Left Atrial Structure and Function Across the Spectrum of Cardiovascular Risk in the Elderly

The Atherosclerosis Risk in Communities Study

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Background—Although left atrial (LA) enlargement is a recognized risk factor for adverse cardiovascular outcomes, emerging evidence supports the importance of LA function. We examined LA emptying fraction (LAEF) across the spectrum of cardiovascular disease burden in a large cohort of elderly adults living in the community.

Methods and Results—We studied 1142 participants in the Atherosclerosis Risk in Communities (ARIC) study who were in sinus rhythm, free of valvular disease, and had acceptable quality 3-dimensional echocardiograms (mean age, 76±5 years; 59% women). We determined the cross-sectional correlates of LAEF and compared LAEF among elderly adults without cardiovascular disease or cardiovascular risk factors (n=201), those with hypertension (n=734), and those with overt heart failure (HF; n=207). In multivariable analysis, lower LAEF was associated with higher LA volumes and worse left ventricular systolic and diastolic functions. Elderly participants free of cardiovascular disease or risk factors had smaller LA volumes than those with hypertension (LA volume max/ body surface area 30.2±6.6 versus 33.0±9.0 mL/m²; P=0.001), but similar LAEF (55.2±10.3% versus 53.8±11.5%, respectively; P=0.357). Participants with HF had higher LA volume (39.8±13.3 mL/m²) and worse LAEF (47.6±14.6%) than participants with hypertension or participants free of cardiovascular disease or risk factors (all P<0.001).

Conclusions—In a community-based cohort, LA function was impaired in participants with prevalent HF, but there were no significant differences in LA function between participants with hypertension and those with free of cardiovascular disease or risk factors, despite greater LA size in the former. (Circ Cardiovasc Imaging. 2016;9:e004010. DOI: 10.1161/CIRCIMAGING.115.004010.)

Key Words: cardiovascular diseases | cardiovascular risk factors | echocardiography | epidemiology | heart failure | hypertension | left atrial

Left atrial (LA) enlargement is a robust predictor of cardiovascular outcomes in the general population1 and a marker of poor prognosis in patients with various cardiovascular diseases.2,3 However, LA function measured by emptying fraction (LAEF)4 or by global peak LA longitudinal strain (LA GLS) may provide incremental value to LA volume in predicting cardiovascular outcomes.5,6

See Editorial by Di Tullio and Homma
See Clinical Perspective

Recent technical advances have increased accessibility and usability of new imaging methods such as 3-dimensional echocardiography (3DE) and cardiac magnetic resonance imaging, and this has motivated interest in more sophisticated study of LA morphology and its function.4 Nevertheless, there are few population-based studies of LA structure and function, and little is known about LA function across the spectrum of cardiovascular risk, particularly among older adults. Therefore, we used both 2DE and 3DE measures to comprehensively assess LA structure and function in a large biracial cohort of elderly men and women. Our aim is to examine the cross-sectional correlates of LAEF as a measure of LA function, and to compare LA structure and function across the spectrum of cardiovascular disease, including elderly adults without evidence of cardiovascular disease or cardiovascular risk factors, those with hypertension, and those with overt heart failure (HF), from the Atherosclerosis Risk in Communities (ARIC) study.

Received June 30, 2015; accepted December 17, 2015.
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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.115.004010
Methods

Study Population
The ARIC study is an ongoing, prospective observational study. Detailed study rationale, design, and procedures have been previously published.9 The original cohort included 15,792 men and women aged 45 to 64 years recruited between 1987 and 1989 (visit 1), selected from 4 communities in the United States: Forsyth County, NC; Jackson, MI; Minneapolis, MN; and Washington County, MD. Subsequently, 3 follow-up visits (visit 2–4) occurred at 3-year intervals, with annual telephone interviews conducted between visits. Between 2011 and 2013, 6101 surviving participants underwent visit 5, when echocardiography was performed in all 4 ARIC field centers. Our analyses were restricted to a subset of 3035 ARIC participants who attended at the first half of visit 5 until December 2012. Among those, participants with insufficient 3DE image quality for LA assessment or with atrial fibrillation or other arrhythmia, as ventricular extrasystoles, at the time of the echocardiogram (n=1779), those with moderate or severe mitral, aortic, or tricuspid valvular heart disease or who underwent valvular replacement surgery (n=64), participants with non-white or non-black race (n=16), and those with missing data on body mass index (BMI) or body surface area (BSA; n=34) were excluded. A total of 1142 participants constitute the sample for the present analysis.

