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