined as BMI at least 30.0 kg/m^2. Diabetes mellitus was considered present if a history of diabetes mellitus or hemoglobin A_{1c} (HbA_{1c}) more than 6.5% was found at baseline. Atrial fibrillation was considered present if a history of atrial fibrillation or atrial fibrillation documented on the baseline electrocardiogram was found in the individual patient. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation. Hypokalemia was defined as serum potassium less than 3.5 mmol/l or use of potassium supplementation drugs in the individual patients. In February 2016 the renin-essay in our local laboratory was changed from plasma renin activity (Gammacoat; DiaSorin, Saluggia, Italy) to direct plasma renin concentration (LIAISON Direct Renin; DiaSorin), and therefore plasma renin activity was measured in 80% of patients at baseline and in 50% of patients at one-year follow-up, whereas the remaining patients had direct plasma renin concentration measured.

Follow-up

All participants were followed up with a clinical visit one year after surgery or initiation of MRA. Complete, partial or absence of biochemical and clinical curation of primary aldosteronism one year after adrenalectomy was defined according to the primary aldosteronism surgical outcome (PASO)-criteria, based on BP, use of antihypertensive drugs, plasma potassium, aldosterone-renin ratio (ARR) and post-surgery SIT if ARR was persistently elevated [15]. Plasma renin was considered persistently low after treatment if plasma renin activity was less than 0.5 μg/l per h or plasma renin concentration less than 4.4 mIE/l at the one-year visit.

Echocardiography

Conventional and two-dimensional speckle tracking echocardiography were performed following a standardized imaging protocol using a GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway). Images were postprocessed in the Echocardiography Core laboratory at the University of Bergen, Norway, on workstations equipped with Image Arena Software version 4.2 (TomTec Imaging Systems GmbH, Unterschleißheim, Germany) for conventional measurements and EchoPac software version BT202 (GE Vingmed Ultrasound) for two-dimensional speckle tracking echocardiography as previously reported [10]. Images were analyzed by the same investigator and proofread by a single expert reader following current guidelines for chamber quantification [16]. LV hypertrophy was identified by validated prognostic sex-specific cutoff values for LV mass index (>47.0 g/m$^{2.7}$ in women and >50.0 g/m$^{2.7}$ in men) [15]. Relative wall thickness (RWT) was calculated as 2× posterior wall thickness/LV internal diameter at end diastole [16]. Concentric remodeling, concentric LV hypertrophy and eccentric LV hypertrophy was defined from RWT and LV mass index in combination [16]. Circumferential LV systolic myocardial function was assessed bymidwall shortening, calculated by validated equations, and considered low if less than 16% in women and less than 14% in men [17]. Longitudinal LV systolic myocardial function was assessed by peak systolic global longitudinal strain (GLS) and was calculated from 17 individual LV segments based on apical imaging planes with frame rate more than 50 fps using Automatic Function Imaging. The endocardial border was tracked automatically by the program and adjusted manually when needed. End-systole was defined by aortic valve closure using pulsed wave Doppler. In eight patients average GLS could not be calculated due to low image quality. GLS was considered low if more than −18.5% in women and more than −16.9% in men [18]. LV filling pressure was estimated from the ratio of early (*E*) transmitral filling velocity to the average of septal and lateral early diastolic mitral annular plane velocity (*e′*) ratio (*E*/*e′* ratio) [19]. Left atrial systolic volume was measured with the biplane Simpson's method using apical four and two chambers view [16], indexed for height^2 and considered enlarged if at least 16.5 ml/m^2 in women and at least 18.5 ml/m^2 in men [15].

Cardiac organ damage was defined by presence of LV hypertrophy, low midwall shortening, low GLS and/or enlarged left atrium, and was defined as persistent when present both at baseline and at one-year follow-up.

