Relations of Serum Aldosterone to Cardiac Structure
Gender-Related Differences in the Framingham Heart Study

Ramachandran S. Vasan, Jane C. Evans, Emelia J. Benjamin, Daniel Levy, Martin G. Larson, Johan Sundstrom, Joanne M. Murabito, Flora Sam, Wilson S. Colucci, Peter W.F. Wilson

Abstract—Aldosterone is associated with myocardial fibrosis in experimental studies and with left ventricular remodeling in heart failure patients. We hypothesized that aldosterone influences ventricular remodeling in people without congestive heart failure in the community. We examined the relations between serum aldosterone and echocardiographic left ventricular measurements in 2820 Framingham Study subjects (mean age 57 years, 58% women, 88% white) free of myocardial infarction and overt heart failure. Serum aldosterone levels were higher in women compared with men. In linear regression models (adjusted for age, systolic blood pressure, weight, height, diabetes, heart rate, hypertension treatment, and ethnicity), left ventricular wall thickness and relative wall thickness were positively related, and left ventricular diastolic dimensions were inversely related to serum aldosterone in women ($P<0.05$ for all), but not in men ($P>0.20$ for all). There was no effect modification of the relations observed in women by menopausal status. The gender-related differences in relations of serum aldosterone to relative wall thickness were consistent across subgroups defined on the basis of sex-specific median values of systolic blood pressure and body mass index. Fractional shortening, left ventricular mass, and left atrial dimensions were not related to serum aldosterone in either sex. In conclusion, in our community-based sample of individuals free of myocardial infarction and heart failure, serum aldosterone was positively associated with a left ventricular geometric pattern suggestive of concentric remodeling (increased left ventricular wall thickness and relative wall thickness but decreased internal dimensions) in women but not in men. Additional investigations are warranted to confirm these findings. **(*Hypertension*. 2004;43:957-962.)**

Key Words: echocardiography ■ aldosterone ■ hypertrophy ■ epidemiology

Several lines of evidence suggest a key role for aldosterone in left ventricular (LV) remodeling.[1] Recent investigations have demonstrated the presence of the mineralocorticoid receptors on cardiac myocytes,[2] as well as local synthesis of aldosterone in human hearts.[3,4] Aldosterone has been demonstrated to influence LV remodeling independent of its impact on systemic blood pressure (BP).[5] These experimental studies are paralleled by clinical reports demonstrating that serum aldosterone levels are elevated in patients with heart failure and denote an adverse prognosis.[6] Furthermore, treatment with aldosterone antagonists results in reduced mortality in heart failure patients[7] and favorable changes in LV remodeling.[8,9]

The aforementioned observations have stimulated interest in the putative role of aldosterone in LV remodeling in the absence of heart failure.[10–15] Primary hyperaldosteronism and systemic hypertension are associated with LV hypertrophy that is reversed by adrenal surgery and treatment with aldosterone antagonists, respectively.[10–17] However, other reports examining the association of serum aldosterone with LV remodeling in individuals without heart failure have yielded inconsistent results.[18–22] For instance, one report underscored that serum aldosterone was associated with LV mass (LVM) in obese blacks, but not in nonobese blacks or in whites (irrespective of body mass).[21] Another report emphasized an association of serum aldosterone with LV geometric pattern, but not with LVM or wall thickness (LVWT).[22] These previous investigations were limited by small samples, selection bias, a focus on hypertensive individuals, sex-pooled analyses, and an inconsistent adjustment for confounders. A recent epidemiological study based on the Augsburg cohort of the MONICA Study noted a positive association of serum aldosterone with LVM in multivariable analyses in women but not in men, but the effect became nonsignificant in nonhypertensive women.[23]

In view of the lack of consistency in published reports noted, we examined the sex-specific relations of serum aldosterone to echocardiographic indices of cardiac structure

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From the National Heart, Lung, and Blood Institute's Framingham Heart Study (R.S.V., J.C.E., E.J.B., D.L., M.G.L., J.S., J.M.M., P.W.F.W.); the National Heart, Lung, and Blood Institute (D.L.), Bethesda, Md; and the Cardiology Section (R.S.V., E.J.B., F.S., W.S.C.), Myocardial Biology Unit (F.S., W.S.C.), and Department of Preventative Medicine and Epidemiology (R.S.V., E.J.B., D.L., M.G.L., J.M.M., P.W.F.W.), Boston University School of Medicine, Mass.

