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ORIGINAL ARTICLE

Prediction of All-Cause Mortality by the Left Atrial Volume Index in Patients With Normal Left Ventricular Filling Pressure and Preserved Ejection Fraction

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Abstract

Objective: To describe the prevalence of left atrial (LA) enlargement (LAE) and its association with all-cause mortality in 10,719 patients with an early diastolic transmitral flow velocity (E) to early diastolic mitral annular velocity (e′) ratio–determined normal left ventricular (LV) filling pressure and preserved LV ejection fraction (LVEF).

Methods: We evaluated 10,719 patients (deceased patients: n=479; mean [SD] age, 65 [14] years; 60% male; surviving patients: n=10,240; mean (SD) age, 54 (16) years; 48% male) with estimated normal LV filling pressure (E/e′ ratio ≤8) and preserved LVEF (≥50%) to determine the impact of LA volume index (LAVi) on all-cause mortality during a mean (SD) follow-up of 2.2 (1.0) years.

Results: In the univariate analysis, with every milliliter per square meter increase in LAVi, all-cause mortality risk increased by 3% (hazard ratio [HR], 1.03; 95% CI, 1.02-1.04; $P<.001$). After adjusting for covariates, LAVi (as a continuous variable) was an independent predictor of all-cause mortality (HR, 1.015; 95% CI, 1.005-1.026; $P=.01$). When LAVi was assessed as a categorical variable with normal LAVi (≤28 mL/m^2) as the reference group, moderate LAVi (34-39 mL/m^2) and severe LAVi (≥40 mL/m^2) were independent predictors of all-cause mortality (HR, 1.34; 95% CI, 1.01-1.79; $P=.04$; and HR, 1.65; 95% CI, 1.18-2.29; $P=.003$, respectively).

Conclusion: LAE was independently associated with an increased risk of all-cause mortality in our large cohort of 10,719 patients with normal LV filling pressure and preserved LVEF.

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Doppler echocardiography is widely used for the hemodynamic evaluation of the left ventricle (LV). For noninvasive assessment of LV filling pressure in patients with preserved ejection fraction, current recommendations suggest evaluation of the early transmitral flow velocity (E) to early diastolic mitral annular velocity (e′) ratio, which is an accurate predictor of LV filling pressure.[1] However, the E/e′ ratio reflects short-term changes in LV filling pressure, which can change moment to moment. In contrast, left atrial (LA) enlargement (LAE) represents a more stable morphologic marker of elevated LV filling pressure.[2-4] The LA is directly exposed to LV pressure during diastole through the open mitral valve and therefore with worsening LV adherence; LA pressure increases to maintain adequate LV filling, which results in LA remodeling, reflected by LA volume (LAV). Therefore, in patients without primary atrial disease or congenital heart or mitral valve disease, changes in LAV usually reflect long-term exposure to abnormal LV filling pressure.

In terms of clinical significance, LAE is a significant predictor of cardiovascular (CV) outcomes and all-cause mortality.[2,3,5-9] However, it is not known whether LAE predicts all-cause mortality in patients with estimated normal LV filling pressure, as determined by the E/e′ ratio. In the present study, we aim to describe the prevalence of LAE and its association with all-cause mortality in 10,719 patients with E/e′ ratio–determined normal LV filling pressure and preserved LVEF.

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METHODS

Patient Selection

We obtained clinical and echocardiographic data from a clinical echocardiographic report database (Cardiovascular Information System) of 10,719 studies that were recorded at the Ochsner Clinic Foundation from January 1, 2006, through December 31, 2010. One echocardiographic study per patient in the database was selected for the analyses. For patients with more than one echocardiographic study, only the first or earliest study in the database was included, and subsequent studies (repeat observations) were excluded. The patients who were selected for the study had an E/e′ ratio of 8 or less, preserved LV systolic function (defined as LVEF ≥50%), and absence of moderate or severe valvular heart disease and irregularly irregular heart rhythm. Patients with missing clinical or echocardiographic information were also excluded from the study. Survival status was obtained from National Death Index for the entire cohort during a mean (SD) follow-up of 2.2 (1.0) years. The end point was death due to all causes. This study was approved by the institutional review board of the Ochsner Clinic Foundation.

