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Serum aldosterone effect on left ventricular structure and diastolic function in essential hypertension

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Abstract

Aldosterone has hypertrophic and profibrotic effects on the heart. This study aims to determine the relationship between serum aldosterone concentration (SAC) and aldosterone-to-renin ratio (ARR) with left ventricular (LV) geometry and diastolic function in essential hypertension (EH). We investigated 213 EH patients (50.3 ± 12.6 years; 57.7% male). SAC, ARR measurements, and echocardiographic analysis were performed for participants. Overall, stepwise multiple regression analysis showed significant associations between SAC and interventricular septum, LV posterior wall thickness, LV amass, LV mass index, e′ velocity, a′ velocity, and E/e′ ratio after adjustment of potentially confounding covariates. When patients were divided into three SAC tertiles, multivariate-adjusted analysis of covariance (ANCOVA) demonstrated a significant increase in LV mass ($P < 0.001$), LV mass index ($P < 0.001$), relative wall thickness ($P = 0.003$), interventricular septum ($P = 0.001$), LV posterior wall thickness ($P = 0.001$) and E/e′ ratio ($P < 0.001$), but a decrease in e′ velocity ($P = 0.002$) from the first to third tertile of SAC. In logistic regression analysis, increased SAC was independently associated with concentric LV hypertrophy [OR: 1.21, 95% CI: 1.11–1.33, $P < 0.001$]. No significant associations were found between ARR and echocardiographic parameters of LV structure or diastolic function. In conclusion, SAC, but not ARR, is independently associated with echocardiographic indices of LV structure and diastolic function and is also related to concentric LV hypertrophy. Our findings suggest that aldosterone's pro-hypertrophic and myocardial fibrosis effects contribute to alterations in LV structure and diastolic function in EH beyond blood pressure.

KEYWORDS
aldosterone, diastolic function, hypertension, left ventricle structure

1 | INTRODUCTION

Aldosterone hormone is synthesized in the zona glomerulosa of the adrenal gland. It is also synthesized locally in various tissues in the body, including the brain, vascular tissue, and the myocardium.[1] The renin-angiotensin system, adrenocorticotropic hormone, and extracellular potassium levels influence aldosterone synthesis.[2] Dietary salt consumption is another essential regulator of adrenal aldosterone production by altering the adrenal sensitivity to angiotensin II response.[3] The classical aldosterone/mineralocorticoid receptor-induced effect

regulates fluid and electrolyte balance.[4] However, the dysregulation of the aldosterone/mineralocorticoid receptor system is linked to many clinical conditions characterized by high cardiometabolic risk and end-organ damage, particularly at the heart, arteries, kidneys, and adipose tissue levels.[5]

Independent of blood pressure, prolonged exposure to high aldosterone levels produces substantial cardiac remodeling and damage due to non-hemodynamic processes.[6] This finding is supported by the reported reversal of cardiac hypertrophy and fibrosis by non-antihypertensive doses of spironolactone, a mineralocorticoid receptor antagonist.[7] This deleterious effect of aldosterone is due to the formation of excessive collagen and myocardial fibrosis,[8] which contribute to cardiac remodeling and increase myocardial stiffness, leading to diastolic dysfunction and left ventricular (LV) hypertrophy.[9,10] LV hypertrophy can occur through ventricular dilatation, wall thickening, or combinations to produce several distinct LV geometric adaptations, including concentric hypertrophy, eccentric hypertrophy, and concentric remodeling.[11]

A growing body of evidence has shown that circulating aldosterone levels, even in the absence of primary aldosteronism, contribute significantly to cardiovascular diseases.[12] Previous studies investigated the relationship between aldosterone and LV structure and diastolic function in essential hypertension.[13–15] Most of these studies were restricted by the small sample size and the lack of consideration of several important confounding factors. Moreover, the effect of aldosterone on LV structure and diastolic function in essential hypertension is still disputed. Therefore, this study investigated the relationship between serum aldosterone level and LV structure, pathological geometric patterns, and diastolic function in a large study sample, well-standardized conditions, and independent of potential confounding factors in patients with essential hypertension.

