Title

Cardiovascular Interactions of Renin-Angiotensin-Aldosterone System Assessed by Cardiac Magnetic Resonance: The Multi-Ethnic Study of Atherosclerosis.

Journal

American Journal of Hypertension, 36(9)

ISSN

0895-7061

Authors

Varadarajan, Vinithra

Marques, Mateus D

Venkatesh, Bharath Ambale

et al.

Publication Date

2023-08-05

DOI

10.1093/ajh/hpad050

Peer reviewed

American Journal of Hypertension, 2023, **36**, 517–523
https://doi.org/10.1093/ajh/hpad050
Advance access publication 19 May 2023
Original Article

Original Article

Cardiovascular Interactions of Renin–Angiotensin–Aldosterone System Assessed by Cardiac Magnetic Resonance: The Multi-Ethnic Study of Atherosclerosis

Vinithra Varadarajan,[1] Mateus D. Marques,[1,2] Bharath Ambale Venkatesh,[3] Matthew Allison,[4] Mohammad R. Ostovaneh,[1,5] Kihei Yoneyama,[1,6] Sirisha Donekal,[3] Ravi V. Shah,[7] Venkatesh L. Murthy,[8] Colin O. Wu,[9] Russell P. Tracy,[10] Pamela Ouyang,[11] Carlos E. Rochitte,[12] David A. Bluemke,[13] and Joao A.C. Lima[1,]

[1]Department of Cardiology, Johns Hopkins University, Baltimore, Maryland, USA;
[2]Department of Medicine, Federal University of Santa Maria, Santa Maria, Brazil;
[3]Department of Radiology, Johns Hopkins University, Baltimore, Maryland, USA;
[4]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California, USA;
[5]Department of Medicine, Pennsylvania State Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA;
[6]Department of Cardiology, St. Marianna University School of Medicine, Kawasaki, Japan;
[7]Cardiovascular Division, Brigham & Women's Hospital, Boston, Massachusetts, USA;
[8]Department of Internal Medicine, University of Michigan Cardiovascular Center, Ann Arbor, Michigan, USA;
[9]Office of Biostatistics Research, NHLBI, NIH, Bethesda, Maryland, USA;
[10]Department of Pathology, University of Vermont, Colchester, Vermont, USA;
[11]Clinical Research Unit, Johns Hopkins Medical Institutes, Baltimore, Maryland, USA;
[12]Heart Institute, University of Sao Paulo Medical School, São Paulo, Brazil;
[13]Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA.

Correspondence: Joao A.C. Lima (jlima@jhmi.edu).

Background: The effects of the renin–angiotensin–aldosterone system in cardiovascular system have been described based on small studies. The aim of this study was to evaluate the relationship between aldosterone and plasma renin activity (PRA) and cardiovascular structure and function.

Methods: We studied a random sample of Multi-Ethnic Study of Atherosclerosis participants who had aldosterone and PRA blood assays at 2003–2005 and underwent cardiac magnetic resonance at 2010. Participants taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were excluded.

Results: The aldosterone group was composed by 615 participants, mean age 61.6 ± 8.9 years, while the renin group was 580 participants, mean age 61.5 ± 8.8 years and both groups had roughly 50% females. In multivariable analysis, 1 SD increment of log-transformed aldosterone level was associated with 0.07 g/m^2 higher left ventricle (LV) mass index ($P = 0.04$) and 0.11 ml/m^2 higher left atrium (LA) minimal volume index ($P < 0.01$). Additionally, higher log-transformed aldosterone was associated with lower LA maximum strain and LA emptying fraction ($P < 0.01$). Aldosterone levels were not significantly associated with aortic measures. Log-transformed PRA was associated with lower LV end diastolic volume index (β standardized = 0.08, $P = 0.05$). PRA levels were not significantly associated with LA and aortic structural or functional differences.

Conclusions: Higher levels of aldosterone and PRA are associated with concentric LV remodeling changes. Moreover, aldosterone was related to deleterious LA remodeling changes.

Keywords: blood pressure; cardiac magnetic resonance imaging; hypertension; left atrium dysfunction; left ventricle remodeling; renin–angiotensin–aldosterone system; vascular remodeling.

Hypertension, diabetes, and traditional cardiovascular risk factors activate the renin–angiotensin–aldosterone system (RAAS) through a locally produced angiotensin II. Overstimulation of this system can contribute to repair of injured tissue, hemodynamic instability that leads to adverse cardiac remodeling and events. Increased circulating angiotensin II leads to aldosterone secretion, cell growth, and catecholamine release. There are several studies showing the association of aldosterone and plasma renin activity (PRA) with left ventricular structural and functional alternations such as directly remodeling the myocardium through increasing collagen content (fibrosis), which contributes to myocardial stiffness while also causing vascular inflammation

Received 10 April 2023; **revised** 12 May 2023; **accepted** 15 May 2023.