Statistical analysis

The study cohort was grouped by treatment, that is, surgical vs. medical treatment of primary aldosteronism. Continuous variables are expressed as mean ± SD when normally distributed and as median with interquartile range for nonnormally distributed data. Categorical variables are expressed as absolute numbers and percentages. Differences between groups were tested by student's unpaired *t* tests for normally distributed continuous variables and Mann–Whitney *U* test for those nonnormally distributed, whereas Pearson's chi-square was used for categorical variables. Within group changes during follow-up were tested with paired samples *t* tests for normally distributed continuous variables and with Wilcoxon signed-rank tests for those nonnormally distributed, whereas uncorrected McNemar tests were used for categorical variables. Univariable and multivariable logistic regression analyses were used to identify factors independently associated with persistent LV hypertrophy, persistently low LV midwall shortening, persistently low LV GLS and persistently enlarged left atrium after treatment. Variables with univariable associations (*P* less than 0.10) and variables with known clinical significance (age, sex, BMI, SBP at baseline and at follow-up, persistently suppressed plasma renin) were included in multivariable stepwise forward regression analyses, and variables that remained significant were included in the final models. In the primary multivariable models (Model 1), we included baseline variables only, whereas follow-up variables were added in secondary models (Model 2). Results from logistic regression analyses are reported as odds ratio (OR) with corresponding 95% confidence intervals (CIs) and *P* values. Reproducibility of measurements of LV mass and midwall shortening was assessed by intraclass correlation coefficients. Statistical significance was defined as Pless than 0.05 unless otherwise is indicated. The study had 80% statistical power to identify 35% differences in prevalence of persistent LV hypertrophy between treatment groups at one-year follow-up with a less than 0.05.

RESULTS

Baseline characteristics

The total study population consisted of 84 patients with primary aldosteronism, 27% women, mean age 56 ± 11 years. The prevalence of diabetes and mean HbA_{1c} was higher in the surgical treatment group ($n = 41$) than in the medical treatment group ($n = 43$), whereas there was no significant difference in duration of hypertension, SBP or DBP, DDD of BP-medication, BMI, renal function or prevalence of atrial fibrillation at baseline (Table 1). The surgical treatment group had higher plasma aldosterone levels and higher prevalence of hypokalemia than the medical treatment group (Table 1).

The prevalence of LV hypertrophy did not differ significantly between groups at baseline, and the majority of patients had enlarged left atrium in both groups (Table 2). The medical treatment group had lower LV midwall shortening, whereas LV GLS did not differ (Table 2).

Changes in clinical characteristics during follow-up

A marked decrease in BP occurred in both groups during follow-up (Table 1). The DDD of BP treatment was significantly reduced in the surgical treatment group at follow-up, but not in the medical treatment group (Table 1). In the surgical treatment group, complete biochemical success was achieved in 85%, and clinical success in 27% of patients using the PASO criteria (Fig. 1). At the one-year follow-up persistently suppressed plasma renin was present in 23% of patients in the medical treatment group, compared with in 5% in the surgery treatment group ($P = 0.016$).

Changes in cardiac organ damage during follow-up

LV mass index decreased in both groups, but a significant reduction in prevalence of LV hypertrophy was only seen after surgery (Table 2, Fig. 2). A reduction in LV inner diameter and an increase in RWT were observed in both groups (Table 2). LV myocardial dysfunction remained common in both groups at one-year follow-up (Table 2). In contrast, the prevalence of enlarged left atrium was reduced by two-thirds at follow-up in both groups (Table 2). E/e' decreased in the two groups (Table 2).

The prevalence of any persistent cardiac organ damage was higher in medically treated patients at one-year follow-up (Fig. 3). In particular, persistent LV hypertrophy was more prevalent in medically treated patients, whereas the prevalences of persistently low LV midwall shortening, persistently low LV GLS and persistent enlarged left atrium did not differ significantly between treatment groups.

The intraobserver reproducibility for LV mass [interclass correlation 0.88 (95% CI 0.71–0.95)] and midwall shortening [interclass correlation 0.91 (95% CI 0.80–0.96) both $P < 0.001$] was good.

Factors associated with persistent cardiac organ damage at one-year follow-up

Left ventricle hypertrophy

In univariable logistic regression analysis, persistent LV hypertrophy was associated with medical treatment of primary aldosteronism, older age, longer duration of hypertension, concomitant diabetes mellitus, higher SBP pre and posttreatment, higher DDD of BP treatment and higher BMI at baseline, and with higher pulse pressure, lower eGFR and low plasma renin at the final visit (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). In stepwise multivariable logistic regression analysis including the baseline covariables, persistent LV hypertrophy was associated with medical treatment of primary aldosteronism independent of significant associations with higher age and BMI and presence of diabetes mellitus (Model 1, Table 3). When significant variables at follow-up were added to the model, also higher pulse pressure was identified as an independent covariate of persistent LV hypertrophy (Model 2, Table 3). Additional adjustment for plasma aldosterone concentration at baseline did not change the results. When analyzing the treatment groups separately, persistent LV hypertrophy was associated with baseline post-SIT aldosterone

TABLE 1. Clinical characteristics at baseline and at one-year follow-up in 84 patients treated surgically or medically for primary aldosteronism.