2 | METHODS

2.1 | Study subjects

A total of 213 previously treated or untreated essential hypertension patients were selected amongst those hospitalized for hypertension evaluation in the cardiology department of Lanzhou University Second Hospital, Lanzhou City, China. Clinical data of patients were obtained from electronic medical records. Patients with secondary hypertension, known coronary artery disease, cardiomyopathies, arrhythmia including atrial fibrillation, valvular heart disease, congestive heart failure, renal failure, diabetes mellitus, thyroid function abnormalities, body mass index > 35 kg/m2, treatment with mineralocorticoid receptor antagonists, such as spironolactone, and unsatisfactory echocardiography were excluded from the study. Secondary causes of hypertension were excluded in all participants by thorough clinical workup according to established guidelines.[16] Amongst the 213 patients, 162 (76.1%) were taking antihypertensive drugs, including combination therapy, 112 patients (52.6%) were treated with calcium channel blockers, 77 (36.2%) with angiotensin-converting enzyme inhibitors, 59 (27.7%) with angiotensin II receptor blockers, 42 (19.7%) with β-blockers, 36 (16.9%) with diuretics and 15 (7%) with other classes of agents.

2.2 | Blood pressure measurements

Office blood pressure was performed by a specially trained physician using the conventional approach, with the subject seated after 5 min of rest and the cuff size adjusted according to the arm circumference of the patient. Non-invasive ambulatory blood pressure monitoring (ABPM) was conducted during a 24 h hospital stay to diagnose, evaluate and follow up hypertension according to center standards. Patient education was conducted by well-trained medical personnel. Blood pressure was obtained every 15–30 min during the day (8 a.m. to 11 p.m.), every 30 min at night (11 p.m. to 6 a.m.), and early in the morning (6:00 a.m. to 8:00 a.m.) using validated devices with the non-dominant arm's cuff size adjusted.

Hypertension was considered if the participant had a history of hypertension and was currently taking antihypertensive drugs, had an office systolic blood pressure (SBP) ≥ 140 mmHg and/or an office diastolic blood pressure (DBP) ≥ 90 mmHg. The diagnostic thresholds for hypertension based on ABPM are: 24 h mean SBP/DBP ≥ 130/80 mmHg; daytime SBP/DBP ≥ 135/85 mmHg; nighttime SBP/DBP ≥ 120/70 mmHg.[17]

2.3 | Measurement of serum aldosterone concentration

Antihypertensive drugs were washed out for at least 4 weeks before testing. If necessary, α-blockers and non-dihydropyridine calcium channel blockers were used to maintain hypertension control. Patients had an unrestricted dietary salt intake, and 24hr urinary sodium excretion was assessed in all the patients. Before testing, any disturbance of serum potassium was corrected to the normal range. The blood samples were taken in the morning after patients had been out of bed (sitting, standing, or walking) for at least 2 h, usually after being seated for 5–15 min. Care was taken in blood collection, and hemolysis was avoided as much as possible. Serum aldosterone concentration (SAC) (ng/dl; conversion factor pg/ml/10 = ng/dl) and plasma renin activity (PRA) (ng/ml/h) were determined by full-automatic chemiluminescence immunoassay (MAGLUMI X8, Shenzhen new industry Biomedical Engineering Co. Ltd, Shenzhen, China). All SAC and PRA measurements were performed in the same core laboratory. The aldosterone to renin ratio (ARR) was calculated as the recommended screening method for detecting primary aldosteronism. The cut-off for a positive ARR was 30 (where aldosterone is measured in ng/dl and renin activity in ng/ml/h), as suggested by the guidelines.[18] At least two measurements of the ARR were taken on two separate days under the same standardized settings before excluding primary aldosteronism in case of negative screening results or if primary aldosteronism is strongly suspected clinically but the initial screening findings are negative.

2.4 | Echocardiographic measurements

An experienced physician performed the echocardiographic assessment in a cardiac ultrasound unit (US GE color ultrasound VIVID E9). Comprehensive 2D echocardiography was conducted according to the current guidelines of the American Society of Echocardiography.[19] Interventricular septum, LV posterior wall thickness, LV end-systolic diameter, LV end-diastolic diameter, LV end-systolic volume, LV end-diastolic volume, LV ejection fraction, and fractional shortening were measured as appropriate. LV mass was calculated by the following formula1 [20]:

$$\text{LVmass} = 0.8\text{x}\left\{1.04\left[(\text{LVEDD} + \text{IVSd} + \text{IVSd} + \text{PWTd})^3 - (\text{LVEDD})\ 3\right]\right\} + 0.6\text{g}$$

where LVEDD is the LV end-diastolic diameter, IVSd is the interventricular septum diameter, and PWTd is the posterior wall thickness diameter.