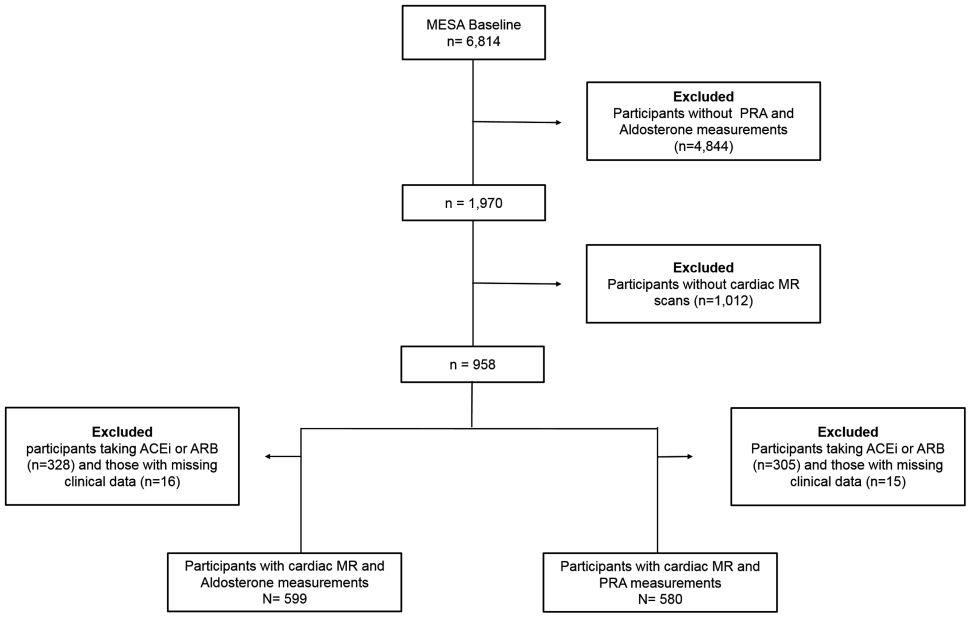

Figure 1. Flowchart delineating inclusion and exclusion criteria of the study population. Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MESA, Multi-Ethnic Study of Atherosclerosis; MR, magnetic resonance; PRA, plasma renin activity.

at the cellular level, peripheral vasoconstriction, and volume overload.[1–6] All of these contribute to heart failure onset. Notably, the blockade of RAAS enables reversing or retarding left ventricle (LV) remodeling changes.[7–10] In this regard, higher LV mass (LVM) and lower LV end diastolic volume (LVEDV) are morphologic features of positive remodeling usually present in diastolic dysfunction.[11–13] Additionally, these LV changes lead to left atrium (LA) volume increases and progressive LA dysfunction.[14,15]

Cardiac magnetic resonance (CMR) is capable of precisely measuring aortic, LV, and LA structural and functional parameters, as well as identifying diffuse myocardial fibrosis.[16,17] The major advantage of CMR over traditional imaging modalities is the capacity to accurately assess all these parameters in a single scan, being considered a reliable tool to follow-up heart failure progression.[18] Therefore, in the current study, CMR was used to assess aorta, LV, and LA morphological and functional measures, and characterize diffuse myocardial fibrosis. The study aimed to determine if higher levels of aldosterone or PRA were associated with aortic, LV, or LA functional and structural remodeling features.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing or expanding on the results after application to and approval by the MESA Publications and Presentations Committee (described at http://www.mesa-nhlbi.org).

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled 6,814 multi-ethnic men and women across 6 medical centers in the United States, from 45 to 84 years, who were free of apparent clinical cardiovascular disease at baseline (2000–2002).[19] During the second and third MESA examination (2003–2005), a random sample of 1,970 participants were enrolled in an ancillary study on body composition. From the appropriate study visit, ancillary study participants had a venous blood sample taken that was stored frozen and later used for PRA and aldosterone levels measurements.[20]

The MESA's fifth follow-up examination occurred from April 2010 to February 2012 and a total of 3,015 participants underwent CMR imaging. Of these, 1,345 participants underwent T1 mapping sequences pre- and post-gadolinium contrast injection for the assessment of diffuse myocardial fibrosis. We included MESA participants who had blood assayed for PRA and aldosterone levels and underwent CMR. In order to minimize medication effects of the RAAS, we excluded those using angiotensin-converting inhibitors or angiotensin receptor blockers during the study time (from clinical and laboratorial data collection at MESA 2 or 3 to the CMR scan at MESA 5) (Figure 1). The study complies with the Declaration of Helsinki, institutional review boards at each center approved the study protocol, and all participants gave written informed consent.