General Examination

Height and weight were measured to calculate body mass index BMI (calculated as weight in kilograms divided by the square of the height in meters). Age, sex, single systolic and diastolic blood pressure measurements, and heart rate were obtained before echocardiographic examination. No other clinical information was available for the study.

Echocardiographic Methods

M-mode and 2-dimensional images were obtained with commercially available instruments that operated at 2.0 to 3.5 MHz. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical 4- and 2-chamber views. The LV dimensions and wall thickness were measured according to guidelines of the American Society of Echocardiography.[10] Intraobserver variability in our laboratory for quantitation of LV dimensions was less than 10%. End-diastolic LV dimensions (ie, interventricular septal dimension, LV internal dimension, and posterior wall thickness) were used to calculate LV mass by an anatomically validated formula, with good reproducibility.[11] Relative wall thickness (RWT) was calculated as 2 × (posterior wall thickness in diastole)/(LV internal diameter).

TABLE 1. Characteristics of Patients With E/e Ratios of 8 or Less and Preserved Ejection Fraction[a,b]

Characteristic	Finding
Age (y)	54.8 (16.2)
Female (%)	48.4
Body mass index	29.7 (7.5)
Systolic blood pressure (mm Hg)	127.9 (18.0)
Diastolic blood pressure (mm Hg)	74.5 (11.3)
Heart rate (/min)	71.6 (13.3)
Ejection fraction (%)	60.2 (4.5)
LV end diastolic diameter (cm)	4.6 (0.5)
Relative wall thickness (cm)	0.37 (0.07)
LV mass index (g/m^2)	77.8 (22.2)
Peak E (m/s)	0.76 (0.17)
Peak A (m/s)	0.70 (0.20)
E/A ratio	1.17 (0.48)
Deceleration time (ms)	218.6 (56.6)
e′ (m/s)	0.12 (0.04)
E/e′ ratio	6.7 (1.5)
Left atrial volume index (mL/m^2)	25.2 (8.2)

[a]E = early transmitral flow velocity; e′ = early diastolic mitral annular velocity; E/A = peak E/peak A; LV = left ventricular.
[b]Data are presented as mean (SD) unless otherwise indicated.

LAV Assessment

LAV was measured using the modified biplane area-length method and was corrected for body surface area or LAV index (LAVi),[12,13] which was categorized as normal (≤28 mL/m^2) or increased (mild: 29-33 mL/m^2; moderate: 34-39 mL/m^2; severe: ≥40 mL/m^2).[10]

Doppler Flow and Tissue Doppler Imaging Measurements

All Doppler measurements were performed according to the guidelines of the American Society of Echocardiography.[1] Early (peak E) and late (peak A) diastolic transmitral flow was measured in the apical 4-chamber view using the pulsed-wave Doppler method by placing the sample volume at the level of the mitral valve leaflet tips. Deceleration time (DT) of early transmitral flow velocity was also measured. The tissue Doppler-derived early diastolic mitral annular velocity (e′) was measured from septal and lateral mitral

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TABLE 2. Clinical and Echocardiographic Characteristics of the Patients by LAVi[a,b]