	Surgery, $n=41$			Medical treatment, $n=43$		
	Baseline	One Year	*P* value	Baseline	One Year	*P* value
Female, *n* (%)	13 (32)			10 (23)		
Age (years)	54 ± 11			58 ± 10		
Duration of hypertension (years)	11.8 ± 8.0			15.2 ± 10.3		
Diabetes mellitus, *n* (%)	2 (5)	3 (7)	1.000	9 (21)*	9 (21)	1.000
Atrial fibrillation, *n* (%)	5 (12)	5 (12)	1.000	4 (9)	4 (9)	1.000
BMI (kg/m^2)	29.2 ± 4.3	28.1 ± 3.7	0.013	30.6 ± 6.3	31.1 ± 6.9**	0.518
Obesity, *n* (%)	15 (39)	12 (32)	0.375	22 (55)	21 (52)	1.000
SBP (mmHg)	145 ± 16	128 ± 14	<0.001	151 ± 20	132 ± 18	<0.001
DBP (mmHg)	87 ± 10	81 ± 9	0.009	89 ± 12	81 ± 12	<0.001
Pulse pressure (mmHg)	58 ± 11	47 ± 13	<0.001	62 ± 18	51 ± 15	<0.001
Controlled hypertension, *n* (%)	20 (51)	31 (79)	0.016	19 (45)	34 (81)	<0.001
Antihypertensive drugs, *n*	2.9 ± 1.1	1.5 ± 1.3	<0.001	3.3 ± 1.6	3.4 ± 1.6**	0.472
Antihypertensive drugs (DDD)	3.4 ± 1.8	1.5 ± 1.6	<0.001	4.0 ± 2.7	4.2 ± 2.0**	0.780
ACEi or ARBs (%)	26 (63)	14 (34)	0.004	32 (74)	26 (60)**	0.109
Calcium channel blocker (%)	37 (90)	17 (41)	<0.001	36 (84)	31 (72)**	0.063
Diuretic (%)	11 (27)	4 (15)	0.059	22 (51)*	10 (23)	<0.001
Mineralocorticoid receptor antagonist (%)	13 (32)	3 (7)	<0.001	12 (28)	43 (100)**	<0.001
Beta blocker (%)	13 (32)	10 (24)	0.250	13 (30)	11 (26)	0.774
Alpha blocker (%)	8 (20)	5 (12)	0.250	10 (23)	10 (23)	1.000
Other antihypertensiva (%)	6 (15)	6 (15)	1.000	12 (30)	9 (21)	0.453
PAC (pmol/l)	782 (502–1177)	213 (141–294)	<0.001	467 (349–725)*	638 (476–1190)**	<0.001
Post-SIT PAC (pmol/l)	373 (289–566)	115 (70–160)	<0.001	251 (194–349)*	–	–
Plasma renin activity (μg/l per h)	0.3 (0.1–0.4)	1.5 (0.7–2.5)	<0.001	0.3 (0.1–0.7)	0.7 (0.2–5.9)	0.004
Aldosterone-to-renin ratio (pmol/μg per h)	2410 (1343–8640)	119 (75–251)	<0.001	2333 (585–4725)	1423 (220–6750)**	0.030
Plasma renin concentration (mIU/l)	6 (2–10)	13 (10–41)	<0.001	7 (3–14)	49 (17–101)**	0.012
Aldosterone-to-renin ratio (pmol/mlU)	81 (55–515)	16 (7–31)	0.012	77 (32–124)	12 (6–67)	0.012
Suppressed plasma renin, *n* (%)	27 (72)	2 (5)	<0.001	25 (60)	10 (23)**	<0.001
Creatinine (mmol/l)	74.5 (62.2–88.0)	90.0 (76.0–126.5)	<0.001	81.5 (69.0–91.0)	89.0 (75.0–109.0)	<0.001
eGFR (ml/min per 1.73 m^2)	95.8 (81.2–104.7)	76.5 (53.7–97.1)	<0.001	88.0 (75.9–101.2)	79.2 (63.2–88.8)	<0.001
Potassium (mmol/l)	3.5 ± 0.4	4.4 ± 0.4	<0.001	3.6 ± 0.4	4.2 ± 0.5	<0.001
Hypokalemia[a], *n* (%)	38 (93)	0 (0)	NA	22 (51)*	7 (16)**	<0.001
HbA_{1c} (%)	5.2 (4.9–5.5)	5.4 (5.1–5.4)	0.002	5.5 (5.3–6.0)*	5.7 (5.4–6.0)**	0.068

