Left atrial structure and function and clinical outcomes in the general population

Sachin Gupta1, Susan A. Matulevicius1, Colby R. Ayers2, Jarett D. Berry1, Parag C. Patel1, David W. Markham1, Benjamin D. Levine1, Kelly M. Chin3, James A. de Lemos1,2, Ronald M. Peshock1,2, and Mark H. Drazner1,2*

1Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, USA; 2Donald W. Reynolds Cardiovascular Clinical Research Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, USA; and 3Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, USA

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Aims
Left atrial (LA) structural and functional abnormalities may be subclinical phenotypes, which identify individuals at increased risk of adverse outcomes.

Methods and results
Maximum LA volume (LAmx) and LA emptying fraction (LAEF) were measured via cardiac magnetic resonance imaging in 1802 participants in the Dallas Heart Study. The associations of LAEF and LAmx indexed to body surface area (LAmx/BSA) with traditional risk factors, natriuretic peptide levels, and left ventricular (LV) structure [end-diastolic volume (EDV) and concentricity0.67 (mass/EDV0.67)] and function (ejection fraction) were assessed using linear regression analysis. The incremental prognostic value of LAmx/BSA and LAEF beyond traditional risk factors, LV ejection fraction, and LV mass was assessed using the Cox proportional-hazards model. Both increasing LAmx/BSA and decreasing LAEF were associated with hypertension and natriuretic peptide levels (P < 0.05 for all). In multivariable analysis, LAmx/BSA was most strongly associated with LV end-diastolic volume/BSA, while LAEF was strongly associated with LV ejection fraction and concentricity0.67. During a median follow-up period of 8.1 years, there were 81 total deaths. Decreasing LAEF [hazard ratio (HR) per 1 standard deviation (SD) (8.0%): 1.56 (1.32–1.87)] but not increasing LAmx/BSA [HR per 1 SD (8.6 mL/m²): 1.14 (0.97–1.34)] was independently associated with mortality. Furthermore, the addition of LAEF to a model adjusting Framingham risk score, diabetes, race, LV mass, and ejection fraction improved the c-statistic (c-statistics: 0.78 vs. 0.77; P < 0.05, respectively), whereas the addition of LAmx/BSA did not (c-statistics: 0.76, P = 0.20).

Conclusion
In the general population, both LAmx/BSA and LAEF are important subclinical phenotypes but LAEF is superior and incremental to LAmx/BSA.

Keywords
Left atrial volume index • Left atrial systolic function • Population

Introduction
Subclinical cardiac structural and functional abnormalities may identify asymptomatic individuals at increased risk of adverse cardiovascular outcomes including mortality.1–3 Although less well studied than left ventricular (LV) abnormalities, both an increased left atrial (LA) volume and reduced LA emptying fraction (LAEF) may be important subclinical phenotypes. The determinants and significance of increased maximum LA volume (LAmx) has received considerable attention,3–14 but less is known about the determinants and prognostic significance of a reduced LAEF in the general population.11,15–18 Further, the extent to which knowledge of LAEF provides clinically meaningful risk information beyond LV structure and function is unclear.

Previous studies addressing LA structure and function have had important limitations, including utilization of highly selected cohorts where imaging was performed for clinical reasons, potentially introducing selection bias.4,8,10,12 Additionally, most prior studies had a small sample size with poor representation of ethnic minorities and did not explicitly state their exclusion...
Therefore, we measured both LAmax and LAEF using cardiac magnetic resonance imaging (MRI) in the Dallas Heart Study (DHS), a population-based sample, and performed a systematic assessment of the determinants and the incremental prognostic value of LAmax and LAEF.

**Methods**

**Study population**

The DHS is a multiethnic population-based study of residents of Dallas County. Demographic information, anthropometric measurements, and other variable definitions have been described previously. B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), and highly sensitive cardiac troponins T (hs-cTnT) levels were measured from frozen venous blood samples.