Characteristic	LAVi			
	Normal (≤28 mL/m^2) (n=7424)	Mild (29-33 mL/m^2) (n=1954)	Moderate (34-39 mL/m^2) (n=849)	Severe (≥40 mL/m^2) (n=492)
Age (y)	52.1 (15.9)	58.4 (15.2)[c]	63.0 (14.5) [c,d]	66.8 (14.9)[c,d,e]
Female (%)	56.9	41.4[c]	38.5[c,d]	34.6[c,d,e]
Body mass index	29.3 (7.4)	30.9 (7.5)[c]	30.5 (7.5)[c]	29.6 (7.0)[d,e]
Ejection fraction (%)	60.5 (4.3)	59.8 (5.6)[c]	59.7 (4.9)[c]	58.6 (5.2)[c,e]
Relative wall thickness (mm)	0.37 (0.07)	0.38 (0.07)[c]	0.38 (0.07)[c]	0.39 (0.07)[c,d,e]
LV mass index (g/m^2)	72.6 (19.3)	85.7 (21.4)[c]	91.1 (24.2)[c,d]	101.7 (26.9)[c,d,e]
Mitral peak E (m/s)	0.75 (0.17)	0.76 (0.18)	0.77 (0.18)[c]	0.79 (0.20)[c,d]
Mitral peak A (m/s)	0.70 (0.19)	0.71 (0.20)[c]	0.73 (0.21)[c,d]	0.67 (0.25)[c,d,e]
E/A ratio	1.17 (0.44)	1.15 (0.44)	1.15 (0.49)	1.39 (0.86)[c,d,e]
Mitral deceleration time (ms)	215 (55)	225 (58)[c]	228 (62)[c]	232 (66)[c,d]
e′ (m/s)	0.12 (0.04)	0.11 (0.04)[c]	0.11 (0.04)[c]	0.11 (0.03)[c]
E/e′ ratio	6.6 (1.5)	6.9 (1.4)[c]	7.0 (1.4)[c]	7.2 (1.4)[c,d,e]
LAVi (mL/m^2)	21.0 (4.4)	30.6 (1.7)[c]	36.5 (1.7)[c,d]	47.6 (8.0)[c,d,e]

[a]E = early transmitral flow velocity; e′ = early diastolic mitral annular velocity; E/A = peak E/peak A; LAVi = left atrial volume index; LV = left ventricular.
[b]Data are presented as mean (SD) unless otherwise indicated.
[c]*P*=.01 to less than .001 compared with normal.
[d]*P*=.001 to less than .001 compared with mild.
[e]*P*=.03 to less than .001 compared with moderate.

annulus in apical 4-chamber view. The mean e′ was calculated for analysis. E/A and E/e′ ratios were calculated using the peak E, peak A, and e′ values.

Statistical Analyses

Continuous variables were summarized as mean (SD), and categorical variables were summarized as frequency. Clinical, echocardiographic, and all-cause mortality data were compared among patients divided into normal (≤28 mL/m^2), mild (29-33 mL/m^2), moderate (34-39 mL/m^2), and severe (≥40 mL/m^2) categories of LAVi. Comparison among LAVi groups and trend assessment was assessed using an analysis of variance model and Mantel-Haenszel statistics.

Univariate association of clinical variables (age, sex, BMI, systolic and diastolic blood pressure, heart rate) and echocardiographic variables (LVEF, RWT, LV mass index, peak E, peak A, E/A, DT, e′, E/e′, LAVi) with the all-cause mortality were assessed using Cox proportional hazards regression models. A multivariable Cox proportional hazards regression model was constructed that included age, sex, BMI, RWT, peak E, peak A, E/A, DT, and e′ as covariates on the basis of their statistically significant univariate association with all-cause mortality. Hazard ratios (HRs), 95% CIs, and corresponding *P* values were reported. The Kaplan-Meier survival analysis was used to compute survival curves by different LAVi categories. A log-rank test was used to assess the difference in survival among the LAVi categories. All statistical analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc). Two tailed $P<.05$ was considered statistically significant.

RESULTS

Clinical and echocardiographic characteristics of the patients are given in Table 1. In this study population (mean [SD] age, 54.8 [16.2] years; 48.4% female), the mean (SD) LAVi was 25.2 (8.2) mL/m^2. Patients were divided into normal, mild, moderate, and severe LAVi groups, and their clinical and echocardiographic characteristics were compared (Table 2). Increased LAVi was identified in 3295 patients (30.7%), and 492 (4.6%) had severe LA enlargement. Compared with patients with normal LAVi, patients with abnormal LAVi had higher age, RWT, LV mass index, mitral peak A, DT, E/e′ ratio, and LAVi (by design) and lower LVEF and e′. BMI was higher in mild and moderate LAVi categories compared with normal LAVi. Patients in the moderate and severe LAVi categories had

TABLE 3. Clinical and Echocardiographic Univariate Predictors of All-Cause Mortality[a]