Institutional review boards from each site approved the study, and informed consent was obtained from all participants. Information on demographics, anthropomorphic measures, and blood pressure was obtained at the time of echocardiography. Standardized and validated interviewer-administered questionnaires included assessment of current medication, the presence of coronary artery disease (CAD) or diabetes mellitus. Established definitions for diabetes mellitus, CAD, and smoking status were used as previously described in the ARIC study.10 Hypertension was defined as systolic blood pressure $\geq 140$ or diastolic blood pressure $\geq 90$ or medication being taken for high blood pressure during the last 4 weeks before visit, but 82% participants were taking antihypertensive medication and also fulfilled the high blood pressure criteria. Prevalent HF was defined by history of HF hospitalization, according to the International Classification of Diseases-Ninth Revision, code 428 in any position, obtained by ARIC study retrospective surveillance of hospital discharges, or Physician Heart Failure Survey with HF onset date prior to visit 5 or self-report of treatment for HF from any study visit or annual follow-up prior to visit 5.11-12 Total cholesterol, high-density lipoprotein cholesterol, and triglycerides levels were measured in a centralized laboratory, N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured using electrochemiluminescent immunoassay (Roche Diagnostics) with a lower detection limit of 5 pg/mL. The assays and their performance have been previously reported.13 Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) Study equation. For the purpose of this study, we defined 3 groups by cardiovascular profile: group 1 (n=201): healthy elderly participants without evidence of CAD, HF, hypertension, diabetes mellitus, or obesity (BMI $\geq 30$ kg/m²); group 2 (n=734): participants with hypertension without CAD or HF; and group 3 (n=207): participants with HF.

Two-Dimensional Echocardiography Protocol
The 2D echocardiographic imaging and analysis protocol have been previously described in detail.14 All echocardiograms were performed using dedicated Philips iE33 Ultrasound systems with Vision 2011, using a preprogrammed acquisition protocol. All studies were acquired and stored digitally and transferred from field centers to a secure server at the Echocardiography Reading Center (ERC; Brigham and Women’s Hospital, Boston, MA), where echocardiographic measures were performed and over-read, using proprietary-validated echocardiographic analysis software, blinded to participants’ clinical characteristics.

Left ventricular (LV) dimensions, wall thickness, and anteroposterior LA dimension were measured from the parasternal long-axis view. A total of 1142 participants constitute the sample for the present analysis.
Table 1. Characteristics of the Study Population by Quartiles of Left Atrial Emptying Fraction

<table>
<thead>
<tr>
<th>LAEF Quartile</th>
<th>Range</th>
<th>Demographic and clinical</th>
<th>2D Echocardiography</th>
<th>Diastolic function</th>
<th>Other 3D Echocardiography data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.1–45.8</td>
<td>LAEF 36.3±8.3</td>
<td>46.8±12.2</td>
<td>46.8±12.2</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td>2</td>
<td>45.9–54.8</td>
<td>LAEF 50.8±2.6</td>
<td>46.7±11.6</td>
<td>46.7±11.6</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td>3</td>
<td>54.9–61.2</td>
<td>LAEF 57.9±1.8</td>
<td>45.4±10.4</td>
<td>45.4±10.4</td>
<td>3.4±0.5</td>
</tr>
<tr>
<td>4</td>
<td>61.3–83.3</td>
<td>LAEF 66.9±4.1</td>
<td>44.6±10.1</td>
<td>44.6±10.1</td>
<td>3.4±0.5</td>
</tr>
</tbody>
</table>

Data are described as mean (SD) for quantitative variables and counts (proportions) for categorical variables. 2D indicates 2-dimensional; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; DD, diastolic dysfunction; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; eGFR, estimated glomerular filtration rate; FAC, fractional area change; GLS, global longitudinal strain; HDL, high-density lipoprotein; HF, heart failure; HR, heart rate; LA, left atrial; LAEF, LA emptying fraction; LAV, LA volume; LV, left ventricle; NT-proBNP, N-terminal pro-brain natriuretic peptide; and RV, right ventricle.