LV mass index was calculated by dividing LV mass by height.[21] Relative wall thickness (RWT) was calculated by the formula (2 × LV posterior wall thickness/LV end-diastolic diameter). A partition value of 0.42 for RWT was used for men and women,[22] and it allows the classification of an increase in LV mass as either concentric (RWT > 0.42) or eccentric (RWT ≤ 0.42) hypertrophy and permits the identification of concentric remodeling (normal LV mass with increased RWT). Doppler echocardiography was used to evaluate LV diastolic function.[23] In the apical four-chamber view, the LV diastolic filling pattern was attained with the sample volume at the tips of the mitral valve. The peak velocity of the early diastolic filling wave (E wave) and the peak velocity of the atrial filling (A wave) was recorded, and the mitral E to A ratio (E/A) was calculated. Pulsed-wave tissue Doppler imaging in the apical four-chamber view was used to obtain mitral annular velocities with the sample volume placed at the septal region of the mitral annulus, and the mitral E/e′ was also calculated.

2.5 | Statistical methods

Clinical and anthropometric characteristics of study participants were expressed as percentages for categorical data and means with SD for continuous data, according to SAC levels (in tertiles). $\chi 2$ test was used to compare SAC groups for categorical data, and analysis of variance (ANOVA) was used for continuous data. Pearson correlation analysis was used to analyze the correlations amongst SAC, ARR, and echocardiographic parameters. The mean values of echocardiographic indices of LV structure and diastolic function were further compared amongst tertiles of SAC using analysis of covariance (ANCOVA) followed by Bonferroni's post hoc test. Important confounders were controlled in each model, including (age, gender, body mass index, high-density lipoprotein, low-density lipoprotein, triglycerides, office SBP, office DBP, office heart rate, 24hr SBP, 24hr heart rate, nighttime DBP, serum sodium, serum potassium, 24hr urine sodium, 24hr urine potassium, antihypertensive medication (angiotensin-converting enzyme inhibitors use, angiotensin II receptor blockers use, beta-blocker use, calcium channel blockers use, and diuretic use), estimated glomerular filtration rate (eGFR), current smoking status, and PRA). Univariate linear regression was performed to assess the correlation between indices of LV structure and diastolic function and each continuously distributed variable individually. Stepwise multivariate regression analysis was done with variables of LV structure and diastolic function as the dependent variables and the inclusion of statistically significant variables found in the univariate analysis as independent variables. A logistic regression analysis was conducted to evaluate the association between SAC (ng/dl) and pathological patterns of LV geometry (concentric LV remodeling, concentric LV hypertrophy, and eccentric LV hypertrophy). The analysis was adjusted for similar confounders in ANCOVA models. About 24 h DBP and nighttime SBP were excluded from the models of analysis because of their high correlation with 24 h SBP ($r = 0.74$; $r = 0.89$, respectively) to avoid multicollinearity in our analysis. A p-value < 0.05 was considered statistically significant. Data were analyzed using SPSS 25.0 statistical package.

3 | RESULTS

A total of 213 study participants (mean age: 50.3 ± 12.6 years; 57.7% male) with SAC (mean: 16.7 ± 7.5 ng/dl) were studied. Table 1 shows the patient's characteristics and the findings of various blood pressure parameters and laboratory data based on SAC levels (in tertiles). There were no differences in age, gender, body mass index, smoking history, and hyperlipidemia between the three tertiles. In addition, all the blood pressure and biochemical parameters were not significantly different between the three tertiles of SAC except for 24 h DBP and PRA, which were higher in the third SAC tertile.

Table 2 shows the comparison of the echocardiographic parameters according to SAC tertiles. Higher values of the interventricular septum, LV posterior wall thickness, LV mass, LV mass index, RWT, E/e′ ratio, and lower e′ velocity were found in the higher tertile than in the lower tertile of SAC. Moreover, in higher tertiles of SAC, the prevalence of concentric hypertrophy geometry was significantly higher than in the lower tertile. From the first to the third tertile of SAC, no significant difference was found in LV end-systolic diameter, LV end-diastolic diameter, LV end-systolic volume, LV end-diastolic volume, LV ejection fraction and fractional shortening, E wave, A wave, E/A ratio, and the prevalence of the other pathological LV geometric pattern (concentric remodeling and eccentric hypertrophy).

Across the entire study sample, SAC is positively correlated with LV end-diastolic diameter, LV end-diastolic volume, interventricular septum, LV posterior wall thickness, LV mass, LV mass index, RWT values, E/e′ ratio, and is negatively correlated with e′ velocity and a′ velocity (Tables S1 in the online-only Data Supplement). Except for the positive correlation with A wave velocity, no correlations were found between ARR and echocardiographic parameters.