**Imaging procedures**

Detailed methods for MRI in the DHS have been reported. Magnetic resonance imaging was performed using a 1.5 Tesla system (Intera; Philips Medical Systems, Best, the Netherlands) with prospective ECG gating. A turbo field-echo sequence (TFE) was used for LA measurements in 95% of the cohort and a steady-state free precession sequence (SSFP) was used in the remaining 5%. Left ventricular mass, LV end-diastolic volume (LVEDV), wall thickness, and ejection fraction were calculated from short-axis sequences. Left ventricular concentricity was defined as LV mass/LVEDV\(^0.67\). Maximum LA volume and minimum LA volume (LAmin) were measured using the biplane area-length method following the American Society of Echocardiography's guidelines (Figure 1). Left atrial emptying fraction was calculated from LAmax and LAmin and was defined as \([\text{LAmax} – \text{LAmin}]/\text{LAmax} \times 100\). Since LAEF captures the information provided by LAmin, analyses were restricted to LAmax indexed to body surface area (LAmax/BSA) and LAEF. All LA images were analysed by a single investigator (S.G.). To address quality control and to ensure the validity of LA measurements, we excluded the images of participants that were done using the SSFP sequence, had the presence of the LV outflow tract in the four-chamber image, unclear demarcation of the confluence of pulmonary veins, congenital heart disease, moderate or severe valve disease or atrial arrhythmias; 52% of these excluded participants were men, 49% were Blacks, median age was 47 years, systolic blood pressure was 130 mmHg, body mass index was 29 kg/m\(^2\), and there were 65 all-cause deaths during the follow-up. The final study cohort included 1802 participants. Further, all images with LAmax values above the 95th percentile and below the 5th percentile were reviewed and any inconsistencies corrected. Additionally, contours were redrawn for a random selection of 2.5% of the images by two investigators (S.G. and S.M.). Intra-observer differences for LAmax and LAEF were 1.9\(\pm\)4.7 mL and 2\(\pm\)1.3\% respectively, while inter-observer differences were 2.0\(\pm\)5.3 mL and 3.6\(\pm\)4.9\% respectively.

**Clinical outcomes**

Participants were followed up from the date of initial examination (July 2000 to January 2002) until death or end of the follow-up on 31 December 2009. Death of a participant was determined using the National Death Index and classified as cardiovascular if it included International Classification of Diseases 10 codes I00–I99. All-cause mortality was used as the primary outcome variable.

Figure 1 The biplane area-length method for left atrial volumes and emptying fraction. Four-chamber image showing minimum left atrial volume (A) and maximum left atrial volume (B), two-chamber image showing minimum left atrial volume (C), and maximum left atrial volume (D). Both the left atrial appendage and pulmonary veins were excluded.
Statistical analyses

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). All P-values are two-sided; P < 0.05 was considered statistically significant. Continuous data are presented as median (25th, 75th percentile) and categorical data are presented as percentages. Differences between the groups were tested by the Wilcoxon rank-sum test.

Univariable associations of gender-specific tertiles of LAmax/BSA and LAEF with baseline characteristics were assessed using the Jonckheere–Terpstra test. Univariable and multivariable linear regression analyses were used to assess the independent associations of baseline characteristics, LV parameters, BNP, NT-pro-BNP, and hs-cTnT with LAmax/BSA and LAEF. All models adjusted for the Framingham risk score (FRS) covariates (age, sex, systolic blood pressure, total cholesterol, HDL cholesterol, and smoking), race, diabetes, and LV ejection fraction. Model 1 included LV wall thickness and LVEDV/BSA. In Model 2, LV wall thickness and LVEDV/BSA were replaced with LV concentricity. Left ventricular mass/BSA replaced LV concentricity in Model 3. Although LAmax/BSA and LAEF were slightly non-normally distributed, findings using transformed LAmax/BSA and LAEF were similar to the untransformed measurements. For ease of understanding, findings observed with untransformed LAmax/BSA and LAEF are presented. The multivariable Cox-proportional hazards model was used to assess the associations of LAmax/BSA with mortality after serially adjusting for FRS, diabetes, and race (Model 1), LV ejection fraction (Model 2), and LV mass/BSA (Model 3). Similar analyses were performed with LAEF. The fully adjusted model included both LAmax/BSA and LAEF to assess their association with mortality independently of each other. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for 1 standard deviation (SD) change in LAmax/BSA (8.6 mL/m²) and LAEF (8.0%). In sensitivity analyses, LV mass/BSA was replaced with LV wall thickness (Model 4) and both LV wall thickness and LVEDV/BSA (Model 5).