Predictor	Hazard ratio (95% CI)	*P* value
Age (y)	1.05 (1.04-1.05)	<.001
Female (%)	0.62 (0.51-0.74)	<.001
Body mass index (Kg/m^2)	0.96 (0.94-0.97)	<.001
Ejection fraction (%)	1.01 (0.99-1.03)	.55
Relative wall thickness (mm)	59.1 (18.8-185.5)	<.001
LV mass index (g/m^2)	1.01 (0.99-1.01)	.08
Mitral peak E (m/s)	0.33 (0.19-0.56)	<.001
Mitral peak A (m/s)	7.21 (4.85-10.72)	<.001
E/A ratio	0.29 (0.22-0.39)	<.001
Mitral deceleration time (ms)	1.002 (1.001-1.004)	.004
e′ (m/s)	0.002 (0.001-0.04)	<.001
E/e′ ratio	1.03 (0.97-1.10)	.33
LAVi (mL/m^2)	1.03 (1.02-1.04)	<.001
LAVi as a categorical variable (mL/m^2)		
≤28[b]	…	…
29-33	1.24 (0.98-1.57)	.07
34-39	1.98 (1.50-2.61)	<.001
≥40	2.52 (1.85-3.44)	<.001

[a]E = early transmitral flow velocity; e′ = early diastolic mitral annular velocity; E/A = peak E/peak A; LAVi = left atrial volume index; LV = left ventricular.
[b]Reference category for comparison with abnormal LAVi.

higher mitral peak E, and patients in the severe LAVi category had higher E/A ratio than those in the normal LAVi category.

During the mean (SD) follow-up period of 2.2 (1.0) years, 479 patients (4.5%) died. Univariate predictors of all-cause mortality were identified (Table 3). LAVi was treated as both a continuous variable and categorical variable with 4 levels. As a continuous variable, with every milliliter per square meter increase in LAVi, all-cause mortality risk increased by 3% (HR, 1.03; 95% CI, 1.02-1.04; *P*<.001). As a categorical variable and compared with the normal LAVi (≤28 mL/m^2) category, patients with moderate and severe LAVi had a significantly higher risk of all-cause mortality (for moderate LAVi: HR, 1.98; 95% CI, 1.50-2.61; for severe LAVi: HR, 2.52; 95% CI, 1.85-3.44; *P*<.001). No significant difference was noted between normal and mild LAVi categories in terms of univariate all-cause mortality prediction. Other parameters univariately associated with all-cause mortality were age, sex, BMI, RWT, mitral peak E, mitral peak A, E/A ratio, DT, and e′. Because the present study lacks information regarding antihypertensive medication use, the results of association between blood pressure and all-cause mortality are essentially uninterpretable. In multivariate analysis, independent association of LAVi, both as a continuous and categorical variable, was assessed. As indicated in Table 4, with every milliliter per square meter increase in LAVi, all-cause mortality risk independently increased by 1.5% (*P*<.001). Furthermore, compared with patients with normal LAVi, patients with moderately and severely increased LAVi had 34% and 65% increased risk of all-cause mortality, respectively; no such difference was observed between normal vs mild LAVi categories. Among other variables included in the multivariate analysis, age (HR, 1.03; 95% CI, 1.02-1.04; *P*<.001), RWT (HR, 9.36; 95% CI, 2.80-31.25; *P*<.001), BMI (HR, 0.95; 95% CI, 0.93-0.97; *P*<.001), and female sex (HR, 0.68; 95% CI, 0.56-0.82; *P*<.001) were significant predictors of all-cause mortality. Similar to the multivariate analysis, Kaplan-Meier survival analysis by LAVi categories revealed statistically significant worse survival in patients with moderately and severely increased LAVi categories compared with those with normal LAVi (Figure).

TABLE 4. Multivariable Predictors of All-Cause Mortality[a,b]

LAVi	Hazard ratio (95% CI)	*P* value
As a continuous variable		
LAVi	1.015 (1.005-1.026)	.01
As a categorical variable (reference group: normal [≤28 mL/m^2])		
Mild (29-33 mL/m^2)	0.99 (0.78-1.27)	.96
Moderate (34-39 mL/m^2)	1.34 (1.01-1.79)	.04
Severe (≥ 40 mL/m^2)	1.65 (1.18-2.29)	.003

[a]E = early transmitral flow velocity; e′ = early diastolic mitral annular velocity; E/A = peak E/peak A; LAVi = left atrial volume index; LV = left ventricular.
[b]Variables included age, sex, body mass index, relative wall thickness, peak E, peak A, peak E to peak A ratio, deceleration time, e′, and LAVi.

