Aortic Root Remodeling and Risk of Heart Failure in the Framingham Heart Study

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Objectives The aim of this study was to investigate the association between aortic root remodeling and incident heart failure (HF).

Background Age-associated increases in aortic root diameter (AoD) might be associated with arterial stiffening, afterload changes, cardiac remodeling, and the development of HF.

Methods The study sample consisted of participants of the Framingham Heart Study Original and Offspring cohorts who underwent serial echocardiographic measurements of AoD and continuous surveillance for new-onset HF. The AoD was measured at baseline, and the change in AoD between 8-year examination cycles was calculated. Pooled repeated observations (total 13,605 person-observations) in multivariable Cox regression analyses were used to relate baseline AoD and change in AoD to the incidence of HF on follow-up. Models were adjusted for known HF risk factors (age, sex, body mass index, blood pressure, hypertension treatment, diabetes, smoking, prior myocardial infarction, and valve disease).

Results With adjustment for clinical risk factors, the risk of incident HF increased with greater AoD at baseline (hazard ratio: 1.19/1 SD; 95% confidence interval: 1.07 to 1.33) as well as increases in AoD over 8 years (hazard ratio: 1.20/1 SD; 95% confidence interval: 1.04 to 1.38). The AoD correlated with left ventricular mass (r = 0.50; p < 0.001) as well as increases in AoD over 8 years (hazard ratio: 1.07 to 1.33). The AoD correlated with left ventricular mass (r = 0.50; p < 0.001). After adjustment for left ventricular mass in addition to clinical risk factors, the association of AoD with incident HF was rendered nonsignificant.

Conclusions Aortic root remodeling is associated with future risk of HF among middle-aged and older adults in the community, potentially because it reflects parallel ventricular-vascular remodeling in those with an enlarged aortic root. Additional studies are warranted to confirm our findings. (J Am Coll Cardiol HF 2013;1:79–83) © 2013 by the American College of Cardiology Foundation

The proximal aorta remodels outwardly with advancing age (1). The age-associated increase in aortic root diameter (AoD) is well-described in epidemiological studies (2,3), and age-related underlying structural changes in the aortic wall (i.e., reduced elastin content and increased collagen deposition) have been demonstrated in post-mortem studies (4,5). The functional consequences of aortic root remodeling include increased proximal aortic stiffness, because mechanical stresses are no longer buffered by arterial wall elastin and are instead transferred to the less extensible collagen fibers (6). Arterial stiffening contributes to increased ventricular afterload, adverse cardiac remodeling, and ventricular dysfunction—factors that are strongly linked to the development of HF (1,7–9).

Few studies have examined the relationship between aortic remodeling and HF, and these investigations have yielded mixed results. In the Cardiovascular Health Study,
an enlarged aortic root in the highest quintile was associated with increased risk for HF in men but not in women (10). These cross-sectional data were potentially subject to reverse causality, and the association of “longitudinal changes” in aortic root size on the incidence of HF has not been previously assessed. Accordingly, we investigated the association of baseline AoD as well as change in AoD over an 8-year period, with incidence of HF in the community. We further evaluated whether associations between baseline or change in AoD varied with the type of incident HF (heart failure with preserved ejection fraction [HFPEF] vs. heart failure with reduced ejection fraction [HFREF]). To achieve these aims, we used the unique resources of the FHS study (Framingham Heart Study), where serial longitudinal echocardiographic characterization and routine surveillance for HF are available in a large community-based sample. We hypothesized that an enlarged aortic root at baseline, representing a marker of both increased proximal aortic stiffness and increased ventricular afterload, might be associated with increased risk of developing HF. We further hypothesized that a greater extent of aortic root remodeling over time (i.e., a greater change in AoD) might be related to greater risk of incident HF. Finally, we also hypothesized that an association between AoD and HF might vary by the type of incident HF, because arterial remodeling and its coupling to ventricular remodeling might differentially impact the development of HFPEF versus HFREF.

**Methods**

Details of the study sample and statistical analyses are provided in Supplementary Methods in the Online Appendix. Briefly, the study sample included participants of the FHS Original and Offspring cohorts undergoing routine serial transthoracic echocardiograms at the FHS study (total 13,605 person-observations). All echocardiograms were performed by trained technicans with standardized protocols. M-mode echocardiographic images of the aortic root were obtained with 2-dimensional echocardiographic guidance, and AoD was measured with the leading-edge to leading-edge technique (11) without awareness of subsequent HF status. The AoD measurements were highly reproducible (12). We further determined arterial stiffness (indexed by the ratio of pulse pressure to stroke volume [PP/SV]) and left ventricular (LV) structural characteristics (relative wall thickness, LV mass) in each participant and defined LV hypertrophy as LV mass ≥ sex-specific median.