Correspondence to Dr Ramachandran S. Vasan, Framingham Heart Study, 73 Mt. Wayte Avenue, Framingham, MA 01702-5827. E-mail vasan@fram.nhlbi.nih.gov

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and function in a large community-based sample. We hypothesized that LVM and LVWT would increase with increasing serum aldosterone. Further, we posited that the relations of serum aldosterone and echocardiographic measures might vary according to sex, body mass index (BMI), and level of systolic BP.

Methods

The design and setting of the Framingham Offspring Study have been detailed previously.[24] Between 1995 and 1998, 3532 participants attended the sixth Offspring Study examination cycle. The Framingham minority cohort Study (Omni Study) began with the recruitment of Framingham residents who were between ages 40 and 75 years, and who considered themselves as belonging to an ethnic minority.[25] Between 1995 and 1998, 506 individuals participated in the first Omni examination cycle (58% women; 36% black, 40% Hispanic). All attendees in both cohorts underwent a routine physical examination, including BP measurements, anthropometry, evaluation of menopausal status (including use of hormone replacement therapy), laboratory assessment of vascular risk factors, electrocardiography, and echocardiography. The study was approved by the Institutional Review Board at Boston Medical Center and all subjects gave written informed consent.

Of 4038 participants at the index examinations, we excluded 1218 subjects for the following reasons: prevalent myocardial infarction or heart failure (n=166), renal insufficiency (serum creatinine >2 mg/dL, n=16), off-site examination (n=37), missing covariates (n=223), and inadequate echocardiograms (n=776; LV measurements not made because of less than optimal images). Subjects with previous myocardial infarction, heart failure, or renal dysfunction were excluded because these conditions influence LV measures and affect serum aldosterone levels. After exclusions, 2820 subjects (1640 women) remained eligible.

Measurement of Serum Aldosterone

A fasting blood sample was obtained on all attendees at the baseline examination with the subjects in a supine position for ≈10 minutes. Blood specimens were centrifuged immediately and serum stored at −70°C without freeze–thaw cycles until serum aldosterone was measured in 2002 to 2003. Aldosterone was measured from extracted and fractionated serum using a highly sensitive radioimmunoassay (Quest Diagnostics) with a sensitivity of <1 ng/dL.[26] The intra-assay coefficient of variation for the assay ranges from 3.8% (for high concentrations) to 6% (low concentrations), with corresponding interassay coefficient of variations varying from 4.0% to 9.8%. The stability of steroids including aldosterone in sera stored at −20°C or lower has been previously established.[27]

Echocardiographic Methods

All subjects underwent M-mode and 2-dimensional echocardiography with Doppler color flow imaging on a Sonos 1000 Hewlett-Packard machine. Digitized images were stored on optical disks and measured using an off-line analysis system. A sonographer or cardiologist (experienced in echocardiography), who were blinded to clinical information and serum aldosterone results, read all echocardiograms. End-diastolic left ventricular internal dimensions (LVID) and the thicknesses of the interventricular septum (IVST), the LV posterior wall (PWT), and the left atrium (LA) size at end-systole were obtained by averaging digital M-mode measurements in at least 3 cardiac cycles using the leading-edge technique, according to the American Society of Echocardiography guidelines.[28] End-diastolic LVWT was calculated as the sum of IVST and PWT; relative wall thickness (RWT) was computed as (IVST+PWT)/LVID. LVM was calculated as $0.8[1.04(\text{LVID}+\text{LVWT})^3-(\text{LVID})^3]+0.6$.[29] Fractional shortening (FS) was used as an indicator of LV systolic function. Excellent interreader and intrareader correlations of echocardiographic measurements were observed, and the mean values of various measurements were consistent across the 4 years of the examination cycle.