DISCUSSION

In the present retrospective study of a large clinical cohort of patients with Doppler-derived estimated normal LV filling pressure (E/e′ ≤8) and preserved LVEF, we found that LAE was independently associated with an increased risk of all-cause mortality. According to the current recommendations, E/e′ should be assessed for noninvasive estimation of LV filling pressures in patients with normal LVEF.[1] A mean E/e′ ratio of 8 or less identifies patients with normal LV filling pressure.[14] The E/e′ ratio accurately reflects the filling pressures at the time of the examination. In contrast, the LAV is a reflection of the

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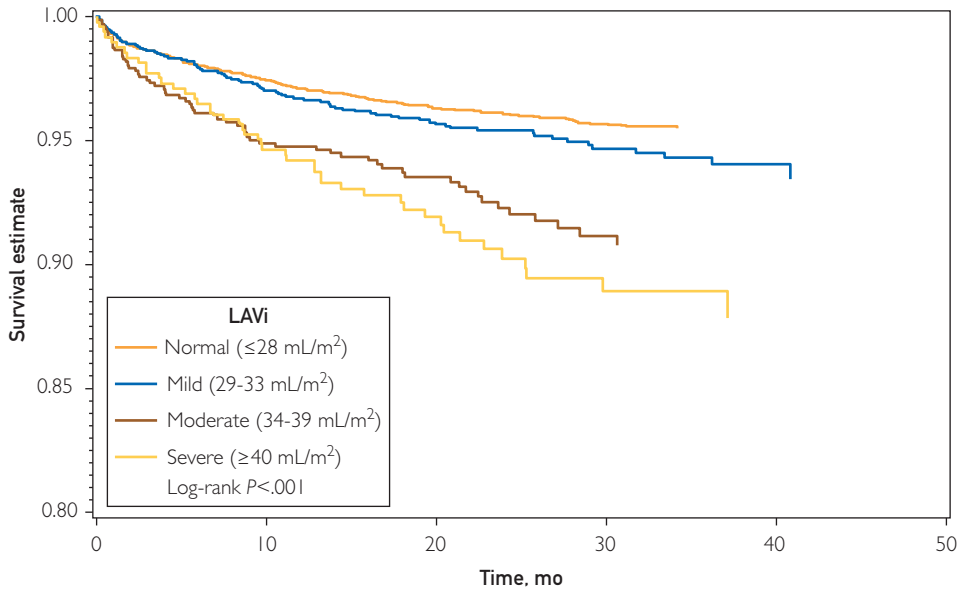

FIGURE. Survival estimate (Kaplan-Meier) by left ventricular volume index (LAVi) in patients with normal left ventricular filling pressure and preserved ejection fraction.

long-term exposure to LV filling pressures.[2-4] A significant association exists between LAV and echocardiographic indexes of diastolic dysfunction.[2,3] Similarly, the association between increased LA size and increased LV filling pressures has been validated against invasive measures.[4,15-17] However, it is important to note that other than abnormal LV filling pressures, several other conditions are associated with LA remodeling and dilatation. In this study, we have excluded patients with LVEFs less than 50% and E/e′ ratios greater than 8. Coincidently, for the selected cohort of patients, other Doppler parameters of diastolic dysfunction were noted to be within their respective normal range. Furthermore, significant mitral valve disease and atrial arrhythmias that can influence LA size were excluded from the study. The LAE noted in our patients was less likely related to 4-chamber enlargement or as seen in athletes because of the clinical nature of this cohort of patients in whom the mean LV end diastolic diameter was within the normal range for both male (4.82 [0.53] cm) and female (4.45 [0.49] cm) patients. On the basis of these patient characteristics, we believe that the increased LA size, noted in 31% of patients in this study, is mainly as result of cumulative LV filling pressure over time.