CMR imaging

The detailed protocol for imaging acquisition and scan parameters has been previously described.[21,22] Briefly, MESA participants without contraindications underwent CMR examinations by using 1.5 T scanners (Avanto: Siemens Medical Systems, Erlangen, Germany) with a 6-channel anterior phased array torso coil and corresponding posterior coil elements. Participants with a glomerular filtration rate ≥45 ml/min (60 ml/min for the site at Northwestern University) and with no history of allergic reaction to contrast agents were qualified to receive Gd. Steady-state free precession sequences were used to obtain cine images of short axis from above the mitral valve plane to the LV apex, one 2-chamber and one 4-chamber views. T1 mapping sequences were used to assess diffuse myocardial fibrosis, 1 short axis pre-contrast modified Look-Locker inversion recovery (MOLLI) image at the mid-slice position was acquired, repeated at 12 and 25 min after an intravenous bolus injection of gadolinium contrast at 0.15 mmol/kg (gadopentetate dimeglumine; Magnevist; Bayer Healthcare Pharmaceuticals, Montville, NJ).[21] The aortic

flow and size measurements were obtained using ascending and descending aorta images, perpendicular to the lumen, at the right pulmonary artery level with a gradient echo phase-contrast cine CMR sequence.[22] All CMR imaging analyses were done by blinded, experienced radiologists.

Image evaluation

The LV structural measures and LV ejection fraction were assessed using the CIM software (version 6.2, Auckland MRI Research Group).[23] The LVM and LVEDV were indexed for body surface area. T1 data analysis was processed on QMass research software (version 7.2, Medis; Leiden University Medical Center, Leiden, The Netherlands) with a Levenberg–Marquardt fitting algorithm. LV endocardial and epicardial borders were traced semi-automatically to extract the mean T1 values.[21] Data on hematocrit levels at the time of the MRI examination were available for 124 participants in the renin group and 128 in the aldosterone group, thus we generated the synthetic extracellular volume (ECV) based on the longitudinal relaxation rate of blood.[24]

LA structure and function were analyzed by using a tissue tracking, semi-automated software (multimodality tissue tracking version 5.0; Toshiba, Tochigi, Japan). LA endocardial and epicardial borders were manually drawn at the ventricular end-systolic frame and then automatically propagated to the other frames. LA minimum and maximum volumes were calculated by using the biplane modified Simpson method and the results were indexed for body surface area. LA strain was calculated by using an automated frame-to-frame pixel pattern–matching technique. LA strain and strain rate were calculated from 2- and 4-chamber views.[25]

The maximum ascending aorta area and distensibility were obtained using an automated software (Artfun, Inserm U678, Paris, France). Transit time was calculated and the distance between ascending and descending aorta was obtained at the precise locations where the through plane velocities were measured, enabling aortic arch pulse wave velocity.[26]

Clinical and laboratorial variables

At all study visits, the participants answered standardized questionnaires to assess the clinical history and the cardiovascular risk factors and underwent physical examinations. Besides the aforementioned measures, blood samples were obtained in the morning in the sitting position after a 12-hour fast. Blood was drawn after the participants had been resting in the sitting position for about 1 hour. Participants were instructed to take their usual medications before the clinic visit.

The blood samples were assayed for PRA and aldosterone levels, as well as the standardized laboratorial measurements in MESA. Aldosterone was measured using a competition-based radioimmunoassay (ALDOCTK-2; Diasorin, Stillwater, MN), while PRA was measured using the Gamma Coat Plasma Renin Activity 125I radioimmunoassay Kit (Diasorin, Stillwater, MN). Aldosterone and PRA assays were performed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Detailed methods for the clinical and laboratorial measurements were previously published.[20] Among the 6,814 participants in MESA, a random sample of 1,970 participated in an ancillary study. From those participants, PRA data were available for 1,801 participants and aldosterone for 1,890 participants. Of these, we included 615 participants who had both aldosterone and cardiac MRI measures available, and 580 participants who had renin and cardiac MRI measures available for the analysis.