*P-value for trend across LAEF categories.
Multivariate Analysis

Three-Dimensional Echocardiography

3DE acquisition was performed using X3-1 transducer iE33 (Philips Medical Systems) on wide-angled mode, with 4-wedged-shaped pyramidal sub-volumes (93°×21°) acquired during a single breath hold >4 consecutive cardiac cycles, at a frame rate of 15 to 25 Hz, depending on the selected line density. Proper gain settings were chosen by the operator to optimize endocardial border detection and to avoid echo images dropout. Imaging volumes were adjusted in size as appropriate to increase volume rate, while maintaining spatial resolution. Image quality was judged on the basis of stitch/artifacts and quality resolution of LA segments throughout the whole cardiac cycle, and in the presence of stitching artifacts or dropout of >2 LA segments the image was excluded from the analysis.

Three-dimensional models of the LA were generated by semi-automated quantification software (4D LV analyses 2.0; TomTec, Unterschleissheim, Germany). All 3DE images were analyzed by a single operator (A.G.) with expertise in 3DE, at the core laboratory of the University Hospital, in Munich, Germany. All 3DE images were analyzed by a single operator (A.G.) with expertise in 3DE, at the core laboratory of the University Hospital, in Munich, Germany.
the orifices of the pulmonary vein were excluded from the tracing (Figure 1). Then, LA endocardial surface was reconstructed throughout the cardiac cycle, resulting in a dynamic cast of LA cavity; for each consecutive frame, the voxel count inside the 3D surface was used to measure LA volume (LAV), resulting in a smooth interpolated LAV time curve allowing detection of the maximal (LAV max) and minimal (LAV min) LA volumes. LA emptying fraction, an estimate of LA reservoir function was calculated as \((\text{LAV max} - \text{LAV min}) / \text{LAV max} \times 100\). In addition, 3DE LA speckle-tracking analysis was automatically performed throughout the cardiac cycle, using P wave as the reference point, and LA GLS, also a surrogate of LA reservoir function was determined.

**Reproducibility Analysis**

3DE LA V measurements were repeated in a randomly selected group of 40 participants by an additional investigator (K.N.) and by the same primary reader at least 1 month later, both blinded to the results of all previous measurements.

**Statistical Methods**

Summary statistics for covariates were calculated as counts and percentages or means and SD for categorical and continuous data, respectively. Comparisons of clinical and echocardiographic characteristics between LAEF quartiles were made using trend tests by regression methods and \(\chi^2\) tests for trend for continuous and dichotomous variables, respectively. NT-proBNP was assessed using Cuzick nonparametric trend test. The correlation between LAEF and other variables was assessed by Pearson coefficients. Log transformation of NT-proBNP was used to satisfy the model assumptions. Using multivariate linear models, we examined the association between LAEF (independent variable) and measures of cardiac structure and function (dependent variables), adjusted for Framingham risk score covariates (age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and smoking), race, diabetes mellitus, LV ejection fraction (LVEF), heart rate, and NT-proBNP. The analyses were performed overall and separately for subgroups (groups 1, 2, and 3).

To assess whether the relationships between LAEF and echocardiographic characteristics were dependent on cardiovascular disease group, tests for interaction were performed using the likelihood ratio test comparing models with and without interaction terms between the categorical classification of cardiovascular disease groups and the LAEF. The ability of LA measurements to discriminate between participants with and without HF was assessed using receiver-operating characteristic curves. The area under the curve was estimated for each parameter along with its 95% confidence interval.

