Relations of Biomarkers Representing Distinct Biological Pathways to Left Ventricular Geometry

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Background—Several biological pathways are activated concomitantly during left ventricular (LV) remodeling. However, the relative contribution of circulating biomarkers representing these distinct pathways to LV geometry is unclear.

Methods and Results—We evaluated 2119 Framingham Offspring Study participants (mean age, 57 years; 57% women) who underwent measurements of biomarkers of inflammation (C-reactive protein), hemostasis (fibrinogen and plasminogen activator inhibitor-I), neurohormonal activation (B-type natriuretic peptide), and renin-angiotensin-aldosterone system (aldosterone and renin modeled as a ratio [ARR]) and echocardiography at a routine examination. LV geometry was defined on the basis of sex-specific distributions of LV mass (LVM) and relative wall thickness (RWT): normal (LVM and RWT <80th percentile), concentric remodeling (LVM <80th percentile but RWT ≥80th percentile), eccentric hypertrophy (LVM ≥80th percentile but RWT <80th percentile), and concentric hypertrophy (LVM and RWT ≥80th percentile). We related the biomarker panel to LV geometry using polytomous logistic regression adjusting for clinical covariates and used backwards elimination to identify a parsimonious set of biomarkers associated with LV geometry. Modeled individually, C-reactive protein, fibrinogen, plasminogen activator inhibitor-I, and ARR were related to LV geometry (P<0.01). In multivariable analyses, the biomarker panel was significantly related to altered LV geometry (P<0.0001). On backwards elimination, logARR alone was significantly and positively associated with eccentric (odds ratio per SD increment, 1.29; 95% confidence interval, 1.06 to 1.58) and concentric LV hypertrophy (odds ratio per SD increment, 1.29; 95% confidence interval, 1.06 to 1.58).

Conclusions—Our cross-sectional observations on a large community-based sample identified ARR as a key correlate of concentric and eccentric LV hypertrophy, consistent with a major role for the renin-angiotensin-aldosterone system in LV remodeling. (Circulation. 2008;118:2252-2258.)

Key Words: aldosterone ■ biological markers ■ echocardiography ■ hypertrophy ■ remodeling ■ renin

Left ventricular (LV) remodeling is a dynamic process characterized by adaptive and maladaptive changes in the myocellular and the extracellular matrix compartments of the myocardium in response to acute and chronic stress.1 The molecular changes that characterize LV remodeling manifest morphologically as alterations in LV geometry that can be assessed by cardiac imaging, typically with the use of echocardiography or magnetic resonance imaging.2

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Concentric remodeling, eccentric hypertrophy, and concentric hypertrophy are LV remodeling phenotypes that have been well characterized in the echocardiography literature.3 Previous research evaluating changes in LV geometry in response to stressors have used experimental models with pressure or volume overload. These investigations have incriminated several processes involving activation of key biological pathways during the LV remodeling process.4 Observations from these experimental and clinical studies have demonstrated the concomitant and heightened activity of inflammatory pathways, the neurohormonal axis (including the natriuretic peptides and the renin-angiotensin-aldosterone system [RAAS]), and hemostatic and fibrinolytic mechanisms in parallel with alterations in LV measurements and function.5-9 The associations and relative contributions of these pathways to abnormal LV geometry in individuals in...
the community have not been systematically investigated. Such knowledge would be valuable because altered LV geometry precedes and predicts cardiovascular morbidity and mortality, including heart failure events, and such biological insights may aid risk stratification and/or elucidate therapeutic targets.

We selected 5 circulating biomarkers (see below) that were routinely measured in Framingham Offspring Study participants and that represent distinct biological domains and evaluated the cross-sectional relations of these biomarkers to LV geometric patterns. We hypothesized that mean levels of these systemic biomarkers will be higher in participants with altered LV geometry than in individuals with normal LV geometry. We further hypothesized that the relations of biomarkers to LV geometry are not confounded by LV systolic function.

Methods

Study Sample and Design

The design, rationale, and characteristics of the Framingham Offspring cohort have been detailed elsewhere. In 1971, 5124 individuals who were the children (or spouses of the children) of the original cohort participants of the Framingham Heart Study were enrolled into the Offspring Study, and these participants have been evaluated approximately every 4 years. At each Heart Study examination, attendees undergo a medical history and physical examination, laboratory testing for cardiovascular disease (CVD) risk factors, electrocardiography, and anthropometry. All participants provided written informed consent, and the institutional review board of Boston University Medical Center approved the study protocol.