Data are presented as mean (±SD), median (interquartile range) or number (%). Differences between groups were tested by unpaired *t* test (normally distributed variables), Mann-Whitney *U* test (nonnormally distributed variables) and Pearsons's chi-square for categorical variables. Within group changes were tested with unpaired *t* tests (normally distributed variables), Wilcoxon signed-rank test (nonnormally distributed) and uncorrected McNemar for categorical variables. ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BP, blood pressure; DDD, defined daily dose; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; PAC, plasma aldosterone concentration; post-SIT, post saline infusion testing.

[a]Hypokalemia was defined as serum potassium less than 3.5 mmol/l or use of potassium supplementation in the individual patients.

*$P < 0.05$ vs. surgical treatment group at baseline.

**$P < 0.05$ vs. surgical treatment group at one-year follow-up.

TABLE 2. Echocardiographic characteristics at baseline and at one-year follow-up in 84 patients, treated surgically or medically for primary aldosteronism.

	Surgery, $n=41$			Medical treatment, $n=43$		
	Baseline	One Year	*P* value	Baseline	One Year	*P* value
LVEDd (cm)	5.04 ± 0.49	4.67 ± 0.45	<0.001	4.99 ± 0.59	4.78 ± 0.56	0.006
IVSd (cm)	1.29 ± 0.32	1.26 ± 0.29	0.520	1.39 ± 0.29	1.34 ± 0.24	0.325
LVPWd (cm)	0.96 ± 0.21	0.97 ± 0.21	0.580	1.00 ± 0.16	1.04 ± 0.17	0.268
LV mass index (g/m$^{2.7}$)	47.4 ± 11.2	42.3 ± 11.3	0.001	52.0 ± 13.6	48.3 ± 12.3*	0.049
Relative wall thickness	0.38 ± 0.10	0.42 ± 0.10	0.031	0.40 ± 0.06	0.44 ± 0.10	0.021
LV hypertrophy, *n* (%)	18 (44)	9 (22)	0.039	26 (60)	22 (51)*	0.206
LV ejection fraction (%)	64 ± 5	65 ± 5	0.450	62 ± 6**	65 ± 4	0.002
GLS (%)	−18.3 ± 3.6	−17.2 ± 7.3	0.414	−17.4 ± 3.1	−16.9 ± 3.1	0.215
Low GLS, *n* (%)	14 (38)	16 (43)	0.564	15 (38)	18 (46)	0.439
Midwall shortening (%)	15.5 ± 2.8	15.1 ± 2.4	0.347	14.2 ± 2.0**	14.5 ± 2.8	0.495
Low midwall shortening, *n* (%)	11 (28)	15 (37)	0.285	23 (53)**	21 (49)	0.637
LV fillingpressure (*E*/*e*')	9.9 ± 3.1	8.8 ± 3.1	<0.001	10.3 ± 2.7	9.3 ± 2.6	0.005
Left atrial volume index (ml/m^2)	19.9 ± 7.7	14.7 ± 4.5	<0.001	20.1 ± 6.0	16.5 ± 8.0	<0.001
Enlarged left atrium (%)	24 (59)	17 (21)	<0.001	24 (56)	8 (18)	<0.001

Data are presented as mean (±SD), median (interquartile range) or number (%). Differences between groups were tested by unpaired *t* test (normally distributed variables), Mann-Whitney *U* test (nonnormally distributed variables) and Pearsons's chi-square for categorical variables. Within group changes were tested with unpaired *t* tests (normally distributed variables), Wilcoxon signed-rank test (nonnormally distributed) and uncorrected McNemar for categorical variables. *E*/*e*', peak early transmitral filling velocity to the average of septal and lateral early diastolic annular plane velocity; EDd, end diastolic diameter; GLS, global longitudinal strain; IVSd, interventricular septal diameter; LV, left ventricle; PWd, posterior wall diameter.