2DE- and 3DE-derived values of the LAV were compared using linear regression with Pearson correlation (Figure I in the Data Supplement). Interobserver and intraobserver variability of 3DE LA measurements were calculated as an absolute difference in the corresponding pair of repeated measurements. For all analyses, 2-sided \(P<0.05\) were considered significant. Analyses were performed using Stata version 13.1 (Stata Corp., College Station, TX).
Results

The final analysis data set included 1142 participants with a mean age of 76±5 years, 674 (59%) were women and 967 (85%) were white. When comparing the subset of ARIC participants included in this analysis with those who attended at visit 5, but who were not included in this study, there were no differences in age or sex, but the former were more likely to be white, to have lower BMI, and lower prevalence of hypertension (Table I in the Data Supplement).

Participants in the lowest quartile of LAEF (median, 38.6%; range 4.1%–45.8%) were older, more likely to be hypertensive, to have HF, lower heart rate, and higher NT-proBNP (Table 1). There were no significant differences regarding sex, race, BMI, cholesterol level, or the presence of diabetes mellitus or CAD by LAEF quartiles. In univariate and multivariate linear regression analyses, LAEF was inversely related to NT-proBNP ($r=-0.29$; $P<0.01$; Table 2).

Associations Between LAEF and Measures of Cardiac Structure and Function

In univariable analyses, lower LAEF was significantly associated with larger LV, RV, and LA volumes, greater LV mass, higher peak E wave velocity, higher E/E' and E/A ratio, lower LVEF, lower mitral annulus peak systolic velocity, and worse peak longitudinal LV strain, and with higher prevalence of moderate diastolic dysfunction (Tables 1 and 2). After adjusting for Framingham risk score covariates, race, diabetes mellitus, LVEF, heart rate, and NT-proBNP, lower LAEF was significantly associated with larger LA volumes, higher E/E' and E/A ratio, higher prevalence of moderate diastolic dysfunction, and worse LV systolic function.

LAEF by Cardiovascular Groups’ Categories

Participants with HF (group 3) had the lowest LAEF, worst LA GLS, and largest LA V max/BSA and LA V min/BSA.
We found that lower LA function was associated with worse LV systolic and diastolic functions and higher plasma levels of NT-proBNP. LAEF was lowest in participants with HF, but there were no significant differences in mean LAEF between participants with hypertension and those free of cardiovascular disease or risk factors.

Our results corroborate previous studies showing an association between LA dysfunction and measures of LV systolic (LVEF, peak LV longitudinal strain, and S'), LV mass, and diastolic dysfunction (E/E' and E/A ratio). In addition, we found a poor correlation between LAEF and LAV max in the overall population, and we demonstrated an inverse association between LAEF and LA max in participants with HF. The decreasing LAEF among HF participants with largest LAV max parallels LV volume response in HF, where the decreased contractility is observed in consequence of significant LV remodeling. However, although the LV functional changes in the progressive stages of HF have been extensively described, the role of LA dysfunction to date has received little attention. Furthermore, our results show that participants with hypertension had significantly higher LA volumes (both LAV max and min), higher LV mass, and worse diastolic function than elderly without cardiovascular disease or risk factors, but no significant differences in LA function were found. One explanation for LA enlargement in hypertensive participants is the Frank–Starling mechanism, as the LA dilates in response to the increased LV end-diastolic pressure and may initially improve its ejection performance. However, in cases of sustained increases in LA and LV pressure, as observed among patients with HF, the LA contractile reserve becomes exhausted, LAEF drops, and LA turns into a passive conduct dictated by ventricular distensibility. Nevertheless, because of the cross-sectional nature of this study, we cannot discern whether the LA dysfunction observed among participants with HF is a consequence of hypertension. Previous study in patients with mild essential hypertension showed a reduction in LA conduit volume and early diastolic strain, without changes in maximal LA volume or systolic strain, when compared with controls.

Table 3. Multivariate Linear Regression Evaluating the Associations Between Left Atrial Emptying Fraction and Other Parameters of Left Atrial Structure and Function, by Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>LA max/BSA, mL/m²</th>
<th>LA max/hf⁴/², mL/hf⁻²</th>
<th>LA min/BSA, mL/m²</th>
<th>LA min/hf⁴/², mL/hf⁻²</th>
<th>LA GLS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=201; Healthy)</td>
<td>30.2±6.6</td>
<td>13.4±3.1</td>
<td>13.5±4.4</td>
<td>5.9±2.0</td>
<td>20.1±5.9</td>
</tr>
<tr>
<td>Group 2 (n=734; Hypertensive)</td>
<td>33.0±9.0</td>
<td>15.5±4.4</td>
<td>15.3±5.8</td>
<td>7.1±2.7</td>
<td>21.5±6.7</td>
</tr>
<tr>
<td>Group 3 (n=207; Heart Failure)</td>
<td>30.2±6.6</td>
<td>15.5±4.4</td>
<td>15.3±5.8</td>
<td>7.1±2.7</td>
<td>19.5±6.3</td>
</tr>
</tbody>
</table>