For the present investigation, 3358 participants who attended the sixth examination cycle (1995–1998) were eligible. We excluded 214 participants because of prevalent CVD or renal dysfunction (defined as having an estimated glomerular filtration rate <60 mL/min per 1.73 m²) and an additional 1025 participants because of missing biomarker measurements or inadequate/unavailable echocardiography data. A diagnosis of CVD included coronary heart disease (angina pectoris, coronary insufficiency, myocardial infarction), peripheral vascular disease (intermittent claudication), cerebrovascular disease (stroke or transient ischemic attack), or heart failure. Prevalent CVD was defined as presence of clinical diagnosis of 1 or more of these conditions at the baseline examination cycle 6 (1995–1998). Heart failure was defined on the basis of Framingham Heart Study criteria for this condition (see Appendix I in the online-only Data Supplement).

Participants excluded for missing biomarker or echocardiography information were more likely to be older, to have diabetes mellitus, and to receive antihypertensive therapy. We excluded participants with heart failure, CVD, or renal dysfunction because these conditions may directly lead to activation of the biological pathways, thus confounding our analysis relating biomarkers to LV remodeling. In addition, LV chamber distortion secondary to myocardial infarction and heart failure may limit the ability to assess geometry accurately. A total of 2119 individuals (913 men, 1206 women) constitute the sample for the present analysis.

Measurement of Biomarkers

Samples for biomarker measurements were drawn on attendees at the index examination after participants had fasted overnight, typically between 8 AM and 9 AM. Participants generally rested for ~5 minutes in a supine position before phlebotomy. All blood samples were frozen at −80°C without any freeze-thaw cycles until biomarker measurements were performed. Fibrinogen and plasminogen activator inhibitor-1 (PAI-1) were measured contemporaneously with the baseline examination (1995–1998); B-type natriuretic peptide (BNP) was measured in 1999; aldosterone in 2003, and C-reactive protein (CRP) and renin in 2004. The long-term stability of these proteins in frozen samples has been established previously.

Plasma fibrinogen was measured by the Clauss method. Plasma PAI-1 was determined with an enzyme-linked immunosorbent assay test for PAI-1 antigen by the method described by DeClerck et al. Serum aldosterone was measured by radioimmunoassay (Quest Diagnostics, Cambridge, Mass), and plasma renin concentration was measured by immunochemiluminometric assay (Nichols assay, Quest Diagnostics). Plasma BNP levels were ascertained with a high-sensitivity immunoradiometric assay (Shionogi, Osaka, Japan).

The following were the average interassay coefficients of variation for the biomarker measurements: fibrinogen, 2.6%; PAI-1, 7.7%; CRP, 2.2%; renin, 2.0% (high concentrations) to 10% (low concentrations); aldosterone, 4.0% (high concentrations) to 9.8% (low concentrations); and BNP, 12.2%.

Assessment of LV Geometry

At the sixth examination cycle, all attendees underwent 2-dimensional echocardiography with Doppler color flow imaging. We used M-mode echocardiography to measure LV end-diastolic dimension (LVEDD) and the end-diastolic thicknesses of the interventricular septum (IVST) and posterior wall (PWT) using a leading edge technique. LV mass (LVM) and relative wall thickness (RWT) were calculated as follows: LVM (g) = 0.801[(LVEDD + IVST + PWT) − (LVEDD)] + 0.6; RWT = (IVST + PWT)/LVEDD. We used a fractional shortening <0.29 (on M-mode) or a reduced ejection fraction (<0.50) on 2-dimensional imaging to identify participants with decreased LV systolic function. The reproducibility of echocardiographic measures was good, as reported previously.

The reproducibility of echocardiographic measures was good, as reported previously. Sex-related differences have been reported in prevalence of abnormal LV geometry, but the prevalence of LV geometric patterns may also be influenced by varying distributions of RWT in men versus women and, consequently, by the use of the same threshold limit for denoting increased RWT in men and women. In addition, LVM and RWT are influenced by age and the presence of comorbid conditions. In addition, the literature is inconsistent on the thresholds used to identify “normal” versus “abnormal” LVM and RWT. To address concerns about the applicability of any thresholds chosen, we evaluated the sex-specific distributions of LVM and RWT in our sample and empirically used the 80th percentile (specified a priori) thresholds of these variables to categorize LV geometry. The 80th percentile cut points for LVM for men and women were 227 and 165 g, respectively. The corresponding RWT cut points for men and women were 0.44 and 0.45, respectively. Thus, we classified participants with values of both LVM and RWT below the 80th percentile as “normal”; elevated LVM and RWT as “concentric hypertrophy”; normal LVM but elevated RWT as “concentric remodeling”; and elevated LVM but normal RWT as “eccentric hypertrophy.”