Statistical Analyses

All analyses were specified a priori and they were sex-specific because of a previous report noting gender-related differences in relations of serum aldosterone to LVM.[30] Serum aldosterone was treated as a continuous variable and as a categorical variable (sex-specific quartiles). Because the distribution of serum aldosterone was positively skewed, raw values were log-transformed.

Multiple linear regression was used to examine the relations of echocardiographic measures with log-transformed serum aldosterone and to test trends across quartiles of serum aldosterone. Two sets of models were considered. Model 1 incorporated age and height, whereas model 2 incorporated age, height, weight, systolic BP, use of BP-lowering medications, diabetes, ethnicity (white versus nonwhite), heart rate, smoking status, and the ratio of serum total-to-high-density lipoprotein cholesterol. We chose this analytical strategy because the relations of serum aldosterone to LV measures may be confounded by BP and obesity. Socioeconomic factors such as marital status, number of children, and physical activity were not incorporated in the models because serum aldosterone was not associated with these variables (data not shown). The following echocardiographic variables were examined separately: LVM, LVID, LVWT, RWT, FS, and LA. Analyses of LA size also adjusted for valvular disease and atrial fibrillation (model 2A). A two-tailed $P<0.05$ was considered statistically significant.

Results

The characteristics of our sample are displayed in Table 1. More than one third of the participants were hypertensive.[31] BP levels were similar across serum aldosterone in both sexes (Table I, available online at http://hyper.ahajournals.org).

Echocardiographic Measures Across Serum Aldosterone Quartiles

In women, serum aldosterone was positively associated with LVWT and RWT and inversely with LV diastolic dimensions. Covariate-adjusted mean values for LVWT and RWT increased whereas LV diastolic dimensions decreased across serum aldosterone quartiles. These results were consistent in age- and height-adjusted and multivariable models. In men, none of the LV measurements was associated with serum aldosterone in either of the models. LV mass, FS, and LA size did not change with serum aldosterone in either sex (Table 2; data for FS not shown).

Relations of Serum Aldosterone and RWT: Effect Modification by Menopausal Status, Use of Antihypertensive Medications, and Obesity

Because the most striking association of serum aldosterone in primary analyses was with RWT, and because this was observed only in women, additional analyses focused on RWT alone to limit the extent of multiple statistical testing. In our sample, one quarter of the women were premenopausal, whereas three-quarters were postmenopausal. Of the latter, 36% (n=427) were using hormone replacement therapy. The relations of serum aldosterone to RWT remained robust on additional adjustment for menopausal status and use of hormone replacement therapy ($P=0.006$ for trend across aldosterone quartiles). Furthermore, there was no effect modification by menopausal status or by hormone replacement therapy ($P>0.30$).

We also evaluated the relations of serum aldosterone to RWT in the following clinical subgroups based on reports in the literature of effect modification by use of BP-

TABLE 1. Characteristics of Study Sample

Variables*	Women (N=1640)	Men (N=1180)
Clinical characteristics		
Age, y	57±10	57±10
Height, m	1.61±0.06	1.75±0.07
Weight, kg	70±14	86±14
Body mass index, kg/m^2	27.0±5.4	28.0±4.0
Smoking, %	14.2	13.6
Total/HDL cholesterol	3.90±1.37	4.83±1.44
Systolic blood pressure, mm Hg	126±20	129±17
Diastolic blood pressure, mm Hg	74±9	77±9
Hypertension, %	33.9	40.5
Hypertension treatment, %	21.3	27.0
Diuretics, %	8.7	4.9
ACE inhibitors, %	7.6	12.6
β-blockers, %	8.8	10.2
Calcium-channel blockers, %	7.2	10.1
Heart rate, bpm	65±9	61±10
Diabetes, %	7.8	11.0
White, %	88	89
Atrial fibrillation, %	0.3	1.0
Serum aldosterone, ng/dL	12.2±7.8	10.6±6.0
Log aldosterone	2.35±0.55	2.22±0.54
Echocardiographic variables		
LV mass, g	142±31	193±43
LV diastolic dimensions, cm	4.55±0.40	5.05±0.45
LV wall thickness, cm	1.83±0.22	2.02±0.25
Relative wall thickness	0.404±0.063	0.402±0.065
Left atrial dimension, cm	3.75±0.45	4.19±0.50
Fractional shortening	0.38±0.05	0.36±0.05
Valve disease, %†	2.3	3.6