Statistical analysis

All continuous variables are presented as mean and SD, and the categorical variables are expressed as frequency. Locally weighted scatterplot smoothing (LOWESS) method was used to assess the linearity of the association of aldosterone and PRA with the CMR measurements. Shapiro–Wilk test was used to test the normality of the variables. Distributions of aldosterone and PRA levels were skewed, so they were logarithmically transformed for regression models. Multivariable linear regression analyses (estimated regression coefficient, *B*) were performed to evaluate the relationship between PRA and aldosterone as independent variable (measured 2003–2005) with LV structure, function, as well as atrial structure and function and aorta structure and distensibility measurements (measured 2010–2012) as dependent variable. Multivariable linear models were adjusted for age, sex, ethnicity, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, estimate glomerular filtration rate, diabetes mellitus status, serum low-density lipoprotein, serum triglycerides, lipid lowering medication use, and smoking status at baseline and for antihypertensive medication at baseline (diuretics, calcium channel blockers, and beta-blockers). Fully adjusted models were individually constructed for all the dependent variables separately. The variables included in the multivariable regression models were chosen *a priori*. For testing interactions of log PRA and aldosterone with gender and race/ethnicity on LV, LA, and aortic structure and function, the likelihood ratio test was used. In order to evaluate the medication effects in the RAAS, we conducted sensitivity analyses including those participants using angiotensin-converting inhibitors or angiotensin receptor blockers. A 2-tailed *P* value of <0.05 was considered statistically significant. The first author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. All statistical analyses were performed using STATA version 15.0 (Stata Corp LP, College Station, TX).

RESULTS

Participant's characteristics

The study examined 2 groups of participants: the aldosterone group with 615 individuals and the renin group with 580 individuals. Among those, 570 individuals had aldosterone and PRA measurements, and were part of both groups. The mean age for the aldosterone and renin groups was 61.6 ± 8.9 and 61.5 ± 8.8, respectively. The proportion of women in both groups was approximately 50%. Both aldosterone and renin groups had higher proportion of Caucasians than the others ethnical groups in MESA (Table 1).

LV measurements and RAAS

After multivariable adjustment, a 1 SD increment in the log-transformed aldosterone level was associated with 0.07 g/m^2 higher LVM index ($P < 0.05$; Table 2). LV end-diastolic volume index was not significantly associated with aldosterone levels. Furthermore, aldosterone levels were not associated with LV function assessed by LV ejection fraction or myocardial diffuse fibrosis assessed by ECV (Table 3). On the other hand, a 1 SD increment in the log-transformed PRA level was associated with 0.08 ml/m^2 lower LVEDV index ($P = 0.05$), but no associations between PRA and LVM index were detected. There was no association between PRA and LV ejection fraction or ECV (Table 3).

Table 1. Demographic and cardiovascular risk factors characteristics for aldosterone and renin groups

	Aldosterone	Renin
Participants characteristics	N = 615	N = 580
Age, mean ± SD	61.6 ± 8.9	61.5 ± 8.8
Gender, N/%		
Female	299/49.9	290/49
Ethnic, N/%		
Caucasian	269/44.9	270/45.3
African American	96/16	94/15.8
Hispanic	145/24.2	142/23.9
Chinese American	89/14.9	89/15.0
SBP (mm Hg), mean ± SD	117.7 ± 18.9	117.7 ± 18.9
DBP (mm Hg), mean ± SD	69.2. ± 9.5	69.2 ± 9.6
Heart rate (beats/min), mean ± SD	64.5 ± 9.6	64.4 ± 9.5
BMI (kg/m^2), mean ± SD	27.3 ± 4.6	27.3 ± 4.6
Smoking, N/%		
Never	295/49.2	288/49.7
Former	233/38.9	235/39.8
Current	71/11.9	68/11.5
eGFR (ml/min/1.73 m^2), mean ± SD	81.5 ± 15.7	81.8 ± 16.5
Total cholesterol (mg/dl), mean ± SD	191.0 ± 32.9	191.2 ± 33.5
HDL cholesterol (mg/dl), mean ± SD	52.4 ± 16	52.0 ± 16
LDL cholesterol (mg/dl), mean ± SD	113.6 ± 29.2	113.8 ± 29.7
Triglycerides (mg/dl), mean ± SD	124.3 ± 63.1	132.6 ± 62.6
Diabetes mellitus status, N/%		
Normal	479/80	474/79.8
Impaired fasting glucose	89/14.9	92/15.5
Untreated diabetes	11/1.8	12/1.9
Treated diabetes	20/3.3	17/2.9
Lipid lowering drugs use, N/%	119/19.9	119/20.0
Any HTN medication use, N/%	145/24.2	143/24
Beta-blockers, N/%	41/6.7	40/6.7
Diuretics, N/%	48/7.80	44/7.39
Calcium channel blockers, N/%	50/8.1	46/7.73
COX-2 inhibitor use, N%	38/6.2	35/5.9
Aldosterone (pg/ml), mean ± SD	147.0 ± 83.0	
LogAldosterone (pg/ml), mean ± SD	4.8 ± 0.5	
Plasma renin activity (ng/ml), mean ± SD		0.9 ± 1.1
LogPlasma Renin Activity (ng/ml), mean± SD		–0.7 ± 1.0

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; SBP, aystolic blood pressure.