Definitions of Covariates

Covariates were defined at the baseline examination. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. A physician measured blood pressure twice on the left arm of the seated participants using a mercury-column sphygmomanometer, and the average of these 2 readings indicated the examination blood pressure. Fasting lipids were measured with standardized assays. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL or receiving hypoglycemic therapy. Valve disease was defined as greater than or equal to mild stenosis or regurgitation of the mitral or the aortic valves on Doppler color flow imaging. We estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula.

Statistical Analyses

Biomarker values were natural logarithmically transformed and standardized within sex to account for sex-related differences in...
biomarker distributions. We used sex-pooled multivariable polytomous logistic regression to relate the biomarkers to LV geometry. First, we related biomarkers individually to LV geometric pattern, adjusting for age and sex. We modeled aldosterone and renin together as the aldosterone-to-renin ratio (ARR) because in our sample such combined modeling has been most informative.23 Second, we identified a set of clinical correlates that are associated with LV geometry using a stepwise backward elimination procedure (criterion for retention in model was $P<0.1$) from among 13 eligible clinical variables: age, sex, body mass index, systolic and diastolic blood pressure, smoking, total to high-density lipoprotein cholesterol ratio, estimated glomerular filtration rate, diabetes mellitus, aspirin use, trypsinogen, hypertension treatment, and valve disease. Third, we tested whether the biomarker panel as a whole was associated with LV geometry after adjusting for the set of clinical covariates identified in the second step. Fourth, we used stepwise backwards elimination to identify the biomarker(s) with the strongest association with LV geometry in a multivariable-adjusted model. A $P$ value threshold of 0.05 was used to indicate statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The clinical characteristics of our sample are displayed in Table 1. A third of the participants had altered LV geometry. The age- and sex-adjusted correlations among the biomarkers are shown in Table I in the online-only Data Supplement. The strongest positive correlation was between fibrinogen and CRP, and the strongest inverse correlation was between PAI-1 and BNP. The distributions of the biomarkers and the LV measures according to LV geometry type are displayed in Table 2 and Table 3, respectively.

Relations of Individual Biomarkers to LV Geometry

In models adjusting for age and sex, ARR, CRP, PAI-1, and fibrinogen were associated with increased odds of altered LV geometry (compared with normal LV geometry that served as referent). BNP was also positively associated with altered LV geometry, but the relations were of borderline statistical significance (Table 4).

Relations of the Biomarker Panel to LV Geometry

The following 10 clinical covariates were identified in the stepwise selection process as key correlates of LV geometry and therefore were included in the analyses of biomarkers: age, sex, body mass index, systolic blood pressure, diastolic blood pressure, hypertension treatment, triglycerides, smoking, diabetes mellitus, and presence of valvular heart disease. In models adjusting for these clinical covariates, the panel of biomarkers was significantly associated with altered LV geometry ($P=0.0001$; Table 5). In both backwards elimination and stepwise forward selection procedures, ARR was the only biomarker that emerged as a significant correlate of altered LV geometry, being positively associated with both concentric and eccentric LV hypertrophy ($P=0.01$ for both; Table 5). We did not observe effect modification of the relations of ARR to LV geometry by age, sex, or hypertension status (all $P$ values for interactions terms exceeded 0.05).