LV indicates left ventricular.
*Values are mean±SD.
†Moderate or greater degree of regurgitation/stenosis on Doppler color flow imaging.

lowering treatment (diuretics can elevate serum aldosterone levels), BP level,[20,23] and obesity:[21] (1) participants not using any antihypertensive medications and those using these agents; (2) participants with a systolic BP at or below the sex-specific median value, and those with systolic BP above the sex-specific median value; and (3) individuals with BMI at or below sex-specific median value, and those with BMI above the sex-specific median value. The positive association of serum aldosterone with RWT was present in women not using any antihypertensive medications, in those with systolic BP below the median value, and evident in both groups with BMI below and above the median value (Figure, results for model 2). There was no effect modification by the BP stage defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Statistical Power

Because LVWT, RWT, and LV diastolic dimensions were related to serum aldosterone in women alone, we assessed statistical power to detect associations in men. In men, we had >80% power to detect a trend for modest changes in LVWT, RWT, and LV diastolic dimensions of 0.017 cm and 0.005 and 0.03 g, respectively, across serum aldosterone quartiles (α=0.05).

Discussion

Principal Findings

Serum aldosterone was positively related to LVWT and RWT, and inversely related to LV internal dimensions in women, but not in men. FS, LV mass, and left atrial size were not related to serum aldosterone in either sex. The direct association of serum aldosterone with RWT in women was not influenced by menopausal status, was present in women not using any antihypertensive medications, and generally was consistent across subgroups defined on the basis of systolic BP level and BMI.

Aldosterone and LV Geometric Pattern

Aldosterone can influence LV remodeling via direct effects on the cardiac extracellular matrix[32] and alterations of cardiac loading conditions through its effects on renal sodium and water retention,[33,34] and augmented conduit artery stiffness.[35] The pattern of increasing LVWT and RWT and decreasing LV diastolic dimensions across serum aldosterone quartiles in women suggests that serum aldosterone is associated with concentric remodeling,[36] consistent with previous reports.[22] Concentric remodeling has been attributed to hemodynamic LV underfilling.[36] The inverse association of LV diastolic dimensions with serum aldosterone would be intuitive in this regard, because volume contraction is a potent stimulus for aldosterone release. It is unclear, though, why such an association is observed in women alone. The lack of association of LV mass with serum aldosterone in women is likely related to opposing influences of serum aldosterone on LVWT and LV diastolic dimensions, the 2 variables used to calculate LV mass.

Gender Differences in Relations of Serum Aldosterone and LV Structure

Only 1 previous investigation performed sex-specific analyses of the relations of serum aldosterone to LV measurements.[23] In that community-based investigation, a positive association of serum aldosterone with LVWT was noted in both sexes in unadjusted analyses but became nonsignificant in men on adjustment for age, systolic BP, and body mass. Thus, the present investigation confirms sex-related differences in relations of serum aldosterone to LVWT and RWT, and documents the consistency of these findings in multiple subgroups. Additionally, our study was adequately powered to detect modest effects of aldosterone on RWT in men.

Perspectives

The observation of an association of serum aldosterone with LV remodeling phenotypes in women but not men is intriguing. It is important to note that sex-related differences have

TABLE 2. Covariate-Adjusted Echocardiographic Left Ventricular Measures Across Quartiles of Serum Aldosterone