LA measurements and RAAS

Aldosterone levels were positively associated with the LA minimum volume index (β standardized = 0.11, $P < 0.05$) but not with LA maximum volume index. Furthermore, multiple function measurements for LA showed that aldosterone levels were associated with atrial dysfunction (lower LA maximum strain, maximum strain rate, and ejection fraction values and higher LA strain rates at early diastolic peak and atrial contraction peak values). Aldosterone levels showed negative association with maximum LA strain and maximum LA strain rate (β standardized = –0.12 for both, $P < 0.05$). Moreover, the LA emptying fraction was negatively associated with aldosterone (β standardized = –0.15, $P < 0.05$). The LA measurements for volume and function did not show significant associations with PRA levels (Table 3).

Aorta measurements and RAAS

The aorta measurements proposed in this study (maximum ascending aorta area indexed to body surface area, ascending aorta distensibility, and pulse wave velocity) were not associated with higher aldosterone or PRA levels (Table 3).

Our sensitivity analyses excluding participants taking angiotensin-converting inhibitors or angiotensin receptor blockers or any hypertensive medication did not significantly change the associations described (Supplementary Table online). The likelihood ratio test did not show any significant interaction or subgroup differences between gender, race, and RAAS.

Table 2. Cardiac magnetic resonance results for aldosterone and renin groups

	Aldosterone	Renin
CMR results	N = 615	N = 595
LV parameters		
LV mass index (g/m^2)	65.6 ± 12.8	65.6 ± 13
LV end-diastolic volume index (ml/m^2)	64.3 ± 13.1	64.5 ± 13.1
LV ejection fraction (%)	61.6 ± 6.9	61.6 ± 6.9
ECV (%)	26.7 ± 3.0	26.6 ± 2.6
LA parameters		
LA maximum volume index (ml/m^2)	34.6 ± 11.3	34.6 ± 11.2
LA minimum volume index (ml/m^2)	16 ± 8.2	15.9 ± 8.1
LAS maximum (%)	32.4 ± 15.5	32.5 ± 15.5
LASR maximum (%/ms)	1.5 ± 1.3	1.5 ± 1.3
LASR early diastolic (%/ms)	–1.2 ± 0.7	–1.2 ± 0.7
LASR atrial contraction (%/ms)	–2.1 ± 1.1	–2.1 ± 1.1
LA emptying fraction (%)	55.6 ± 11.3	55.6 ± 11.2
Aorta parameters		
Area index (cm^2/m^2)	5.11 ± 1.1	5.1 ± 1.1
Distensibility (mm Hg^{-1} × 10^{-3})	1.7 ± 1.1	1.7 ± 1.1
Pulse wave velocity (m/s)	8.9 ± 3.7	8.8 ± 3.7

Results are reported as mean ± SD. Abbreviations: CMR, cardiac magnetic resonance; ECV, extracellular volume; LA, left atrium; LAS, left atrium strain; LASR, left atrium strain rate; LV, left ventricle.

DISCUSSION

This study investigated the RAAS biomarkers of both aldosterone and PRA with CMR changes in a large, multi-ethnic population cohort and found that higher aldosterone levels were positively associated to LV hypertrophy characterized as higher LVM. Additionally, aldosterone levels were associated to LA remodeling, expressed by higher LA volume and lower LA functional measures. Higher PRA was associated with concentric remodeling characterized by lower LV volume. These findings highlight the potential role of aldosterone in the pathophysiologic pathway to diastolic dysfunction.[4]

There are several studies demonstrating the relation between aldosterone and myocardial hypertrophy in animals but many aspects still remain to be clarified in humans.[2,27] Besides hypertrophy, aldosterone has been associated to myocardial fibrosis.[28–30] It is not clear if the fibrosis is caused directly by an excess of mineralocorticoids, as a consequence of aldosterone-mediated hypertrophy or if the fibrosis is a repair for the inflammation's damage present in the hyperaldosteronism.[31] Assuming that one of these mechanisms, or all together, contribute to generating myocardial fibrosis, it would be reasonable to expect an association between higher aldosterone levels and diffuse myocardial fibrosis. However, higher aldosterone levels were not associated with greater ECV percentages. Only 263 participants had ECV measures in the aldosterone group, which could explain the lack of association between ECV and higher aldosterone levels.