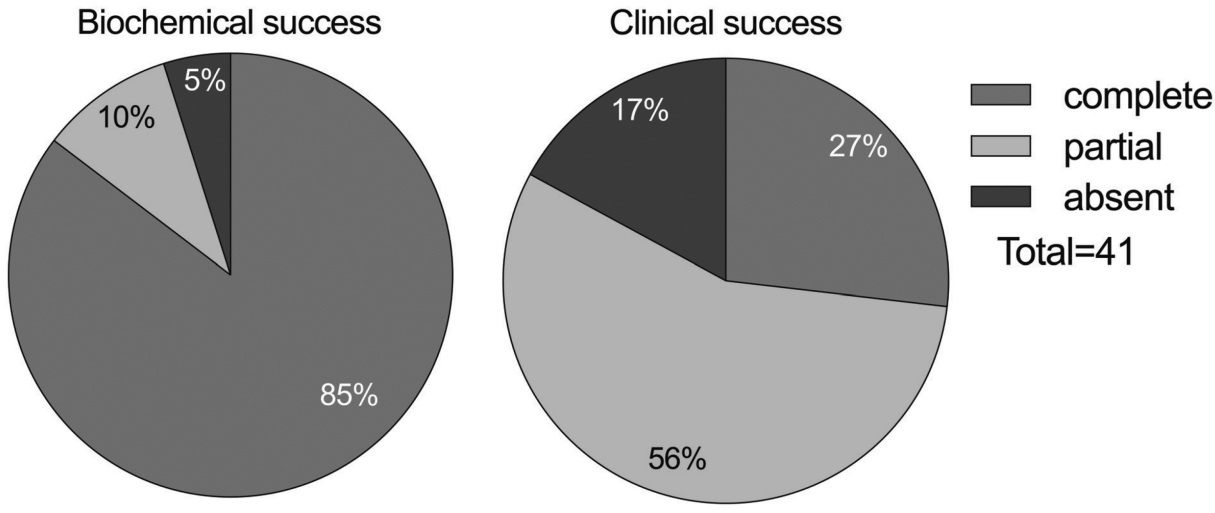

FIGURE 1 Rates of clinical and biochemical success in surgically treated patients according to the primary aldosteronism surgical outcome-criteria.

concentration [OR 1.08 (95% CI 1.01–1.14), $P = 0.020$], independent of significant associations with age, BMI and presence of diabetes mellitus in the medical treatment group. DDD of antihypertensive treatment at baseline [OR 2.10 (95% CI 1.08–4.09), $P = 0.029$] was the strongest predictor of persistent LV hypertrophy in the surgical treatment group.

Circumferential left ventricle systolic myocardial function

In univariable logistic regression analysis, persistently low LV midwall shortening was associated with medical treatment of primary aldosteronism, older age, longer duration of hypertension and lower eGFR at baseline and with suppressed plasma renin and persistent LV hypertrophy at follow-up (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). When including the baseline covariables in a stepwise multivariable logistic regression analysis, persistently low LV midwall shortening was associated with lower eGFR and medical treatment group (Model 1, Table 3). In a secondary model adding the follow-up variables, lower eGFR at baseline and suppressed plasma renin at the one-year visit were significant covariates of persistently low LV midwall shortening (Model 2, Table 3).

Longitudinal left ventricle systolic myocardial function

In univariable logistic regression analysis, persistently low LV GLS was associated with higher HbA_{1c}, obesity and persistent LV hypertrophy (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). In stepwise multivariable logistic regression analysis, only HbA_{1c} remained a significant