The association of LAE and mortality, CV as well as all-cause, has been reported in a few population-based studies[2,5-8] and in several high-risk populations, such as patients with dilated cardiomyopathy,[18] LV dysfunction,[19] atrial arrhythmias,[20] and acute myocardial infarction.[21] In addition, LAE appears to be an independent predictor of CV disease and all-cause mortality independent of abnormal LV geometry, including concentric remodeling and LV hypertrophy,[8,22] which is itself a powerful predictor of prognosis.[8,22-27] Only a few of these studies used LAVi, which is more accurate and reproducible, as a measure of LA size and were performed in a population with preserved LV systolic function as determined by LVEF. However, the association between LAE by LAVi and all-cause mortality has not been evaluated in patients with Doppler-derived normal LV filling pressure and preserved LVEF. In the present study, LAVi independently predicted an increased risk of all-cause mortality. The higher risk of all-cause mortality with increasing LA size was in line with other studies that used different classification criteria and population samples.[3,6-8]

Prior observational studies, including 6657 patients without baseline histories of atrial fibrillation or significant valvular heart disease, have

found that an LAVi of 34 mL/m^2 or greater is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke.[9] For comparison, the association with all-cause mortality was further evaluated by stratifying LAVi into normal, mild, moderate, and severely dilated LAVi categories, as recommended by the American Society of Echocardiography.[10] As shown, compared with normal LAVi, both moderately and severely increased LAVis were independent predictors of all-cause mortality. On the other hand, our data did not reveal any increase in all-cause mortality associated with mildly increased LAVi. These findings identify a LAVi of 34 mL/m^2 or higher as a cutoff value for increased all-cause mortality risk and are consistent with prior observations.[8,9] Our findings are also in agreement with the revised American Society of Echocardiography recommended upper normal indexed LAV of 34 mL/m^2.[28]

Older age, male sex, lower BMI, and higher RWT were other significant predictors of all-cause mortality. Furthermore, none of the Doppler-derived parameters of diastolic function, including peak A, peak E, E/A ratio, e′, or DT, were significant independent predictors of all-cause mortality. These results might be explained by the fact that, in contrast to LA size, these parameters, to various degrees, are preload sensitive and change instantaneously.[1] Another explanatory argument could also be made that the values of these parameters were within their respective normal range and so were not predictive of all-cause mortality in this selected patient population. Regardless, these findings highlight the importance of assessing cumulative burden of abnormal LV filling pressure as it relates to all-cause mortality outcome.

Several study limitations are worth emphasizing. First, this was a retrospective analysis of an echocardiographic report database, and we do not have access to considerable potentially important clinical data, including reason for referral, history of hypertension, diabetes mellitus, coronary artery disease, heart failure, atrial fibrillation, stroke, renal failure, and use of medications. Second, data were not available on cause of death or CV events, although all-cause mortality is certainly an important end point. Third, the current retrospective study cannot address the issue of causality and underlying mechanisms governing the observed associations. Fourth, there may be selection bias, considering that our cohort was not population based but rather consisted of patients referred for echocardiography for routine clinical indications. We strongly believe, however, that the findings from the present study have significant clinical importance because of the very large sample of patients who are likely reflective of what is commonly encountered by large, busy clinical CV practices.

CONCLUSION

Our data, which were collected on the basis of retrospective analysis of a large clinical echocardiographic cohort, indicates that LAE has important prognostic implications in terms of all-cause mortality prediction in patients with estimated normal LV filling pressure determined as an E/e′ ratio of 8 or less and preserved LVEF. The measurement of LAV by LAVi is highly feasible and reliable in most echocardiograms, enhancing its utility in comprehensive LV hemodynamic assessment. These data have potentially important clinical applications for the large number of general physicians and medical specialists, including experts in CV diseases, who frequently order echocardiographic studies, as well as the large number of clinicians who perform and/or report these studies throughout the world. Additional studies are needed to expand the understanding of the natural history of LA remodeling and the effect of such changes on clinical outcomes, as well as potential therapies to prevent LAE and potentially improve CV and all-cause mortality.

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