Table 2. Distribution of Biomarker Concentrations in the Study Sample According to LV Geometric Pattern

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Geometry</td>
<td>Concentric Remodeling</td>
</tr>
<tr>
<td></td>
<td>(n=609)</td>
<td>(n=122)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrinogen, mg/dL</td>
<td>306 (274, 351)</td>
</tr>
<tr>
<td></td>
<td>PAI-1, ng/mL</td>
<td>22.4 (15.3, 23.0)</td>
</tr>
<tr>
<td></td>
<td>CRP, mg/L</td>
<td>1.30 (0.72, 2.73)</td>
</tr>
<tr>
<td></td>
<td>ARR</td>
<td>0.64 (0.39, 1.10)</td>
</tr>
<tr>
<td></td>
<td>BNP, pg/mL</td>
<td>4.60 (4.00, 11.1)</td>
</tr>
</tbody>
</table>

Values are median (25th, 75th percentile).
Table 3. Echocardiographic Characteristics According to LV Geometric Pattern

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Geometry (n=609)</th>
<th>Concentric Remodeling (n=122)</th>
<th>Eccentric Hypertrophy (n=121)</th>
<th>Concentric Hypertrophy (n=61)</th>
<th>Normal Geometry (n=790)</th>
<th>Concentric Remodeling (n=179)</th>
<th>Eccentric Hypertrophy (n=174)</th>
<th>Concentric Hypertrophy (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass, g</td>
<td>178 (26)</td>
<td>181 (29)</td>
<td>254 (32)</td>
<td>269 (39)</td>
<td>130 (20)</td>
<td>133 (19)</td>
<td>185 (17)</td>
<td>188 (25)</td>
</tr>
<tr>
<td>LWT, cm</td>
<td>1.90 (0.14)</td>
<td>2.20 (0.16)</td>
<td>2.15 (0.16)</td>
<td>2.56 (0.26)</td>
<td>1.71 (0.13)</td>
<td>1.98 (0.15)</td>
<td>1.95 (0.12)</td>
<td>2.26 (0.15)</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>5.07 (0.35)</td>
<td>4.53 (0.30)</td>
<td>5.69 (0.31)</td>
<td>5.10 (0.31)</td>
<td>4.55 (0.31)</td>
<td>4.09 (0.25)</td>
<td>5.08 (0.24)</td>
<td>4.55 (0.28)</td>
</tr>
<tr>
<td>RWT</td>
<td>0.38 (0.04)</td>
<td>0.49 (0.04)</td>
<td>0.38 (0.04)</td>
<td>0.50 (0.07)</td>
<td>0.38 (0.04)</td>
<td>0.49 (0.05)</td>
<td>0.38 (0.03)</td>
<td>0.50 (0.05)</td>
</tr>
<tr>
<td>FS &lt;0.29, n (%)</td>
<td>28 (5)</td>
<td>3 (3)</td>
<td>13 (11)</td>
<td>6 (10)</td>
<td>16 (2)</td>
<td>3 (2)</td>
<td>13 (7)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless indicated otherwise. LWT indicates LV wall thickness; FS <0.29, fractional shortening (measured on echo) <0.29.

In subgroup analyses, the association of the biomarker panel and of ARR with LV geometry was robust in analyses restricted to the subgroup of participants with fractional shortening >0.29, with normal LV ejection fraction on 2-dimensional imaging, and without LV regional wall motion abnormalities (Table 5). The results were also similar when analyses were repeated after 19 participants with left bundle-branch block were excluded (data not shown). In secondary analyses (sensitivity analyses), relations of ARR to geometry were unaffected when geometry was defined with the 75th percentile or 90th percentile values used as thresholds to identify abnormal LVM and RWT (Table II in the online-only Data Supplement). Similarly, relations of ARR to geometry remained the same when LVM indexed to body surface area was used to define geometry (Table III in the online-only Data Supplement). In addition, when aldosterone alone (instead of ARR) was modeled, the results were consistent with our primary results (aldosterone being related positively to concentric and eccentric hypertrophy; data not shown).

Discussion

Principal Findings

We observed that 4 biomarkers representing the RAAS (ARR), hemostasis (PAI-1 and fibrinogen), and inflammation (CRP) were positively associated with altered LV geometry in age- and sex-adjusted models. In multivariable-adjusted models, the relations of CRP, PAI-1, and fibrinogen were no longer statistically significant, suggesting that the relations of these biomarkers to LV geometry are likely mediated via other clinical covariates in the models. ARR emerged as the only significant biomarker in multivariable models, suggesting that the relative balance of aldosterone to renin plays an important role in LV remodeling.

Of note, in our investigation, the relation of BNP to geometry was of borderline significance (P=0.05). The weak association of this marker of the important natriuretic peptide system may be because more than a third of the participants evaluated had BNP levels that were at the lower end of the assay detection limit (4 pg/mL), which may have limited analyses of this biomarker.