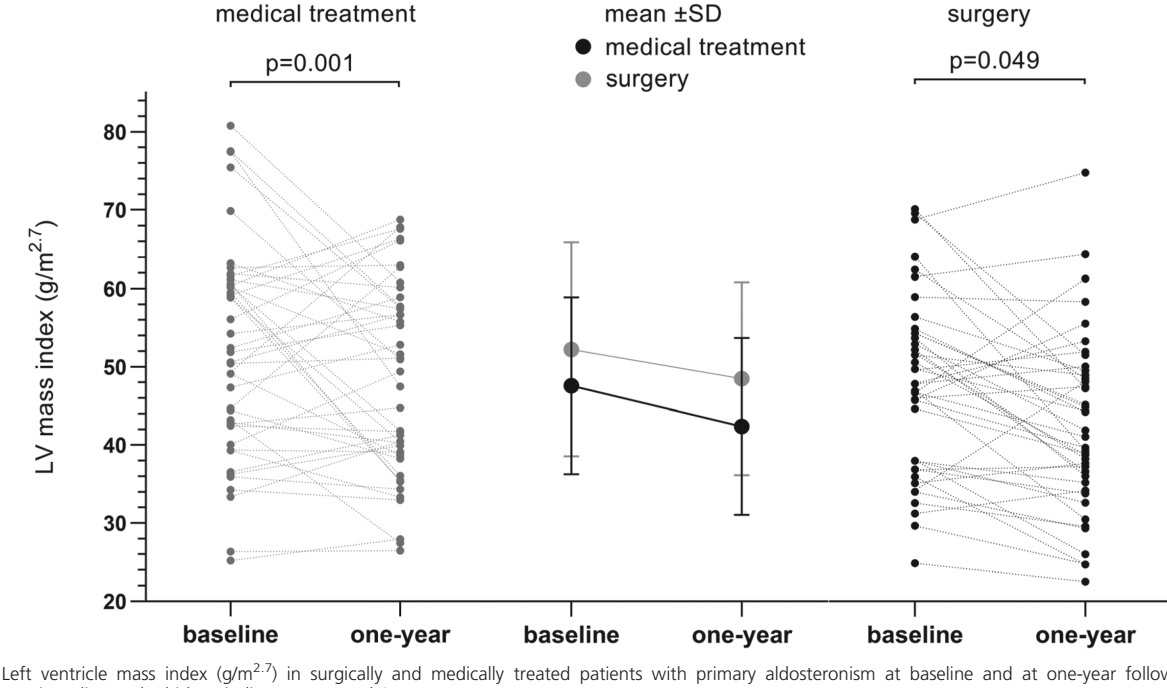

FIGURE 2 Left ventricle mass index ($g/m^{2.7}$) in surgically and medically treated patients with primary aldosteronism at baseline and at one-year follow-up. Each dot represents a patient, line and whiskers indicate mean and SD.

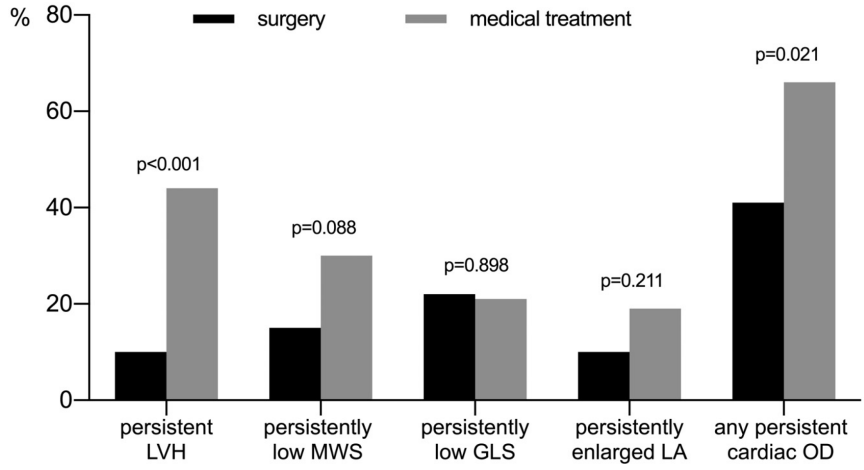

FIGURE 3 Prevalences of different types of persistent cardiac organ damage in surgically and medically treated patients with primary aldosteronism at one-year follow-up. GLS, global longitudinal strain; LA, left atrium; LVH, Left ventricular hypertrophy; MWS, midwall shortening; OD, organ damage.

TABLE 3. Factors associated with cardiac organ damage in 84 patients treated surgically or medically for primary aldosteronism