In fully adjusted ANCOVA, we found a significant increase in LV mass ($P < 0.001$), LV mass index ($P < 0.001$), and RWT ($P = 0.003$) across

TABLE 1 Patients characteristics, blood pressure parameters, and laboratory data according to serum aldosterone concentration tertiles

Variable	Tertile 1 (<12.68 ng/dl) N = 71	Tertile 2 (12.68–19.44 ng/dl) N = 71	Tertile 3 (>19.44 ng/dl) N = 71	P value
SAC, ng/dl	9.1 ± 2.9	16.2 ± 2.2	24.8 ± 5.5	
PRA, ng/ml/h	1.3 ± 5.8	4.7 ± 5.2	6.2 ± 5.0	<0.001
ARR, ng/dl/ng/ml/h	10.9 ± 8.4	11.0 ± 9.1	11.6 ± 7.8	0.847
Age, years	48.8 ± 12.6	50.8 ± 13.1	51.4 ± 11.9	0.435
Male, %	64.8%	62.0%	46.5%	0.059
Body mass index, kg/m2	25.6 ± 2.4	25.5 ± 2.6	25.6 ± 3.1	0.979
Current smokers, %	28.2%	29.6%	19.7%	0.349
Total cholesterol, mmol/l	4.2 ± 1.1	4.2 ± 0.7	4.2 ± 0.8	0.995
LDL, mmol/l	3.1 ± 1.2	2.8 ± 1.4	2.6 ± 1.1	0.077
HDL, mmol/l	1.1 ± 0.9	1.2 ± 1.2	1.2 ± 1.1	0.868
Triglycerides, mmol/l	2.1 ± 1.6	2.1 ± 1.1	2.2 ± 1.3	0.954
Hyperlipidemia, %	59.2%	67.6%	59.2%	0.488
Serum sodium, mmol/L	139.4 ± 2.3	139.7 ± 2.6	139.2 ± 2.5	0.586
Serum potassium, mmol/L	3.6 ± 1.0	3.7 ± 1.1	3.7 ± 1.0	0.899
24hr urine sodium, mmol/24 h	203.1 ± 99.7	210.9 ± 88.2	204.3 ± 88.4	0.864
24hr urine potassium, mmol/24 h	49.8 ± 24.2	52.3 ± 22.5	50.0 ± 23.9	0.775
eGFR, mL/min/1.73 m^2	97.3 ± 21.3	93.9 ± 16.3	90.3 ± 15.9	0.069
Office SBP, mmHg	144 ± 19	150 ± 19	151 ± 23	0.087
Office DBP, mmHg	90 ± 12	92 ± 14	94 ± 16	0.336
Office HR, b.p.m.	79 ± 13	82 ± 12	80 ± 12	0.392
Mean BP	108 ± 13	111 ± 14	113 ± 17	0.164
ABPM				
24 h SBP, mmHg	133 ± 13	133 ± 13	133 ± 15	0.927
24 h DBP, mmHg	81 ± 8	81 ± 10	84 ± 9	0.042
24 h HR, b.p.m.	75 ± 8	76 ± 9	74 ± 9	0.240
Daytime SBP, mmHg	136 ± 13	136 ± 13	137 ± 16	0.961
Daytime DBP, mmHg	83 ± 9	83 ± 10	83 ± 12	0.959
Daytime HR, b.p.m.	78 ± 9	80 ± 9	77 ± 9	0.167
Nighttime SBP, mmHg	125 ± 16	124 ± 14	125 ± 16	0.914
Nighttime DBP, mmHg	74 ± 10	77 ± 10	77 ± 10	0.083
Nighttime HR, b.p.m.	67 ± 9	68 ± 9	66 ± 9	0.515
Early morning SBP, mmHg	135 ± 17	135 ± 14	134 ± 17	0.890
Early morning DBP, mmHg	84 ± 10	84 ± 10	83 ± 13	0.959
Early morning HR, bpm	74 ± 12	78 ± 11	72 ± 11	0.019
Antihypertensive treatment, %				
ACEi, %	35.2%	40.8%	32.4%	0.566
ARBs, %	32.4%	23.9%	26.8%	0.519
β-blocker, %	19.7%	11.3%	28.2%	0.041
CCB, %	46.5%	56.3%	54.9%	0.445
Diuretics, %	18.3%	15.5%	16.9%	0.905

Values are given as mean ± SD for continuous variables and percentage for categorical data.

Abbreviations: SAC, serum aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone to renin ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration according to the MDRD (modification of diet in renal disease) formula to estimate GFR; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II type-1 receptor blocker; CCB, calcium channel blocker.