RAAS and LV Geometry

In our study, ARR was positively associated with eccentric LV hypertrophy and concentric LV hypertrophy, the LV geometric patterns characterized by elevated LVM. Previous literature on the association of the RAAS biomarkers with LV geometry is limited, and some studies have yielded inconsistent results. Schunkert et al24 demonstrated an association between aldosterone and LVM in women but not in men. Muscholl et al25 demonstrated that in people with essential hypertension, elevated levels of aldosterone were associated with concentric LV hypertrophy and eccentric LV hypertrophy. Some investigators have reported an association of mineralocorticoids with eccentric LV hypertrophy.28 Tanabe et al29 reported that concentric LV hypertrophy is the most common geometric pattern in primary aldosteronism. The aforementioned studies used modest-sized samples, did not adjust for a panel of clinical covariates, and were often limited to individuals with hypertension or samples with primary hyperaldosteronism. Yet, all have consistently invoked a role for aldosterone in LV remodeling.

Table 4. Results of Age- and Sex-Adjusted Polytomous Logistic Regression Analysis Relating Biomarkers Individually to LV Geometric Pattern

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Normal Geometry (n=1399)</th>
<th>Concentric Remodeling (n=301)</th>
<th>Eccentric Hypertrophy (n=295)</th>
<th>Concentric Hypertrophy (n=124)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Referent</td>
<td>1.20 (1.05–1.37)</td>
<td>1.34 (1.18–1.53)</td>
<td>1.45 (1.19–1.76)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PAI-1 Referent</td>
<td>1.15 (1.01–1.32)</td>
<td>1.47 (1.29–1.68)</td>
<td>1.71 (1.40–2.09)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CRP Referent</td>
<td>1.19 (1.04–1.35)</td>
<td>1.52 (1.33–1.73)</td>
<td>1.68 (1.39–2.03)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>ARR Referent</td>
<td>0.96 (0.85–1.09)</td>
<td>1.16 (1.02–1.32)</td>
<td>1.35 (1.11–1.65)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>BNP Referent</td>
<td>0.94 (0.82–1.07)</td>
<td>1.12 (0.98–1.28)</td>
<td>1.19 (0.99–1.43)</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Data are odds ratios (95% confidence intervals) for 1-SD increment in log-marker, comparing altered geometry types individually with normal geometry (referent). *P for differences among the 4 LV geometric patterns.
Indeed, increased levels of aldosterone correlate with myocardial fibrosis and hypertrophy in both experimental models and clinical studies. In addition, treatment with angiotensin-converting enzyme inhibitors and aldosterone antagonists leads to regression of LV hypertrophy in spontaneously hypertensive rats and humans. Blockage of the angiotensin receptor has been shown to reduce LV hypertrophy, and ameliorating renal artery stenosis decreases circulating levels of renin and aldosterone, leading to LV hypertrophy regression. Furthermore, “aldosterone escape” in people treated with angiotensin-converting enzyme inhibitors attenuates these benefits, confirming the importance of mineralocorticoids in LV remodeling. It has been argued that higher levels of aldosterone (especially relative to renin, ie, elevated ARR) may mediate cardiovascular morbidity that is a consequence of RAAS activation. Thus, previous findings in the published literature provide a physiological basis for our observations. In addition, aldosterone is a risk factor for hypertension and is associated with increased fluid retention. The effects of aldosterone may be mediated by both direct myocardial effects and indirect effects through its influence on clinical risk factors. The effects of aldosterone on both preload and afterload may also explain why both eccentric LV hypertrophy and concentric LV hypertrophy are associated with the ARR.

As noted above, previous reports investigated the relations of biomarkers of several biological pathways to LV structural measurements. However, our investigation is incremental in several respects. Whereas earlier studies evaluated biomarkers individually, we used a multimarker strategy, which permitted a comparison of several biomarkers in relation to their contributions to LV geometry while limiting multiple testing. Previous literature focused on individual LV measurements (eg, LV mass or wall thickness), whereas we assessed relations of biomarkers to LV geometry. An additional strength of our report is the demonstration of these relations in a large cohort of free-living individuals without prevalent CVD, avoiding potential confounding by preexisting CVD, which can activate several of the pathways investigated.