To assess model discrimination, Harrell’s c-statistics were calculated for models with and without LA parameters and compared using bootstrap resampling.

Results

Men had larger LAmax than women (median: 74 vs. 68 mL, P = 0.001), but this difference was largely attenuated when indexed to the BSA (median: 37 vs. 36 mL/m², P = 0.11) (Figure 2). In contrast, women had higher LAEF than men (median: 52 vs. 54%, P < 0.001). Blacks had slightly larger LAmax/BSA than Whites (median: 36 vs. 35.5 mL/m², P = 0.02) and lower LAEF (median: 52 vs. 54%, P < 0.001) (Figure 2). Although the relationship between LAEF and LAmax/BSA was statistically significant, this relationship was weak and unlikely to be clinically meaningful (Figure 3). Baseline

Figure 2 Distribution of maximum left atrial volume/body surface area and left atrial emptying fraction stratified by sex and race. The median (25th, 75th percentile) values of maximum left atrial volume/body surface area (mL/m²) were men; 37 (31, 43), women; 36 (31, 41), Blacks; 36 (31, 42), and Whites; 35.5 (30, 41). The median (25th, 75th percentile) values of left atrial emptying fraction (%) were men; 52 (46, 56), women; 55 (50, 59), Blacks; 52 (46, 57), and Whites; 54 (49, 58).
characteristics of participants stratified by increasing tertile of LAmax/BSA and decreasing LAEF are shown (Table 1).

**Association with left ventricular structure and function**

In univariable analyses, larger LAmax/BSA was significantly associated with LVEDV/BSA (rho = 0.45 for men and 0.36 for women, \(P < 0.001\) for both). In addition, larger LAmax/BSA was associated with greater LV mass, LV wall thickness, and higher LV ejection fraction (\(P \leq 0.01\) for all) but not with concentric LV morphology (Table 1). In multivariable analysis (Table 2), LVEDV/BSA (Model 1) was the variable most strongly associated with LAmax/BSA. Left ventricular mass/BSA (Model 3) was also significantly associated with LAmax/BSA. In another model where LVEDV/BSA and LV wall thickness were replaced by LV concentricity\(^{0.67}\) (Table 2, Model 2), LAmax/BSA was not associated with LV concentricity\(^{0.67}\).

Lower LAEF was associated with greater LV mass, LV wall thickness, and lower LV ejection fraction (\(P < 0.001\) for all) (Table 1). Although LAEF had a weak inverse association with LVEDV/BSA both in univariable (Table 1) and in multivariable analyses (Table 2, Model 1), the association between LAEF and LVEDV/BSA was much weaker than the association between LAmax/BSA and LVEDV/BSA. Again in contrast with LAmax/BSA, a reduced LAEF was significantly associated with increased LV concentricity\(^{0.67}\) (Table 2, Model 2) in multivariable analysis.

**Association with biomarkers**

Both a higher LAmax/BSA and a lower LAEF were associated with higher natriuretic peptide levels (Table 1). In multivariable analysis, both larger LAmax/BSA (\(\beta = 0.26\) for 1 SD change in log NT-pro-BNP) and lower LAEF (\(\beta = -0.22\) for 1 SD change in log NT-pro-BNP) (\(P < 0.001\) for both) were independently associated with higher NT-pro-BNP levels. Similar associations were observed with BNP. These associations persisted when we added LV mass/BSA or LVEDV/BSA and wall thickness as covariates (data not shown). However, LAEF but not LAmax/BSA was associated with hs-cTnT both in univariable (Table 1) and in multivariable analyses [odds ratio per 1 SD (8.0%) decrease in LAEF: 1.25 (1.10–1.42); \(P = 0.008\)].

**Incremental prognostic value of maximum left atrial volume and left atrial emptying fraction**

Over a median follow-up period of 8.1 years, there were 81 total deaths (32 due to cardiovascular causes). Using the Hosmer–Lemeshow test, all models had a \(P\)-value of \(>0.05\), suggesting that the models with and without LA parameters were well calibrated.

In univariable analysis, both larger LAmax/BSA and lower LAEF were associated with mortality: HR for 1 SD (8.6 mL/m\(^2\)) increase in LAmax/BSA: 1.33 (1.09–1.62) and per 1 SD (8.0%) decrease in LAEF: 2.02 (1.74–2.35) (\(P < 0.001\) for both).