TABLE 2 Echocardiographic characteristics of patients according to serum aldosterone concentration tertiles

Variable	Tertile 1 (<12.68 ng/dl) N = 71	Tertile 2 (12.68–19.44 ng/dl) N = 71	Tertile 3 (>19.44 ng/dl) N = 71	P value
LV mass, g	127.6 ± 34.8	153.6 ± 37.0	154.3 ± 41.6	<0.001
LV mass index, g/m$^{2.7}$	31.9 ± 7.3	39.1 ± 8.7	39.5 ± 9.7	<0.001
Relative wall thickness	0.39 ± 0.1	0.43 ± 0.1	0.44 ± 0.1	<0.001
Interventricular septum, mm	8.4 ± 1.7	9.3 ± 2.0	9.7 ± 1.7	<0.001
LV posterior wall, mm	8.9 ± 1.4	9.7 ± 1.7	10.1 ± 1.4	<0.001
LV end-diastolic diameter, mm	45.1 ± 3.8	45.6 ± 4.2	45.5 ± 5.0	0.775
LV end-systolic diameter, mm	27.3 ± 3.3	26.6 ± 3.4	27.0 ± 3.8	0.576
LV end-diastolic volume, ml	93.6 ± 18.3	96.2 ± 20.3	96.3 ± 24.0	0.692
LV end-systolic volume, ml	27.8 ± 7.5	26.6 ± 8.2	27.9 ± 9.4	0.596
LV ejection fraction, %	70.3 ± 6.0	71.2 ± 4.9	70.8 ± 5.3	0.587
Fractional shortening, %	39.8 ± 5.1	40.8 ± 4.6	40.0 ± 4.6	0.456
E wave velocity, m/s	0.75 ± 0.2	0.73 ± 0.2	0.77 ± 0.2	0.490
A wave velocity, m/s	0.80 ± 0.2	0.81 ± 0.2	0.84 ± 0.2	0.599
E/A ratio	0.99 ± 0.4	0.96 ± 0.3	0.96 ± 0.3	0.197
e′ velocity, m/s	0.08 ± 0.02	0.07 ± 0.02	0.06 ± 0.02	<0.001
a′ velocity, m/s	0.10 ± 0.02	0.10 ± 0.02	0.10 ± 0.01	0.244
E/e′ ratio	9.9 ± 2.8	11.7 ± 2.9	13.2 ± 3.3	<0.001
Patterns of LV hypertrophy				
Normal LV, %	67.6%	36.6%	35.2%	<0.001
Concentric remodeling, %	22.5%	29.6%	23.9%	0.594
Concentric hypertrophy, %	5.6%	19.7%	28.2%	0.002
Eccentric hypertrophy, %	4.2%	14.1%	12.7%	0.113

Values are given as mean ± SD for continuous variables and percentage for categorical data.
Abbreviations: LV, left ventricle; E, peak mitral flow velocity in early diastole; A, peak mitral flow velocity in late diastole; e′, peak early diastolic mitral annular velocity; a′: peak late diastolic mitral annular velocity.

increasing values of SAC in the total study population, as shown in Figure 1. Furthermore, from the first to the third tertile of SAC, mean values of the interventricular septum and LV posterior wall thickness increased significantly (P = 0.001 for both). Regarding LV diastolic indices, the mean mitral e′ velocity decreased (P = 0.002), and the mitral E/e′ ratio increased (P < 0.001) significantly from the first to the third tertile of SAC.

The univariate linear regression analysis was performed to show the relationships between continuously distributed variables and the indices of LV structure and diastolic function, as shown in Tables S2 and S3 in the online-only Data Supplement, and the statistically significant variables were included in the stepwise multiple regression analysis.

Stepwise multiple regression analysis revealed that the positive relationship between SAC and interventricular septum, LV posterior wall thickness, RWT, LV mass, and LV mass index remained significant after adjustment for significant covariates. These covariates included nighttime DBP, 24 h urine sodium for interventricular septum (partial r = 0.39); 24 h SBP and 24 h urine sodium for LV posterior wall thickness (partial r = 0.40); age, nighttime DBP, eGFR, and triglycerides for RWT (partial r = 0.21); 24 h SBP and 24 h urine sodium for LV mass (partial r = 0.44) and LV mass index (partial r = 0.45), as shown in Table 3.

Furthermore, after adjustment of the potential covariates, stepwise multiple regression analysis showed that SAC was related to the following echocardiographic parameters of LV diastolic function: e′ velocity (P < 0.001) after adjustment for age and nighttime DBP (partial r = −0.34), a′ velocity (P = 0.009) after adjustment for office heart rate (partial r = −0.18) and E/e′ ratio (P < 0.001) after adjustment for age (partial r = 0.39), as shown in Table 4.