**Hemostatic Factors, Inflammation, and LV Geometry**

Biomarkers of hemostasis (fibrinogen and PAI-1) and inflammation (CRP) have been related previously to LV remodeling. In our study, these biomarkers were positively associated with eccentric LV hypertrophy and concentric LV hypertrophy only in age- and sex-adjusted models but not in multivariable models (including multimarker modeling biomarkers individually; data not shown), suggesting that the relations may be confounded or perhaps mediated by clinical risk factors. CRP has been previously related to hypertension, central obesity, and diabetes mellitus. PAI-1 has been related to hyperlipidemia, hypertension, and the metabolic syndrome. Investigators of the Fibrinogen Studies Collaboration reported associations between several metabolic and behavioral cardiovascular risk factors and fibrinogen levels. Thus, the attenuation of the association of these biomarkers with LV geometry in the multivariable models may not imply that these pathways do not contribute to the development of altered LV geometry.

**Strengths and Limitations**

Our study is strengthened by large sample size, standardized measurements of biomarkers and clinical variables, use of the sex-specific distributions of LV mass and RWT to define LV geometry, and a conservative analysis strategy to minimize multiple testing.

However, several limitations need to be acknowledged. First, we tested only a small set of biomarkers available at a routine examination and that are known to be representative of some of the physiological systems implicated in LV remodeling. Other biomarkers and biological pathways that were not tested may be important in influencing LV remodeling. Second, these biomarkers varied in the analytical precision of their assays, and this may have influenced our results. Notably, a substantial proportion of BNP levels were at the lower end of the assay detection limit (4 pg/mL), which may have limited analyses of this biomarker. Third, our analysis is cross-sectional and does not imply a causal relation between biomarkers and altered LV geometry, notwithstanding the biological plausibility of such a relation. It is also possible (as in LV hypertrophy and hypertension) that activation of these pathways may be a consequence of altered LV geometry. Fourth, we lack information on diastolic function and therefore were unable to adjust for these indices in our models. Fifth, blood pressure was measured only during a single visit to the Heart Study and only in the left arm. It would have been desirable to obtain multiple mea-
urements on several occasions and on both arms to adjust appropriately for blood pressure. Sixth, we do not have contemporaneous information on other blood pressure indices (eg, central artery pressure, pulse wave velocity) and therefore did not adjust for these measures. Finally, our sample comprised white individuals of European ancestry, and our results may not be generalizable to other ethnicities.

**Conclusions**

LV geometry is an important intermediate phenotype for the study of CVD, including heart failure. Our observations suggest that higher levels of aldosterone relative to renin (as reflected by the ARR) are a key correlate of altered LV geometry. Indeed, RAAS activation has been previously implicated in the development of risk factors for heart failure (stage A), morbidity of heart failure (stage C), and refractory heart failure (end-stage or stage D). By implicating ARR, an indicator of RAAS activity, in structural LV changes (stage B heart failure), we add to the body of scientific evidence that highlights the role of this pathway in influencing heart failure risk. In addition, observations from clinical trials demonstrate the ability of RAAS inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) in preventing or reversing adverse remodeling of LV. Thus, our observational data add to the body of evidence demonstrating that RAAS activity is related to altered LV geometry, which precedes and predicts future occurrence of CVD and stroke.

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**Disclosures**

None.

**References**

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Several biological processes have been individually implicated in left ventricular (LV) remodeling, but the relative contributions of these pathways are unclear. Such knowledge would be useful because LV remodeling precedes and predicts cardiovascular morbidity and mortality, and biological insights may aid risk stratification, elucidate therapeutic targets, or both. We used a multimarker strategy, which permitted a comparison of several biomarkers in relation to their contributions to LV remodeling while limiting multiple testing, to relate 6 biomarkers representing inflammation (C-reactive protein), hemostasis (fibrinogen and plasminogen activator inhibitor-1), neuroendocrine activation (B-type natriuretic peptide), and the renin-angiotensin-aldosterone system (aldosterone to renin ratio) to the 4 mutually exclusive patterns of LV geometry (ie, concentric remodeling, eccentric hypertrophy, concentric hypertrophy, and normal geometry).