As mentioned above, we expected that diffuse myocardial fibrosis would be associated with both RAAS measures, but PRA levels were not related to ECV, contradicting previous reports based on animals.[4,32] MESA participants were free of cardiovascular disease at baseline and this healthy status could require higher levels of

Table 3. Association between cardiac magnetic resonance measurements and aldosterone and plasma renin activity levels

	Aldosterone (pg/ml)[a]			Plasma renin activity (ng/ml)[a]		
	N	*β*[b]	*P*	*N*	*β*[b]	*P*
LV parameters						
LV mass (g/m^2)[c]	601	0.07	0.04	580	0.00	0.95
LV end-diastolic volume (ml/m^2)[c]	601	0.07	0.06	580	–0.08	0.05
LV ejection fraction (%)	601	0.00	0.95	580	0.05	0.28
ECV (%)	274	–0.02	0.90	268	–0.05	0.42
LA parameters						
LA maximum volume (ml/m^2)[c]	570	0.05	0.20	553	0.02	0.73
LA minimum volume (ml/m^2)[c]	570	0.11	0.01	553	0.03	0.55
LAS maximum (%)	570	–0.12	<0.01	553	–0.02	0.57
LASR maximum (%/ms)	570	–0.12	0.01	553	0.00	0.92
LASR early diastolic (%/ms)	568	0.14	<0.01	551	0.04	0.30
LASR atrial contraction (%/ms)	562	0.13	<0.01	545	–0.05	0.33
LA emptying fraction (%)	570	–0.15	<0.01	553	–0.02	0.66
Aorta parameters						
Area (cm^2/m^2)[c]	346	0.09	0.08	340	0.05	0.41
Distensibility (mm Hg^{-1} × 10^{-3})	343	–0.06	0.28	337	0.02	0.72
Pulse wave velocity (m/s)	422	–0.09	0.07	413	–0.02	0.71

Abbreviations: ECV, extracellular volume; LA, left atrium; LAS, left atrium strain; LASR, left atrium strain rate; LV, left ventricle. Regression model adjusted for age, sex, ethnicity, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, estimate glomerular filtration rate, diabetes mellitus status, serum low-density lipoprotein, serum triglycerides, lipid lowering medication use, and smoking status at baseline and for antihypertensive medication at baseline (diuretics, calcium channel blockers, and beta-blockers).
[a]Aldosterone and plasma renin activity values were log-transformed for this analysis.
[b]Results are reported as standardized *β* coefficients.
[c]Measures indexed for body surface area.

aldosterone or PRA and a longer follow-up to detect myocardial fibrosis, as well as aorta structural and functional changes.

Our study showed no significant associations between aortic parameters and aldosterone and renin which is in contrast to the previous established studies.[33,34] However, in MESA, body mass index was shown to be inversely related to aortic stiffness and distensibility which may explain our finding as well.[35] Inflammatory markers, insulin resistance, and glucocorticoids may play a role in addition to aging and body mass index in the relationship between RAAS and aortic parameter which warrants further research.

This study had utilized the cardiac MRI for the measurement of LV, LA, and aortic structure and function. Cardiac MRI has been established as noninvasive gold standard modality to measure both atrial and ventricular volumes and deformation given its excellent ability to define endo- and epicardial borders. In addition, contrast-enhanced MRI provides easy detection and quantification of myocardial fibrosis and ECV by T1 mapping. Moreover, compared with echocardiogram, MRI has better spatial resolution with excellent reproducibility and can provide tremendous information of cardiac chambers from a single scan.[36]

Our study has some limitations, this is an ancillary study of MESA designed to evaluate clinical and laboratorial outcomes using a single aldosterone and PRA blood assay. The adaption to an imaging outcome resulted in different sample size and few participants with some CMR measures. Secondly, there are no available data on the diagnosis of hyperaldosteronism and hence we did not have the capacity to exclude participants with hyperaldosteronism in our analysis. Further research can help investigate the association of RAAS and cardiac remodeling in patients without hyperaldosteronism. Thirdly, we could not exclude participants taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. It is feasible that those individuals have the greatest prevalence of cardiac or vascular change resulting from RAAS dysfunction. However, the sensitivity analysis including these individuals confirmed our results. Despite these limitations, the results are derived from a large multi-ethnic population study using CMR, to add knowledge to previous reports on animals or smaller sample studies.

Our results demonstrated that higher aldosterone levels are associated to positive LV remodeling, higher LA volumes, and LA dysfunction. PRA was associated to concentric LV remodeling features as well. Further studies specifically designed to evaluate RAAS and cardiovascular interactions could confirm our findings and definitively define the role of renin and aldosterone in the heart and vascular system.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

ACKNOWLEDGMENTS

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

FUNDING

This research was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS), and by a grant from Bayer Healthcare for the use of gadolinium contrast agent.

DISCLOSURE

The authors declared no conflict of interest.