All participants were under continuous surveillance for the development of HF, with each event adjudicated by a panel of 3 physicians according to the Framingham HF criteria (13). The ejection fraction closest to and preceding the date of a HF event was used to classify incident HF as HFPEF (ejection fraction ≥45%) or HFREF (ejection fraction <45%), where assessments of ejection fraction were eligible if performed after HF onset (e.g., during hospital admission) or within 1 year before HF onset provided that no intervening myocardial infarction occurred (14).

**Results**

**Baseline characteristics.** As shown in Table 1, pooling participants from the Original and Offspring cohorts provided a sample with a wide age range (20 to 95 years), with a total of 13,605 person-observations (in 6,493 unique subjects, 3,518 women) and 415 incident HF events for the analysis with baseline AoD; 7,098 person-observations (in 4,523 unique participants, 2,434 women); and 228 incident HF events for the analysis modeling change in AoD.

**Association of baseline AoD with incident HF.** In the entire sample, higher mean baseline AoD was associated with increased risk of incident HF (Table 2). This risk persisted after adjustment for clinical risk factors for HF, including age, sex, body mass index, systolic and diastolic blood pressure, hypertension treatment, diabetes mellitus, smoking, prior myocardial infarction, and valvular heart disease. There was no effect modification by sex (p for interaction = 0.99). Excluding 314 individuals with valvular heart disease gave similar results (hazard ratio: 1.13/1-SD larger baseline AoD; p = 0.018).

In the subset of participants with PP/SV, LV mass, and relative wall thickness measurements (10,941 observations), the association between baseline AoD and incident HF remained significant after adjusting for PP/SV or relative wall thickness in addition to clinical risk factors (Table 2). However, after adjusting for LV mass, the association of baseline AoD with incident HF (248 events) was rendered statistically nonsignificant. The AoD correlated with LV mass (Pearson r = 0.50; p < 0.001). There was no significant interaction of AoD by the presence versus absence of LV hypertrophy (p for interaction = 0.51).

**Association of change in AoD with incident HF.** A greater increase in AoD over 8 years was associated with increased risk of incident HF (Table 3). This risk persisted after adjustment for clinical risk factors for HF and accounting for potential interindividual relatedness and intraindividual repeated observations in our sample (by cluster analysis). Exclusion of patients with valvular heart disease gave similar results (hazard ratio: 1.20/1-SD increase in AoD over 8 years; p = 0.019). After adjusting for LV mass in addition to clinical risk factors in the subset of participants with LV mass measurements (5,633 observations, 79%), the association of change in AoD with incident HF (135 events) was rendered statistically nonsignificant (Table 3). There was no significant effect modification by...
the presence versus absence of LV hypertrophy (p for interaction = 0.56).

**Association of AoD with type of incident HF.** In the entire sample, HF events were classified as HFREF in 238 cases, HFPEF in 122 cases, and unknown in 55 cases. Upon adjustment for clinical risk factors for HF, increasing baseline AoD was significantly related to an increased risk of HFREF, but the association with HFPEF failed to reach statistical significance (Table 4). Similar trends were found for the association between change in AoD and each type of HF. The tests for interaction comparing the risks of HFREF versus HFPEF were not statistically significant in either analyses (p = 0.51 and 0.67, respectively), indicating that the risk of HFPEF was similar to the risk of HFREF with increasing baseline or change in AoD. Therefore, the failure to reach statistical significance in the analyses for HFPEF was likely due to the modest number of events.

**Supplementary analyses.** Recognizing that body mass index might not always relate to AoD (15), we repeated our analyses adjusting AoD by height and found similar results (Online Table 1).

**Discussion**

In our community-based sample of middle-aged and older adults, a larger aortic root at baseline was associated with increased risk of future HF. Furthermore, those with greater aortic root dilation over an 8-year period experienced...
Table 4  Relationship Between Baseline AoD or Change in AoD and Incidence of HFPEF Versus HFREF Over 8 Years

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>Number of Events</th>
<th>HR (95% CI)/1 SD*</th>
<th>Number of Events</th>
<th>HR (95% CI)/1 SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFREF</td>
<td>238</td>
<td>1.20 (1.08–1.35)</td>
<td>152</td>
<td>1.22 (0.997–1.503)</td>
</tr>
<tr>
<td>HFPEF</td>
<td>122</td>
<td>1.13 (0.96–1.33)</td>
<td>55</td>
<td>1.11 (0.81–1.53)</td>
</tr>
<tr>
<td>p for interaction</td>
<td>0.51</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, body mass index, systolic and diastolic blood pressure, hypertension treatment, diabetes mellitus, smoking, prior myocardial infarction, and valvular heart disease. (Adjusted for age, sex, body mass index, systolic and diastolic blood pressure, hypertension treatment, diabetes mellitus, smoking, prior myocardial infarction, and valvular heart disease, and baseline AoD. *p value for comparison of risk of heart failure with preserved ejection fraction (HFPEF) versus heart failure with reduced ejection fraction (HFREF).