We performed this analysis in a large cohort of free-living individuals without prevalent cardiovascular disease. In age- and sex-adjusted models, we observed that all biomarkers were strongly and positively related to altered LV geometry, specifically to eccentric and concentric hypertrophy. In multivariable models, aldosterone to renin ratio emerged as the major correlate of LV geometry, with strong positive associations with both eccentric and concentric hypertrophy. Our observations are consistent with a fundamental role for the renin-angiotensin-aldosterone system in influencing LV remodeling in the community in individuals free of overt cardiovascular disease.
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Supplementary Information for Velagaleti et al., Relations of Biomarkers Representing Distinct Biological Pathways to Left Ventricular Geometry

I. Appendix I: Framingham Heart Study heart failure criteria

II. Appendix Table A. Correlations among Biomarkers

III. Appendix Table B. Models relating ARR to geometry; Results of sensitivity analyses

IV. Appendix Table C. Model relating ARR to geometry; geometry defined using LV mass indexed to body-surface area (N = 2119)
Appendix I. Framingham Heart Study heart failure criteria

The major criteria are:

History of paroxysmal nocturnal dyspnea or orthopnea, presence of jugular venous distention, hepatojugular reflux, pulmonary rales, presence of third heart sound, increasing radiographic cardiomegaly, X-ray evidence of acute pulmonary edema, presence of a third heart sound, and evidence of weight loss >4.5 kg during the first 5 days of treatment for suspected heart failure.

The minor criteria are:

History of a nocturnal cough, dyspnea on ordinary exertion, presence of bilateral ankle edema, hepatomegaly, heart rate more than 120 beats per minute and X-ray evidence of bilateral pleural effusions and/or pulmonary vascular congestion.
Appendix Table A. Correlations among Biomarkers.

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen</th>
<th>PAI-I</th>
<th>CRP</th>
<th>BNP</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>1.00</td>
<td><strong>0.15</strong></td>
<td>0.48</td>
<td>-0.004</td>
<td>-0.11</td>
</tr>
<tr>
<td>PAI-I</td>
<td></td>
<td>1.00</td>
<td><strong>0.28</strong></td>
<td>-0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td>1.00</td>
<td>-0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td><strong>0.13</strong></td>
</tr>
<tr>
<td>ARR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

Cells display Pearson correlation coefficients for log-transformed and sex-standardized mean biomarker values, calculated on a sample of 2119 individuals. Values in bold indicate correlations that are statistically significant at a p-value threshold of 0.05.

PAI-1 = plasminogen activator inhibitor 1; CRP = C-reactive protein; BNP = B-type natriuretic peptide; ARR = aldosterone to renin ratio.
Appendix Table B. Models relating ARR to geometry; Results of sensitivity analyses

<table>
<thead>
<tr>
<th></th>
<th>Normal geometry</th>
<th>Concentric Remodeling</th>
<th>Eccentric Hypertrophy</th>
<th>Concentric Hypertrophy</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Model relating ARR to geometry; 75th percentile of LVM and RWT as threshold (N = 2119)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARR Referent</td>
<td>0.93 (0.82 – 1.06)</td>
<td>1.12 (0.99 – 1.28)</td>
<td>1.20 (1.01 – 1.43)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td><strong>C. Model relating ARR to geometry; 90th percentile of LVM and RWT as threshold (N = 2119)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARR Referent</td>
<td>0.97 (0.82-1.14)</td>
<td>1.29 (1.09-1.52)</td>
<td>1.47 (1.08-1.99)</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

Results of secondary analyses in which geometry was defined based on the 75th and 90th percentile values as cut-points, instead of the 80th percentile as used in primary analysis.

Data represent odds ratios (95% confidence intervals) for 1 SD increase in logARR, comparing altered geometry types individually to normal geometry (referent).

* indicates p-value for differences among the 4 LV geometric patterns.

Models include the following covariates: age, sex, body-mass index, systolic and diastolic blood pressure, smoking status, diabetes, triglycerides, hypertension treatment and valve disease.
### Appendix Table C. Model relating ARR to geometry; geometry defined using LV mass indexed to body-surface area (N = 2119)

<table>
<thead>
<tr>
<th></th>
<th>Normal geometry</th>
<th>Concentric Remodeling</th>
<th>Eccentric Hypertrophy</th>
<th>Concentric Hypertrophy</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>Referent</td>
<td>0.96 (0.84-1.09)</td>
<td>1.19 (1.03-1.35)</td>
<td>1.18 (0.99-1.42)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Data represent odds ratios (95% confidence intervals) for 1 SD increase in logARR, comparing altered geometry types individually to normal geometry (referent).

* indicates p-value for differences among the 4 LV geometric patterns.

Model includes the following covariates: age, sex, body-mass index, systolic and diastolic blood pressure, smoking status, diabetes, triglycerides, hypertension treatment and valve disease.