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

REFERENCES

1. Guang C, Phillips RD, Jiang B, Milani F. Three key proteases—angiotensin-I-converting enzyme (ACE), ACE2 and renin—within and beyond the renin-angiotensin system. *Arch Cardiovasc Dis* 2012; **105**:373–385. https://pubmed.ncbi.nlm.nih.gov/22800722/
2. Catena C, Colussi G, Brosolo G, Novello M, Sechi LA. Aldosterone and left ventricular remodeling. *Horm Metab Res* 2015; **47**:981–986. https://pubmed.ncbi.nlm.nih.gov/26566103/
3. Sun Y. Intracardiac renin-angiotensin system and myocardial repair/remodeling following infarction. *J Mol Cell Cardiol* 2010; **48**:483–489. https://pubmed.ncbi.nlm.nih.gov/19682461/
4. Sciarretta S, Paneni F, Palano F, Chin D, Tocci G, Rubattu S, Volpe M., Role of the renin-angiotensin-aldosterone system and inflammatory processes in the development and progression of diastolic dysfunction. *Clin Sci (Lond)* 2009; **116**:467–477. https://pubmed.ncbi.nlm.nih.gov/19200056/
5. Iwashima Y, Horio T, Kuroda S, Takishita S, Kawano Y. Influence of plasma aldosterone on left ventricular geometry and diastolic function in treated essential hypertension. *Hypertens Res* 2002; **25**:49–56. https://pubmed.ncbi.nlm.nih.gov/11924725/
6. Adebiyi A, Akinosun O, Nwafor C, Falase A. Relationship between plasma aldosterone levels and left ventricular mass in hypertensive Africans. *Int J Hypertens* 2013; **2013**:762597.
7. Wachtell K, Bella JN, Rokkedal J, Palmieri V, Papademetriou V, Dahlöf B, Aalto T, Gerdts E, Devereux RB. Change in diastolic left ventricular filling after one year of antihypertensive treatment: the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. *Circulation* 2002; **105**:1071–1076. https://pubmed.ncbi.nlm.nih.gov/11877357/
8. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, Shelton B. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. *Circulation* 1995; **91**:2573–2581. https://pubmed.ncbi.nlm.nih.gov/7743619/
9. Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. *Circulation* 2002; **105**:2512–2517. https://pubmed.ncbi.nlm.nih.gov/12034658/
10. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**:709–717. https://pubmed.ncbi.nlm.nih.gov/10471456/
11. Van Heerebeek L, Borbély A, Niessen HWM, Bronzwaer JGF, Van Der Velden J, Stienen GJM, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006; **113**:1966–1973. https://pubmed.ncbi.nlm.nih.gov/16618817/
12. Borbély A, Van Der Velden J, Papp Z, Bronzwaer JGF, Edes I, Stienen GJM, Paulus WJ. Cardiomyocyte stiffness in diastolic heart failure. *Circulation* 2005; **111**:774–781. https://www.ahajournals.org/doi/10.1161/01.CIR.0000155257.33485.6D
13. Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. *N Engl J Med* 2004; **351**:1097–1105. https://pubmed.ncbi.nlm.nih.gov/15356307/
14. Teo SG, Yang H, Chai P, Yeo TC. Impact of left ventricular diastolic dysfunction on left atrial volume and function: a volumetric analysis. *Eur J Echocardiogr* 2010; **11**:38–43. https://pubmed.ncbi.nlm.nih.gov/19828485/
15. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009; **2**:10–15. https://pubmed.ncbi.nlm.nih.gov/19808559/
16. Flett AS, Hayward MP, Ashworth MT, Hansen MS, Taylor AM, Elliott PM, McGregor C, Moon James C. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. *Circulation* 2010; **122**:138–144. https://pubmed.ncbi.nlm.nih.gov/20585010/
17. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol* 2008; **52**:1574–1580. https://pubmed.ncbi.nlm.nih.gov/19007595/
18. Heckbert SR, Post W, Pearson GDN, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2006; **48**:2285–2292. https://pubmed.ncbi.nlm.nih.gov/17161261/
19. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002; **156**:871–881. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L35215769
20. Allison MA, Jenny NS, McClelland RL, Cushman M, Rifkin D. The associations of adipokines with selected markers of the renin–angiotensinogen–aldosterone system: the Multi-Ethnic Study of Atherosclerosis. *J Hum Hypertens* 2015; **29**:127–133. https://www.nature.com/articles/jhh201440
21. Liu CY, Liu YC, Wu C, Armstrong A, Volpe GJ, Van Der Geest RJ, Liu Y, Hundley WG, Gomes AS, Liu S, Nacif M, Bluemke DA, Lima João AC. Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2013; **62**:1280–1287.
22. Ohyama Y, Teixido-Tura G, Ambale-Venkatesh B, Noda C, Chugh AR, Liu CY. Ten-year longitudinal change in aortic stiffness assessed by cardiac MRI in the second half of the human lifespan: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J Cardiovasc Imaging* 2016; **17**:1044–1053. https://pubmed.ncbi.nlm.nih.gov/26758407/
23. Donekal S, Venkatesh BA, Liu YC, Liu CY, Yoneyama K, Wu CO, Nacif M, Gomes AS, Hundley WG, Bluemke DA, Lima Joao AC. Interstitial fibrosis, left ventricular remodeling, and myocardial mechanical behavior in a population-based multiethnic cohort: the Multi-Ethnic Study of Atherosclerosis (MESA) study. *Circ Cardiovasc Imaging* 2014; **7**:292–302.
24. Treibel TA, Fontana M, Maestrini V, Castelletti S, Rosmini S, Simpson J, Nasis A, Bhuva AN, Bulluck H, Abdel-Gadir A, White SK, Manisty C, Spottiswoode BS, Wong Timothy C, Piechnik SK, Kellman P, Robson MD, Schelbert EB, Moon James C. Automatic measurement of the myocardial interstitium: synthetic extracellular volume quantification without hematocrit sampling. *JACC Cardiovasc Imaging* 2016; **9**:54–63. https://pubmed.ncbi.nlm.nih.gov/26762875/