Concentric LV remodeling, concentric LV hypertrophy, and eccentric LV hypertrophy were present in 25.4%, 17.8%, and 10.3% of the study participants. Table 5 displays the association between SAC as a continuous independent variable and abnormal geometric LV patterns derived from the logistic regression model. After multivariate adjustments, such as age, gender, and body mass index, the association between SAC and concentric LV hypertrophy was highly significant (OR: 1.21, 95% CI: 1.11–1.33, P < 0.001) and is modulated by age (P = 0.007), office SBP (P = 0.03), 24 h SBP (P = 0.009) and 24 h urine sodium (P = 0.001). No significant associations were found between SAC and the risk of eccentric LV hypertrophy and concentric

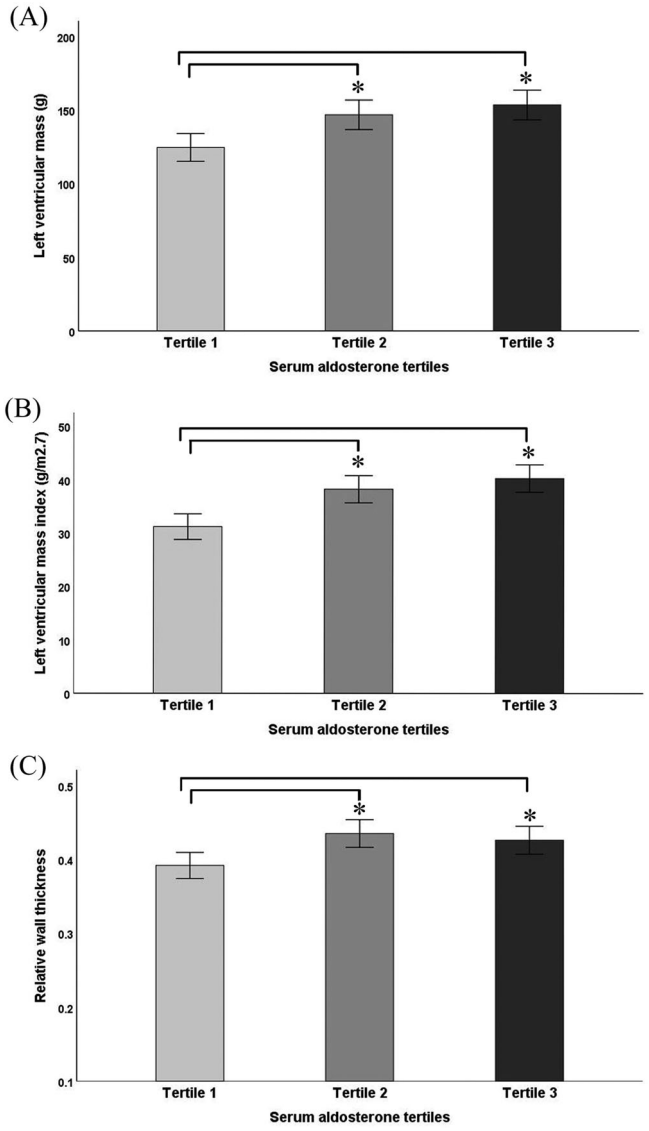

FIGURE 1 Figures (A–C) show left ventricular mass, left ventricular mass index, and relative wall thickness values according to tertiles of serum aldosterone concentration levels. Mean values for echocardiographic parameters of each ANCOVA analysis are shown. *$P < 0.05$

LV remodeling. Furthermore, no associations were detected between ARR and abnormal LV geometric patterns (Tables S4 in the online-only Data Supplement).

4 | DISCUSSION

The present study in patients with essential hypertension has shown that higher levels of circulating aldosterone, but not ARR, were associated with increased LV mass, LV mass index, RWT, interventricular septum, and LV posterior wall thickness values. Our study has also revealed that the elevation of aldosterone levels is associated, in part, with the impairment of LV diastolic function via the increase in E/e′ ratio and decrease in mitral e′ velocity and a′ velocity. These associations remained consistent after controlling various confounders, such as age, body mass index, blood pressure, 24 h urine sodium, eGFR, and PRA. Furthermore, we demonstrated increased SAC independently associated with concentric LV hypertrophy. Finally, age, office SBP, 24 h SBP, and 24 h urine sodium are important effect modifiers for concentric LV hypertrophy risk associated with SAC.

A growing body of evidence shows that aldosterone, even within the physiological range, is implicated in the development and progression of cardiovascular diseases.[12] In several experimental studies, aldosterone has exhibited profibrotic and prohypertrophic effects independent of blood pressure and circulating plasma volume.[24] This finding is supported by preventing cardiac fibrosis with non-hypertensive doses of spironolactone, an aldosterone receptor antagonist.[7] Serum aldosterone has been linked to cardiac structure and function in population-based studies and essential hypertension patients.[14,25] In line with these observations, our findings also supported that excessive aldosterone secretion in primary aldosteronism is not compulsory for aldosterone-mediated changes in LV structure and diastolic function.