	Model 1			Model 2		
Outcome variable	**Variable**	**OR (95% CI)**	***P* value**	**Variable**	**OR (95% CI)**	***P* value**
Persistent LV hypertrophy	Medical treatment group	4.88 (1.26–18.88)	0.022	Medical treatment group	4.73 (1.20–18.68)	0.027
	Age (years)	1.09 (1.02–1.17)	0.013	BMI (kg/m^2)	1.18 (1.02–1.38)	0.027
	BMI (kg/m^2)	1.20 (1.04–1.38)	0.012	Diabetes mellitus	9.44 (1.57–56.7)	0.014
	Diabetes mellitus	6.48 (1.20–34.83)	0.030	Pulse pressure at follow-up	1.08 (1.02–1.13)	0.005
Persistently low midwall shortening	Medical treatment group	3.20 (0.94–11.04)	0.066	Persistently low plasma renin	6.11 (1.39–26.7)	0.016
	eGFR (ml/min per 1.73 m^2)	0.96 (0.94–0.99)	0.003	eGFR (ml/min per 1.73 m^2)	0.96 (0.94–0.99)	0.004
Persistent low GLS	HbA_{1c} (%)	2.37 (1.12–5.02)	0.024	HbA1c (%)	2.37 (1.12–5.02)	0.024
Persistently enlarged left atrium	BMI	1.18 (1.02–1.37)	0.013	BMI (kg/m^2)	1.18 (1.02–1.37)	0.031
	eGFR (ml/min per 1.73 m^2)	0.96 (0.93–0.99)	0.027	eGFR (ml/min per 1.73 m^2)	0.96 (0.93–0.99)	0.017
	Atrial fibrillation	6.01 (0.95–37.91)	0.081	Atrial fibrillation	6.01 (0.95–37.91)	0.056

Multivariable stepwise logistic regression analyses. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HbA_{1c}, hemoglobin A_{1c}; LV, left ventricle; OR, odds ratio.

covariable (Model 1, Table 3). Adding SBP and suppressed plasma renin at one-year follow-up did not change the results (Model 2, Table 3).

Left atrium enlargement

In univariable logistic regression analyses, persistently enlarged left atrium was associated with known atrial fibrillation, lower eGFR and obesity at baseline and higher pulse pressure and E/e' at one-year follow-up (all $P < 0.10$) (Table S1, http://links.lww.com/HJH/B921). In the stepwise multivariable logistic regression analysis, lower eGFR and higher BMI remained significant covariables (Model 1, Table 3). Adding SBP, pulse pressure, suppressed plasma renin and E/e' at one-year follow-up did not change the results (Model 2, Table 3).

DISCUSSION

The current study expands current knowledge of persistent cardiac organ damage in relation to surgical and medical treatment of primary aldosteronism. Despite a large reduction of LV hypertrophy, particularly in surgically treated patients, many patients with primary aldosteronism remained with persistent cardiac organ damage at one-year follow-up in both treatment groups, and consequently with a high residual risk of developing cardiovascular events. The main drivers of persistent cardiac organ damage were metabolic comorbidities and suboptimal MRA treatment.

We found that persistent LV hypertrophy was more common in medically than surgically treated patients. This finding contrasts the results from a recent meta-analysis indicating similar reduction of LV mass with both treatments [13], but confirms observations in two small studies finding significant reduced LV mass index in surgically treated patients only [12,20]. Of note, the higher prevalence of persistent LV hypertrophy in the medical treatment group was independent of significant associations with obesity and diabetes mellitus, both factors associated with higher prevalence and less reversibility of LV hypertrophy in essential hypertension [21]. Several studies advocate that BP reduction is the main confounder of LV mass index reduction in primary aldosteronism [22,23]. In the present study, higher SBP both at baseline and follow-up was significantly associated with persistent LV hypertrophy in univariable analyses. However, these associations became

nonsignificant in the adjusted models. Of note higher arterial stiffness, as reflected by posttreatment pulse pressure, was also independently associated with persistent LV hypertrophy. Catena et *al.* [22] demonstrated an association between changes in LV mass index and pretreatment plasma aldosterone concentration in both surgically and medically treated patients. In contrast, the present study demonstrated an independent association between higher post-SIT-aldosterone concentration and persistent LV hypertrophy only in the medical treatment group. Taken together, the multifactorial pathophysiology of persistent LV hypertrophy in primary aldosteronism is clearly demonstrated.

To our knowledge this is the first study investigating changes in longitudinal LV systolic myocardial function assessed by GLS after specific primary aldosteronism treatment. Of note, GLS remained unchanged independent of treatment group during one-year follow-up in the present study, despite reduction in LV mass. Lower LV GLS has been associated with presence of myocardial fibrosis by gadolinium enhanced cardiac magnetic resonance imaging [24]. The persistently low LV GLS in both treatment groups may therefore reflect presence of cardiac fibrosis, which is more extensive in primary aldosteronism than in essential hypertension, and less modifiable by treatment than cardiomyocyte hypertrophy [25]. However, the strongest predictor of persistently low GLS in our study was higher HbA_{1c}, reflecting the importance of disturbed glucose metabolism for LV myocardial function, in line with previous reports in essential hypertension [26].