In multivariable-adjusted analysis (Table 3), LAmax/BSA was weakly but significantly associated with mortality after serially adjusting for FRS, diabetes, race, and LV ejection fraction (Models 1 and 2), but was not associated with mortality after adjustment for LV mass/BSA (Model 3). When LV mass/BSA was serially replaced with LV wall thickness and LVEDV/BSA, LAmax/BSA remained associated with mortality independently of LV wall thickness (Model 4) but not LVEDV/BSA (Model 5). The addition of LAmax/BSA to the baseline models did not improve the c-statistic.

In contrast to LAmax/BSA, LAEF was not only more strongly associated with mortality, but the addition of LAEF significantly improved the c-statistic in all the models except when adjusted for LVEDV/BSA (Model 5) where we observed a trend but did...
not reach statistical significance \((P = 0.15)\) (Table 3). LAEF remained associated with mortality in a model that adjusted for LAmax/BSA in addition to traditional risk factors and LV parameters (Figure 4). Consistent findings were observed when cardiovascular death was used as the outcome variable (data not shown).

### Discussion
An increased LA volume and reduced LAEF were associated with well-established risk factors for mortality including hypertension, natriuretic peptides, and LV structural and functional abnormalities. Both increasing LA volume and decreasing LAEF were associated with mortality independent of traditional risk factors and LV parameters, with stronger associations observed for LAEF. Additionally, LAEF was associated with hs-cTnT, an established risk marker for mortality, and provided modest improvement in the discrimination of total mortality. These data suggest that in the general population, both LA volume and LAEF are important subclinical phenotypes but LAEF is superior and incremental to LA volume with regard to the assessment of mortality risk.

Our study that has a large proportion of women and ethnic minorities is the largest to assess inter-individual variability in LA structure and function in the general population using cardiac MRI. We observed a considerable variability in both LA volume and LAEF. Although both men and women had similar LA volume after indexing for the BSA,28 women had slightly higher LAEF than men. These findings are consistent with our prior observation that LV ejection fraction was higher in women than in men.32 Further, we demonstrated that LA volume and LAEF were only weakly associated with one another and also differ in their relationship to LV structure and function. Specifically, LA volumes have been observed to be associated with LV concentric remodelling,4 whereas LAEF was only weakly associated with LV concentric remodelling and was more strongly associated with LV concentric remodelling. It is possible that increased LAmax and reduced LAEF have an interaction and represent different pathophysiological pathways thus providing complementary prognostic information.

Although an enlarged left atrium is an established marker for adverse outcomes in the general population,3,5,7,33 there are scant data systematically assessing the determinants and prognostic

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### Table 1  Baseline characteristics stratified by gender-specific tertiles of maximum left atrial volume/body surface area and left atrial emptying fraction \((n = 1802)\)

<table>
<thead>
<tr>
<th></th>
<th>Increasing LAmax/BSA (mL/m²)</th>
<th>Decreasing LAEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1 ((n = 628))</td>
<td>Tertile 2 ((n = 629))</td>
</tr>
<tr>
<td>Age, years</td>
<td>43 (36–52)</td>
<td>41 (35–49)</td>
</tr>
<tr>
<td>Men, %</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>White</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125 (116–137)</td>
<td>124 (114–136)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>1.6 (0–9)</td>
<td>3 (0–12)</td>
</tr>
<tr>
<td>NT-pro-BNP, pg/mL</td>
<td>23 (10–47)</td>
<td>28 (14–55)</td>
</tr>
<tr>
<td>Detectable hs-cTnT, %</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>LV mass/BSA, g/m²</td>
<td>78 (68–89)</td>
<td>79 (70–90)</td>
</tr>
<tr>
<td>LVH, (BSA), %</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>LVEDV/BSA, mL/m²</td>
<td>48 (42–54)</td>
<td>51 (46–57)</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>73 (68–77)</td>
<td>74 (69–78)</td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>11.3 (10.1–12.5)</td>
<td>11.0 (10.1–12.3)</td>
</tr>
<tr>
<td>LV concentricity, g/mL0.67</td>
<td>7.3 (6.3–8.4)</td>
<td>7.0 (6.2–8.0)</td>
</tr>
<tr>
<td>LAmax, mL/m²</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LAEF, %</td>
<td>53 (48–58)</td>
<td>54 (50–59)</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; LVH, left ventricular hypertrophy.
The thresholds of LVEDV/BSA were: <32.9 mL/m² (Tertile 1), 33.0–39.7 mL/m² (Tertile 2), and ≥39.8 mL/m² (Tertile 3). The thresholds for LAEF for men were: ≥54.2% (Tertile 1), 48.1–54.1% (Tertile 2), and <48% (Tertile 3). The thresholds for LAEF for women were: ≥57.5% (Tertile 1), 51.6–57.4% (Tertile 2), and ≥51.5% (Tertile 3).