Group definitions: group 1—elderly participants without evidence of CAD, HF, hypertension, diabetes mellitus, or obesity (body mass index ≥30 kg/m²); group 2—participants with hypertension without CAD or HF; group 3: participants with HF. Multiple linear regression analysis models adjusted for Framingham risk score covariates (age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein-cholesterol, and smoking) + race + diabetes mellitus + LV ejection fraction + heart rate + NT-proBNP. BSA indicates body surface area; CAD, coronary artery disease; GLS, global longitudinal strain; HF, heart failure; LA, left atrial; LAEF, left atrial emptying fraction; and LAV, LA volume.
whereas other study has described LA enlargement along with LVH.\textsuperscript{25} In this study, in spite of the overall negative association between LA function and diastolic dysfunction, in the subset of hypertensive participants, there were no significant differences in LA volume or function by diastolic dysfunction grading (Table III in the Data Supplement). However, our sample consists of elderly participants, who mostly presented elevated blood pressure, although taking antihypertensive medication. Thus, our results likely represent an older and homogeneous population with more severe stages of hypertension than results from previous reports.

LA dysfunction has previously been described in HF patients with preserved\textsuperscript{19,26} or reduced LVEF,\textsuperscript{20} but to date LAEF has not been considered for HF echocardiographic recognition. However, the diagnosis of HF with preserved EF is particularly challenging as diastolic dysfunction, LV hypertrophy, and LA enlargement coexist in patients with HF with preserved EF and in those with hypertension. Thus, our findings showing lower LAEF in participants with HF (47.6±14.6\%) than in those with hypertension and free of cardiovascular disease or risk factors (55.2±10.3\%) might contribute as an additional discriminating feature to the diagnosis of HF with preserved EF. However, the discriminative accuracy of any single measurement is limited, and additional studies will be required, to assertively present cutoff values for the determination of LAEF abnormality.

Many limitations of this analysis should be noted. Our population sample considers the evaluation of elderly subjects from a longitudinal study >24 years, being limited by the survival bias of this population. Moreover, we only included a subset of ARIC participants, and the proportion of images suitable for the 3D LA analysis was limited. This is partly explained by the fact that at the time of 3DE acquisition, the latest 3D technology, which has higher image quality, was not yet available, and the focus was LV analysis. Thus, participants were frequently excluded from this study by the absence of the LA roof in the 3D volume pyramid. We were unable to assess phasic atrial function, using gated 3DE, in consequence, variations on passive and active LA emptying were not considered. The subset of ARIC participants included in this study was more likely to be white, to have lower BMI, and lower prevalence of hypertension than those who attended to visit 5, but were not included in this study. We attempted to address these issues by using LA measures indexed to body size, stratifying results by hypertension status, and adjusting for race in our multivariate models. Most hypertensive participants were taking antihypertensive medication (89\%) and presented high blood pressure (82\%). Thus, we present an older and homogeneous hypertensive group, but no further associations between categories of hypertension severity and LAEF can be provided. The definition for prevalent HF was based on Gothenburg criteria and unadjudicated hospitalization International Classification of Diseases-Ninth Revision codes; this approach captures participants with previous or current symptoms of HF, as recommended by American College of Cardiology/American Heart Association.
staging of HF, but the echocardiography evaluation was not assessed at the time of incident HF. Finally, this is an observational cross-sectional study, and long-term studies are needed to assess the prognostic value of LAEF assessment.