Also circumferential LV systolic myocardial function assessed by midwall shortening did not improve during follow-up in either group, in line with results from Catena et *al.* [22]. In contrast, previous studies in essential hypertension have demonstrated that LV hypertrophy regression is accompanied by improved circumferential LV systolic myocardial function, in particular during the first treatment year, although additional smaller improvements may be observed up to three years after initiation of treatment [27,28]. However, one-year regression of LV hypertrophy in the present study resulted from reduced LV inner diameter without change in LV wall thickness. This might explain the lack of improved midwall shortening. A similar LV geometric adaptation to specific treatment of primary aldosteronism has previously been described by Rossi *et al.* [12].

Enlarged left atrium is a common type of hypertensive organ damage, particularly prevalent in women and in obese individuals [29], which predisposes to atrial fibrillation and heart failure. Previous studies on change in left atrial size during primary aldosteronism treatment have yielded diverging results [12,20,30,31]. Two studies found reduction in left atrial anterior-posterior diameter in surgically treated, but not in medically treated patient [12,30], whereas others found no change in either group [20,31]. However, it is well demonstrated that left atrial volume index, as used in the present study, is superior to left atrial anterior-posterior diameter in reflecting actual left atrial size [32]. Thus, the present results add to previous publications by demonstrating a marked reduction in the prevalence of left atrial enlargement in both medically and surgically treated patients with primary aldosteronism, indicating improved LV diastolic function.

Hundemer *et al.* [33] recently related the excess risk of cardiovascular events in medically treated primary aldosteronism to low plasma renin activity after treatment. In the present study, 23% of medically treated patients had suppressed plasma renin at one-year follow-up, indicating insufficient mineralocorticoid receptor blockade due to suboptimal titration of MRA treatment in these patients. This might reflect adverse effects of MRA treatment, physician inertia or poor patient drug adherence, all major problems in management of hypertension [34]. Persistently low plasma renin was also associated with persistent LV hypertrophy, and was an independent confounder of persistently low LV midwall function, adding to a recent publication by Köhler et *al.* [35].

Some limitations of our study should be highlighted. First, the impact of BP on persistent cardiac organ damage may have been underestimated since ambulatory BP was not included in the study. However, 80% of participants had optimally controlled BP at the follow-up visit. On the contrary, drug adherence was not assessed, which would have been of particular value in the medical treatment group. Second, the full effect of primary aldosteronism treatment on regression of cardiac organ damage may not have been achieved after one-year only [27,28]. Third, differences in antihypertensive treatment prior to study inclusion may have influenced cardiac structure and function at baseline, particularly in patients treated with MRA prior to study inclusion. However, MRA treatment did not differ significantly between the treatment groups at baseline. Fourth, the prevalence of obesity was high in the study cohort and generalizing results to other populations may not be appropriate. Concomitant glucocorticoid excess has been associated with presence of metabolic risk factors and with decrease of LV mass index during follow-up after adrenalectomy [30,36]. However, this was not assessed in our cohort. Furthermore, it must be acknowledged that unilateral and bilateral primary aldosteronism are different conditions with different pathogenesis, that may influence prognosis and bias treatment outcome [37]. Finally, the study sample size was calculated based upon persistent LV hypertrophy. The study cohort was small, and type 2 errors cannot be ruled out for other measures of persistent cardiac organ damage. The small study sample also precluded sex-specific analyses.

In conclusion, the present study on primary aldosteronism demonstrates that many patients remain with persistent LV hypertrophy and other types of cardiac organ damage after one year, also among those surgically treated. Thus, many patients with primary aldosteronism remain with a high cardiovascular risk despite treatment. Although persistent LV hypertrophy was less prevalent after surgical treatment, persistent LV systolic myocardial dysfunction was common in both treatment groups. Presence of metabolic comorbidities like obesity, diabetes mellitus and impaired glucose metabolism were identified as major confounders of persistent cardiac organ damage. This points to the importance of a general risk factor management to optimally reduce cardiac organ damage and associated cardiovascular events in primary aldosteronism. As demonstrated, persistent cardiac organ damage was more common in medically treated patients with low plasma

renin at follow-up, indicating that MRA dosing was suboptimal. These findings emphasize the importance of biochemical assessment during follow-up and the need for more detailed recommendations on optimal MRA dosages and their indicators in primary aldosteronism.

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Conflicts of interest

The authors declare no conflicts of interest.

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