*\(P < 0.01\).

**\(P < 0.05\).

***\(P < 0.001\).

\*\(P < 0.01\) for comparison across the three groups.
utility of LAEF. To our knowledge, the prior studies addressing this question demonstrated that reduced LA passive emptying during dobutamine stress was associated with adverse cardiac events and that reduced LAEF when compared with increased LAmax had a more robust association with the risk of atrial fibrillation or atrial flutter. A recent study demonstrated that in patients with established coronary artery disease and an LVEF \( \geq 50\% \), a measure of LA function (based on LA emptying fraction and LV outflow tract time velocity integral) assessed by echocardiography was associated with subsequent heart failure hospitalization. Our study is consistent with and substantially extends these data. We find that both increased LAmax and reduced LAEF were associated with mortality in the general population independently of traditional risk factors. Associations of LAmax with mortality were significantly attenuated after further adjustment for LV ejection fraction, and LAmax was no longer associated with mortality after adjusting for LV mass or LVEDV. In contrast, associations of LAEF with mortality were only modestly attenuated after adjustment for LV structure and function. Although our study does not address why LAEF has more prognostic utility than LAmax,
it does call attention to the need for further study of LAEF, a parameter which heretofore has been relatively underappreciated.

The mechanisms linking LA structural and functional abnormalities with adverse clinical outcomes are uncertain. Since the associations of LA abnormalities with mortality persisted in multivariable models which adjusted for traditional risk factors, LV structure, and function, it appears that LAmax and LAEF either capture additional information from other unmeasured factors or contribute directly or indirectly to risk. Although LA structural and functional abnormalities increase risk for atrial arrhythmias,16 we believe it is unlikely that atrial fibrillation is the sole mediator of the increased mortality. There is increasing evidence that LA structural and functional abnormalities result from alterations in extracellular matrix and ion channels and reflect pathophysiological changes in renin secretion, levels of angiotensin II, aldosterone, transforming growth factor-beta1, sympathetic stimulation, and markers of systemic inflammation such as C-reactive protein.34

Limitations

Our study has several limitations. We measured total LAEF and were unable to assess phasic atrial function. Further studies using time-volume curves obtained by tracing the LA in short-axis views would be able to better assess the prognostic value of LAEF as a novel predictor. Although the TFE sequence and biplane area-length methods are associated with greater variability in LA measurements when compared with the SSFP sequence and short-axis method,20 biplane area-length-based assessment of LA volume is a well-studied and valid measure of LA volume.28 The use of prospective ECG gating may result in slight underestimation of LAEF since with prospective gating, the smallest LA volumes following complete atrial contraction may not be captured. Since direct measurements of parameters of diastolic dysfunction such as the peak flow rate were not available, we were unable to determine the association of LA parameters with diastolic dysfunction. Approximately one-third of the overall DHS population did not have suitable LA images and could not be included in this study. Excluded subjects had different characteristics than those included in the study, and the associations of LA structure and function with the outcome may be different in such subjects. Despite the large size of the cohort, there were few cardiovascular deaths during the follow-up period.

Conclusions

There is considerable variability in both LAmax and LAEF in the general population. Although these two traits were only weakly associated with each other, both appear to be important phenotypes as they were associated with traditional risk factors, natriuretic peptide levels, and LV structural and functional abnormalities. In particular, reduced LAEF appears to be a novel, important subclinical phenotype for it has a strong and independent association with subsequent mortality in the general population.

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