Notwithstanding these limitations, our study had several strengths. The study was large in size; the sample was derived from a community-cohort comprising elderly adults from multiple sites and included whites and blacks with a wide range of cardiovascular risk profiles. To date, most studies on LA structure and function used 2DE, but 3DE has been shown to be more accurate, reproducible and with superior clinical value than 2DE. To our knowledge, this is the largest 3DE study assessing LA function in elderly from the community. These findings contribute to a fuller understanding of LA function and contribute to normative data on 3DE LA volumes and function.

In summary, we observed that LAEF was lowest in participants with HF, but, despite increases in LA size, there were no significant differences in mean LAEF between participants with hypertension and those free of cardiovascular disease or risk factors. In addition, lower LAEF was associated with higher NT-proBNP and worse LV systolic and diastolic functions. These results highlight for the potential of LAEF as an imaging biomarker and suggest that impairment in LA function may play a role in the pathophysiology of heart failure.

Acknowledgments
We thank the staff and participants of the Atherosclerosis Risk in Communities (ARIC) study for their important contributions.

Sources of Funding
The Atherosclerosis Risk in Communities (ARIC) study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN26821100005C, HHSN26821100006C, HHSN26821100007C, HHSN26821100008C, HHSN26821100009C, HHSN26821100010C, HHSN26821100011C, and HHSN26820 1100012C). This work was also supported by National Heart, Lung, and Blood Institute cooperative agreement NHLBI-HC-11-08 (Dr Solomon), grants R00-HL-107642 (Dr Cheng) and K08-HL-116792 (Dr Solomon), grants R00-HL-107642 (Dr Cheng) and K08-HL-116792 (Dr Shah), and a grant from the Ellison Foundation (Dr Cheng). The Atherosclerosis Risk in Communities (ARIC) study: design and objectives, The ARIC investigators. American journal of epidemiology. 1989;129:687–702.


**CLINICAL PERSPECTIVE**

In this community-based cohort, left atrial (LA) function was impaired in elderly participants with prevalent heart failure (HF), but there were no significant differences in LA function between participants with hypertension and those free of cardiovascular disease or risk factors, despite greater LA size in the former. In addition, worse LA function was associated with worse left ventricular systolic and diastolic functions, and higher plasma levels of N-terminal pro-brain natriuretic peptide. The diagnosis of HF with preserved ejection fraction is challenging as diastolic dysfunction, left ventricular hypertrophy, and LA enlargement coexist in patients with HF with preserved ejection fraction and in those with hypertension. Our findings highlight the potential of LAEF as an imaging biomarker and suggest that impairment in LA function may play a role in the pathophysiology of heart failure.
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Circ Cardiovasc Imaging, 2016;9:e004010
doi: 10.1161/CIRCIMAGING.115.004010
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/2/e004010

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Figure Legend
Supplementary Figure 1: A) Correlation between 2DE LAV/BSA and 3DE LAV max/BSA volume measurement; B) Bland-Altman plot comparing the measurement of LAV by 2DE and 3DE.

Difference 3D LAV max - 2D LA volume = 5.9 ml/m$^2$ P25-75 [1.9-10.5]

Two dimensional LAV and 3DE maximum LAV were highly correlated ($r= 0.70$, p <0.001), although we observed a systematic underestimation of the LAV by the 2DE technique (3D LAV max - 2D LAV = 5.9 ml/m$^2$ P25-75 [1.9-10.5]). The interobserver variability was higher than the intraobserver variability, and all variability values of 3DE measures of LA size and function were <10%.
Supplementary Table 1: Comparison between the characteristics of the participants included in this study and the ARIC participants who attended visit 5 but were not included in this study.