Abbreviations as in Table 2.

A greater risk of incident HF on follow-up. The association of aortic root remodeling with HF persisted after adjusting for clinical risk factors and did not seem to be specific for either HFPEF or HFREF. A greater aortic root size was related to greater LV mass, suggesting the presence of parallel arterial-ventricular remodeling in the progression to HF in those with a larger aortic root.

We recently described the trajectory of aortic root remodeling over the adult life course and observed that gradual enlargement of the aortic root in community-based adults was principally related to increases in age and body mass index and decreases in PP (16). We had postulated that the extent of aortic root remodeling might carry implications for development of future HF in our cohort and now demonstrate this association between a larger AoD and incident HF in the present investigation. However, we observed, contrary to our hypothesis of a differential impact on the risk of HF with preserved versus reduced ejection fraction, that a greater AoD was associated with similarly increased risks of both types of HF: the point estimates showed 20% to 22% increased risk of HFREF and 11% to 13% increased risk of HFPEF, for each 1-SD increase in baseline AoD or longitudinal change in AoD (albeit not reaching statistical significance in HFPEF).

The relationship between aortic root size and HF was previously examined in the Cardiovascular Health Study (10), where a larger aortic root dimension (in the highest quintile) was associated with an increased risk of incident HF in men but not in women, adjusting for other known risk factors for HF. It is unclear why this association was seen only in men in that cohort. Reasons for the differences between the prior and current results with regard to women might be related to the older age of participants or the presence of black women in the Cardiovascular Health Study. The investigators reported in their discussion that aortic root dimension was not selectively predictive of HF with reduced systolic function in their study, but results for this specific analysis were not shown. The association between AoD and HF was independent of the pattern of LV hypertrophy (indicated by relative wall thickness) or degree of arterial stiffening (as estimated by the PP/SV ratio) in our study, and there was lack of a differential association of AoD with the type of HF (HFPEF vs. HFREF). These data suggest that the type of LV remodeling response (concentric vs. eccentric) and hence the type of HF that ensues (HFPEF vs. HFREF) might be determined by factors other than aortic root remodeling. Indeed, prior studies have shown that cardiac remodeling in response to increased afterload is highly influenced by factors other than the degree of pressure overload, such as sex (17).

The correlation between aortic root size and LV mass, observed in both the Cardiovascular Health Study (10) and our present study of Framingham participants, deserves mention. These observations are consistent with the presence of combined arterial and ventricular remodeling that is known to occur with aging (1) and is important for the preservation of optimal ventricular-vascular coupling for maximal cardiac efficiency (18,19). The association between aortic root dimension and HF persisted after adjusting for electrocardiographic LV hypertrophy in the Cardiovascular Health Study (in men only) but was attenuated after adjusting for echocardiographic LV mass in the present study. One possible interpretation is that LV hypertrophy mediates the progression to HF in the presence of aortic root remodeling. Postmortem studies have shown that there is increased collagen and reduced elastin content in age-associated vascular remodeling (4,5), which might contribute to increased LV afterload, a known trigger for LV hypertrophy. Although these changes might occur with preserved ventricular-vascular coupling in “healthy” aging, in “unsuccessful” aging there might be loss of optimal ventricular-vascular coupling, leading to the development of decompensated HF (1,7–9). Alternatively, another potential interpretation of our findings is that aortic remodeling is a marker rather than mediator of increased afterload and that combined ventricular-vascular remodeling represents compensatory mechanisms that fail to accommodate the increased loads at the onset of HF.

We acknowledge that aortic root measurement by the leading edge to leading technique includes 1 thickness of the aortic wall (hence differences in measured AoD might represent thickening of the aortic wall rather than increase in diameter per se). The PP/SV ratio is not an ideal measure of arterial wall stiffness, but tonometry–basis measurements were not available at baseline in these participants. The observational nature of our study precludes conclusions with regard to causality, and the generalizability of our findings to other races/ethnicities is uncertain. Strengths of our study include the large community-based sample and the availability of serial, standardized measurements, as well as systematic surveillance and adjudication of outcomes.
Conclusions

Aortic root remodeling is associated with future risk of HF among middle-aged and older adults in the community. Combined arterial and ventricular remodeling associated with progression to HF might represent a valid target for the development of preventive strategies.

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REFERENCES


Key Words: aortic root • general community • heart failure • remodeling • risk.

APPENDIX

For supplementary text and tables, please see the online version of this article.