Echo Variables	Model	Log (Aldosterone)		Quartiles of Serum Aldosterone (range, ng/dL)				
				Women				
		β*	*P*	Q1 (1–7)	Q2 (8–10)	Q3 (11–15)	Q4 (16–90)	*P* for Trend
LVM, g	1	0.91	0.51	142	139	142	143	0.39
	2	0.16	0.89	142	141	142	142	0.89
LVID, cm	1	−0.04	**0.02**	4.58	4.55	4.54	4.52	**0.04**
	2	−0.04	**0.02**	4.57	4.56	4.54	4.52	**0.03**
LVWT, cm	1	0.02	**0.005**	1.82	1.80	1.83	1.85	**<0.005**
	2	0.02	**0.03**	1.82	1.81	1.83	1.84	0.06
RWT	1	0.01	**0.001**	0.399	0.397	0.406	0.412	**<0.001**
	2	0.008	**0.002**	0.401	0.399	0.405	0.411	**0.005**
LA, cm	1	0.002	0.92	3.77	3.72	3.75	3.76	0.95
	2A	−0.015	0.40	3.77	3.74	3.74	3.74	0.30
				Men				
				Q1 (1–6)	Q2 (7–9)	Q3 (10–13)	Q4 (14–52)	*P* for Trend
LVM, g	1	3.02	0.18	192	194	191	197	0.28
	2	1.70	0.40	192	194	190	197	0.42
LVID, cm	1	−0.01	0.67	5.05	5.07	5.03	5.06	0.98
	2	−0.02	0.49	5.05	5.07	5.03	5.06	0.97
LVWT, cm	1	0.02	0.10	2.01	2.02	2.01	2.04	0.34
	2	0.01	0.26	2.02	2.02	2.01	2.03	0.62
RWT	1	0.005	0.13	0.402	0.400	0.402	0.406	0.44
	2	0.004	0.22	0.402	0.401	0.402	0.405	0.64
LA, cm	1	0.020	0.45	4.17	4.18	4.19	4.19	0.49
	2A	−0.001	0.96	4.18	4.19	4.18	4.18	0.92

Abbreviations are defined in the text. *P* values ≤0.05 are in bold.

Model 1 indicates age and height; Model 2, age, height, weight, heart rate, systolic blood pressure, hypertension prescription medication, diabetes, race, smoking, total/HDL cholesterol; Model 2A, age, height, weight, heart rate, systolic blood pressure, hypertension prescription medication, diabetes, race, smoking, total/HDL cholesterol, arterial fibrillation, and valve disease (for LA).

*β is the regression coefficient (increase in echo variable per unit increase in log aldosterone).

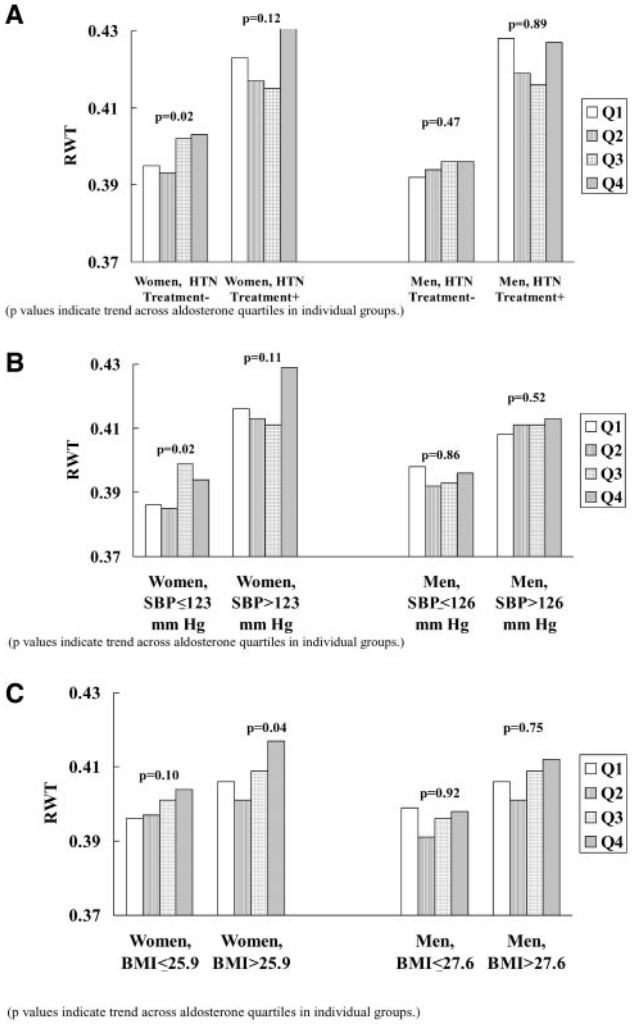
been reported in LV remodeling responses to pressure overload.[37] Women demonstrate a greater degree of increase in LVWT and concentric hypertrophy,[37] partly explained by molecular differences in the LV remodeling process.[38,39] Likewise, adrenal responses to angiotensin II vary between the sexes, and the nonmodulation phenotype (characterized by a blunted adrenal response) is less common in women.[40]