<table>
<thead>
<tr>
<th></th>
<th>Participants attending visit 5 echocardiogram not included in the analysis</th>
<th>Participants included in the analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.1 ± 5.1</td>
<td>76.1 ± 5.3</td>
<td>0.841</td>
</tr>
<tr>
<td>Men (n, %)</td>
<td>1922 (42.0)</td>
<td>468 (41.0)</td>
<td>0.531</td>
</tr>
<tr>
<td>White (n, %)</td>
<td>3473 (75.9)</td>
<td>967 (84.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.8 ± 5.7</td>
<td>27.4 ± 5.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker (n, %)</td>
<td>263 (5.9)</td>
<td>64 (5.8)</td>
<td>0.825</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>3964 (86.6)</td>
<td>930 (81.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>1469 (32.5)</td>
<td>320 (28.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>CAD (n, %)</td>
<td>87 (1.9)</td>
<td>19 (1.7)</td>
<td>0.584</td>
</tr>
<tr>
<td>HF (n, %)</td>
<td>762 (16.7)</td>
<td>207 (18.1)</td>
<td>0.234</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>181.0 ± 42.1</td>
<td>179.4 ± 40.5</td>
<td>0.258</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>62.9 ± 10.7</td>
<td>61.2 ± 9.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI, body mass index; CAD, coronary artery disease; HF, heart failure; HR, heart rate;
Supplementary Table 2: Multivariate linear regression evaluating the associations between LAEF and other potential interactions that were not significant at the p<0.05 level, but were significant at the p<0.10, by subgroups

<table>
<thead>
<tr>
<th>LAEF (%)</th>
<th>Group 1 (n=201) (“Healthy”)</th>
<th>Group 2 (n=734) (Hypertensive)</th>
<th>Group 3 (n=207) (Heart Failure)</th>
<th>P value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (SE)</td>
<td>P value</td>
<td>Coefficient (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>NT-proBNP (mmol/l)#</td>
<td>95.7 [52.1, 177.6]</td>
<td>-2.69 (0.86)</td>
<td>0.002</td>
<td>132.4 [72.9, 234.3]</td>
</tr>
<tr>
<td>Normal diastolic function</td>
<td>89 (44.3)</td>
<td>1.94 (1.53)</td>
<td>0.208</td>
<td>205 (28.1)</td>
</tr>
<tr>
<td>Moderate diastolic dysfunction</td>
<td>56 (27.9)</td>
<td>-4.51 (1.68)</td>
<td>0.008</td>
<td>246 (33.7)</td>
</tr>
</tbody>
</table>

Group Definitions: Group 1 - elderly participants without evidence of CAD, HF, hypertension, diabetes or obesity (BMI≥30 kg/m²); Group 2 - participants with hypertension without CAD or HF; Group 3 - participants with HF. Multiple linear regression analysis models adjusted for Framingham risk score covariates (age, sex, systolic blood pressure, total cholesterol, HDL cholesterol and smoking) + race + diabetes + LVEF + HR+ NT-proBNP. * Log transformation has been used for correlations and multivariate analysis
Supplementary Table 3: Parameters of LA structure and function by diastolic function categories, among hypertensive participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Diastolic function (n=205)</th>
<th>Mild DD (n=148)</th>
<th>Moderate DD (n=246)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAV max /BSA (ml/m²)</td>
<td>33.2 ± 8.1</td>
<td>32.1 ± 9.3</td>
<td>33.9 ± 9.4</td>
<td>0.335</td>
</tr>
<tr>
<td>LAV max/ht²/³ (ml/ht²/³)</td>
<td>15.4 ± 4.2</td>
<td>15.0 ± 4.4</td>
<td>16.1 ± 4.5</td>
<td>0.076</td>
</tr>
<tr>
<td>LAV min/BSA (ml/m2)</td>
<td>15.2 ± 5.3</td>
<td>14.2 ± 5.6</td>
<td>15.9 ± 5.7</td>
<td>0.135</td>
</tr>
<tr>
<td>LAV min/ht²/³ (ml/ht²/³)</td>
<td>7.0 ± 2.5</td>
<td>6.6 ± 2.6</td>
<td>7.5 ± 2.6</td>
<td>0.024</td>
</tr>
<tr>
<td>LA GLS (%)</td>
<td>-20.1 ± 6.4</td>
<td>-20.6 ± 6.5</td>
<td>-19.1 ± 6.0</td>
<td>0.068</td>
</tr>
<tr>
<td>LAEF (%)</td>
<td>54.3 ± 11.4</td>
<td>55.8 ± 11.2</td>
<td>52.7 ± 11.6</td>
<td>0.108</td>
</tr>
</tbody>
</table>

DD, Diastolic dysfunction; *P value for trend across diastolic function categories