In essential hypertension, cardiac remodeling is marked by myocyte hypertrophy and increased interstitial fibrosis due to increased collagen production and decreased collagen breakdown.[26] This condition causes structural and functional alterations in the heart, including LV hypertrophy, LV systolic, and diastolic dysfunction.[27]

We identified strong associations between echocardiographic measures of LV structure, such as LV mass and LV mass index, and SAC. These findings are consistent with previous research that found a positive relation between aldosterone levels and cardiac mass in patients with essential hypertension.[14,28] In other studies, however, no associations were detected between aldosterone levels and any variable of LV structure in essential hypertension patients.[15,29] These contradictory results could be due to the heterogeneity of the research participants evaluated, such as variances in dietary salt intake. Human studies indicated that aldosterone requires a substantial dietary salt intake to manifest its adverse effect on the heart.[30] The 24 h urine sodium excretion is a reliable estimate of daily salt intake.[31] Catena et al.[32] revealed a correlation between urine salt excretion and LV remodeling reversal following medicinal and surgical treatment in primary aldosteronism patients. Our study showed that 24 h urinary sodium excretion is an independent predictor for the increased echocardiographic parameters of LV structure associated with SAC in patients with essential hypertension.

LV Pathological geometric patterns are linked to a higher risk of cardiovascular events, and concentric hypertrophy, particularly, is related to the highest risk.[33] Previous studies reported conflicting results on the relationship between aldosterone levels and the development of various LV geometric patterns. Muscholl et al.[34] demonstrated the highest aldosterone levels in patients with LV remodeling and eccentric hypertrophy in patients with essential hypertension. Another study, however, observed significantly high aldosterone levels in essential hypertension patients with concentric LV hypertrophy.[28] We also found a higher risk of concentric LV hypertrophy with increasing aldosterone levels after adjusting covariates. This finding is supported by

TABLE 3 Stepwise multivariate analysis with echocardiographic indexes of left ventricular hypertrophy as the dependent variable (standardized β)

Variables	Interventricular septum	LV posterior wall	Relative wall thickness	LV mass	LV mass index
SAC	0.370**	0.383**	0.198*	0.402**	.427**
Age			0.162*		
24hr SBP		0.192*		0.274**	0.187*
Nighttime DBP	0.133*		0.133*		
24hr urine sodium	0.251**	0.140*		0.207*	0.198*
eGFR			−0.197*		
Triglycerides			0.203*		

*$P < 0.05$.
**$P < 0.001$.
Abbreviations: SAC, serum aldosterone concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

TABLE 4 Stepwise multivariate analysis with echocardiographic indexes of left ventricular diastolic function as the dependent variable (standardized β)

Variables	E	A	E/A ratio	e′ velocity	a′ velocity	E/e′ ratio
SAC				−0.322**	−0.178*	0.381**
Age		0.288**	−0.302**	−0.346**		0.195*
Office heart rate					0.203*	
Nighttime DBP	−0.150*			−0.159*		

*$P < 0.05$.
**$P < 0.001$.
Abbreviations: SAC, serum aldosterone concentration; DBP, diastolic blood pressure.

TABLE 5 Logistic regression analysis relating serum aldosterone concentration to abnormal geometric left ventricular patterns

LV geometric pattern	Concentric Hypertrophy		Eccentric Hypertrophy		Concentric Remodeling	
Predictors[a]	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)
SAC	‘0.001*	1.21(1.11–1.33)	0.124	1.06 (0.98–1.15)	0.872	1.00 (0.94–1.06)
Age	0.007*	1.09 (1.02–1.16)	0.110	1.05 (0.99–1.13)	0.181	0.97 (0.93–1.01)
Office SBP	0.03*	0.95 (0.92–1.00)	0.167	1.03 (0.99–1.07)	0.345	1.01 (0.99–1.04)
24 h SBP	0.009*	1.07 (1.02–1.12)	0.862	1.01 (0.95–1.06)	0.03*	0.95 (0.91–1.00)
24 h heart rate	0.139	0.94 (0.87–1.02)	0.896	1.01 (0.92–1.10)	0.042*	1.06 (1.00–1.13)
Nighttime DBP	0.925	1.00 (0.93–1.09)	0.603	1.02 (0.94–1.11)	0.038*	1.07 (1.00–1.13)
24 h urine sodium	0.001*	1.01 (1.01–1.02)	0.160	1.01 (1.00–1.01)	0.374	1.00 (0.99–1.00)
eGFR	0.065	1.03 (1.00–1.07)	0.262	1.02 (0.98–1.06)	0.001*	0.95 (0.92–0.98)
LDL	0.497	1.19 (0.72–1.98)	0.686	1.12 (0.66–1.89)	0.047*	1.39 (1.00–1.91)
HDL	0.700	0.91 (0.57–1.46)	0.015*	1.96 (1.14–3.35)	0.463	1.15 (0.80–1.64)