The potential mechanisms underlying the gender-related differences observed in our study merit comment. Both estrogen and aldosterone receptors are present in cardiac fibroblasts and myocytes.[2,33] Estrogen and aldosterone also elicit similar rapid nongenomic responses that use common signaling pathways (protein kinase C) that are known to be involved in the regulation of cell growth and the composition of the interstitial matrix.[41] Additional studies are warranted to investigate if interactions between the signaling effects of estrogen and aldosterone receptors contribute to the observed sex-related differences in LV remodeling.

The favorable effect on survival of the mineralocorticoid receptor antagonist spironolactone in the RALES trial was consistent for men and women with overt heart failure.[7] An important reason for the sex-differences in aldosterone relations observed in individuals free of heart failure in our sample as opposed to the consistent therapeutic effect for spironolactone in the RALES trial may be that patients with heart failure have serum aldosterone 10-fold higher than individuals without heart failure.[42] It is conceivable that LV effects may be more pronounced in women when serum aldosterone is within the normal range. It is noteworthy, though, that the mineralocorticoid receptor antagonist eplerenone effectively lowers elevated BP in both men and women with hypertension.[43] Additional research is needed to confirm our findings and to understand the basis for the sex-related differences observed in our investigation.

Strengths and Limitations

The large community-based sample, the independent evaluation of echocardiographic and aldosterone measurements blinded to each other, the use of sex-specific analyses a priori, and the assessment of relations in multiple subgroups



Relations of relative wall thickness (RWT) and serum aldosterone quartiles (sex-specific Q1–4) in women and men. Bars indicate sex-specific least square means adjusted for age, height, weight, systolic BP, antihypertensive treatment (when applicable), diabetes, race, and heart rate. A, Data for participants dichotomized according to use of antihypertensive treatment at the examination. B, Data for individual subgroups divided at the sex-specific median systolic BP. C, Data for subjects dichotomized at the sex-specific median BMI value (in kg/m^2 units). *P* values indicate trend across aldosterone quartiles in individual groups.

strengthen the present investigation. It is important, however, to acknowledge several limitations. We did not obtain blood samples after ≈1 hour of rest, as described in some clinical research protocols for aldosterone measurements. Serum aldosterone values may have been slightly elevated because participants were ambulatory before phlebotomy. Ideally, use of 24-hour urinary aldosterone measurements may provide a better indication of aldosterone secretion. We were unable to use 24-hour urinary aldosterone because of the constraints inherent in a large epidemiological investigation.

We used M-mode measurements of LVM that may be prone to error when the LV is distorted. We avoided this problem in part by excluding subjects with myocardial infarction and heart failure. Any measurement errors would be random and would bias us toward the null hypothesis of no association between serum aldosterone and LV measurements. An additional limitation is that we did not assess LV diastolic function. We performed multiple statistical testing in relating several echocardiographic measurements to serum aldosterone, but all comparisons were defined a priori. Our study sample was predominantly white, and we adjusted for ethnicity as a covariate, but we had very limited statistical power to assess effect modification of the relations of serum aldosterone to LV structure by ethnicity. Lastly, our cross-sectional investigation does not permit any causal inference regarding serum aldosterone and LV remodeling.

Conclusions

In our community-based sample of individuals free of myocardial infarction and heart failure, serum aldosterone was related to increased wall thickness and RWT and decreased LV diastolic internal dimensions—a pattern consistent with concentric remodeling[36]—in women but not in men. Additional investigations are warranted to elucidate the mechanisms underlying these gender-related differences.

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