25. Zareian M, Ciuffo L, Habibi M, Opdahl A, Chamera EH, Wu C. Left atrial structure and functional quantitation using cardiovascular magnetic resonance and multimodality tissue tracking: validation and reproducibility assessment. *J Cardiovasc Magn Reson* 2015; **17**:52.
26. Noda C, Ambale Venkatesh B, Ohyama Y, Liu CY, Chamera E, Redheuil A. Reproducibility of functional aortic analysis using magnetic resonance imaging: the MESA. *Eur Heart J Cardiovasc Imaging* 2016; **17**:909–917. https://pubmed.ncbi.nlm.nih.gov/26358693/
27. Somanna NK, Yariswamy M, Garagliano JM, Siebenlist U, Mummidi S, Valente AJ, Chandrasekar B. Aldosterone-induced cardiomyocyte growth, and fibroblast migration and proliferation are mediated by TRAF3IP2. *Cell Signal* 2015; **27**:1928–1938. https://pubmed.ncbi.nlm.nih.gov/26148936/
28. Young M, Head G, Funder J. Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. *Am J Physiol* 1995; E657–662. https://pubmed.ncbi.nlm.nih.gov/7485478/
29. Ramires FJA, Sun Y, Weber KT. Myocardial fibrosis associated with aldosterone or angiotensin II administration: attenuation by calcium channel blockade. *J Mol Cell Cardiol* 1998; **30**:475–483. https://pubmed.ncbi.nlm.nih.gov/9515025/
30. Brilla CG, Weber KT. Mineralocorticoid excess, dietary sodium, and myocardial fibrosis. *J Clin Med* 1992; **120**:893–901.
31. Rocha R, Stier CT, Kifor I, Ochoa-Maya MR, Rennke HG, Williams GH, Adler GK. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinology* 2000; **141**:3871–3878. https://pubmed.ncbi.nlm.nih.gov/11014244/
32. Tokuda K, Kai H, Kuwahara F, Yasukawa H, Tahara N, Kudo H, Takemiya K, Koga M, Yamamoto T, Imaizumi T. Pressure-independent effects of angiotensin II on hypertensive myocardial fibrosis. *Hypertension* 2004; **43**:499–503. https://www.ahajournals.org/doi/abs/10.1161/01.hyp.0000111831.50834.93
33. Mahmud A, Feely J. Aldosterone-to-renin ratio, arterial stiffness, and the response to aldosterone antagonism in essential hypertension. *Am J Hypertens* 2005; **18**:50–55. https://academic.oup.com/ajh/article/18/1/50/149691
34. Mark PB, Boyle S, Zimmerli LU, McQuarrie EP, Delles C, Freel EM. Alterations in vascular function in primary aldosteronism: a cardiovascular magnetic resonance imaging study. *J Hum Hypertens* 2014; **28**:92–97. https://pubmed.ncbi.nlm.nih.gov/23884211/
35. Logan JG, Kang H, Kim S, Duprez D, Kwon Y, Jacobs DR. Association of obesity with arterial stiffness: the Multi-Ethnic Study of Atherosclerosis (MESA). *Vasc Med* 2020; **25**:309–318. https://journals.sagepub.com/doi/10.1177/1358863X20918940
36. Donekal S, Ambale-Venkatesh B, Berkowitz S, Wu CO, Choi EY, Fernandes V, Yan R, Harouni AA, Bluemke DA, Lima Joao AC. Inter-study reproducibility of cardiovascular magnetic resonance tagging. *J Cardiovasc Magn Reson* 2013; **15**:37. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3667053/