Data represented odds ratios (OR) with a 95% confidence interval (95% CI) relating different pathological patterns of LV geometry to serum aldosterone concentration (SAC in ng/dl) as independent variables. They were adjusted for: age, gender, body mass index, HDL, LDL, triglycerides, office systolic blood pressure, office diastolic blood pressure, office heart rate, 24hr systolic blood pressure, 24hr heart rate, nighttime diastolic blood pressure, serum sodium, serum potassium, 24hr urine sodium, 24hr urine potassium, antihypertensive medication (angiotensin-converting enzyme inhibitor use, angiotensin II type-1 receptor blocker use, β-blocker use, calcium-channel blocker use, diuretic use), $eGFR^{MDRD}$, current smoking status, and renin activity.
Abbreviations: SAC, serum aldosterone concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*Significant p-value < 0.05.
[a]Non-significant predictors are not shown in the table.

the reported decrease in LV mass index in patients with concentric LV hypertrophy with the administration of mineralocorticoid receptor blockers.[35]

In the recent study, the constant association between aldosterone and echocardiographic measures of LV structure, even after controlling the renin activity, points to a renin-independent interaction between aldosterone and LV geometry.

ARR is a crucial predictor of blood pressure, a potent risk factor for LV hypertrophy.[35] A cross-sectional observation, which assessed 2119 Framingham Offspring Study subjects on a community-based sample, identified ARR as a key indicator of concentric and eccentric LV hypertrophy.[36] However, our research found no association between ARR levels and either LV structure or abnormal patterns of LV geometry. Variations in dietary sodium consumption, the incidence of co-morbidities, and aldosterone-renin determining factors, such as continuing medication, could affect aldosterone and renin levels,[37] resulting in these contradictory results.

Regarding the relationship between aldosterone and LV diastolic function, our findings showed a significant association between SAC and e′ velocity, a′ velocity, and E/e′ ratio after adjustment for potential confounders, such as age, blood pressure, and LV mass index. This finding is in line with previous studies, which reported a significant association between aldosterone levels and different indices of LV diastolic function in essential hypertension patients.[28,29] The results are consistent with the aldosterone-stimulating effect on myocardial fibrosis,[38] which is related to LV stiffness and diastolic dysfunction.[39] On the contrary, Catena et al.[14] found no association between aldosterone levels and LV diastolic indices in patients with hypertension. A possible cause of these inconsistent findings is that many factors may affect diastolic function, including age.[40] We identified no associations between ARR levels and doppler measures of LV diastolic function except for a weak and positive correlation with the A wave that had no further significance after controlling the confounding variables.

Our results found no associations between systolic function, as assessed by the LV ejection fraction and fractional shortening, and aldosterone or ARR levels. This finding is consistent with prior suggestions that asymptomatic structural changes and abnormalities in LV diastolic function, such as impaired relaxation and ventricular filling, can be recognized before developing the overt clinical disease.[41]

Previous research found that blocking aldosterone receptors substantially reduced LV hypertrophy in patients with essential hypertension.[42] Furthermore, adding a small dose of the aldosterone antagonist, canrenone, to angiotensin-converting enzyme inhibitors and calcium channel blockers improved LV diastolic dysfunction independent of lowering blood pressure.[43] Based on these findings and current data, preventing aldosterone-mediated effects on the heart appears crucial, even in hypertensive patients receiving antihypertensive medications.

5 | CONCLUSION

In conclusion, our observations indicate that aldosterone is related to LV structural changes, such as increased LV mass index and concentric LV hypertrophy, and decreased LV diastolic function in patients with essential hypertension. This association supports the concept of the potential aldosterone-mediated effects on the cardiovascular system even in the absence of primary aldosteronism. Our findings also favor the notion that aldosterone antagonists might help patients with essential hypertension delay or perhaps halt the occurrence of abnormal geometric patterns and diastolic dysfunction, implying the need for more observational and interventional research in this area.

AUTHOR CONTRIBUTIONS

Ekhlas Mahmoud Al-Hashedi and Xu Zhao conceptualized the study and were the main contributor to the collection and analysis of data, as well as wrote the first draft of the article. Ayman A. Mohammed, and Havyarimana Juvenal contributed to the collection and analysis of data. Jing Yu was the supervisor and responsible for the content's integrity and accuracy. All authors contributed to revising the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors have no conflict of interest

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