Clinical Investigation

Prognostic Value of Left Atrial Functional Measures in Heart Failure With Reduced Ejection Fraction

DANIEL MODIN, MB,[1] MORTEN SENGELØV, MB,[1] PETER GODSK JØRGENSEN, MD, PhD,[1] FLEMMING JAVIER OLSEN, MD,[1] NIELS ESKE BRUUN, MD, DMSC,[1,3] THOMAS FRITZ-HANSEN, MD,[1] DITTE MADSEN ANDERSEN, MD,[1] JAN SKOV JENSEN, MD, PhD, DMSC,[1,2] AND TOR BIERING-SØRENSEN, MD, PhD, MPH[1]

Denmark; and Aalborg

ABSTRACT

Background: The prognostic value of LA functional measures in heart failure patients with reduced ejection fraction (HFrEF) is unclear. Therefore, this study investigated the prognostic value of left atrial (LA) functional measures such as the left atrial emptying fraction (LAEF) and the minimal LA volume compared with left atrial volume index (LAVI) in HFrEF patients.

Methods and Results: A total of 818 HFrEF patients with left ventricular ejection fractions <45% underwent echocardiography. LA volumes were determined by the area-length method from the apical 2-chamber and apical 4-chamber views. LAEF, minimal LA volume indexed to body surface area (MinLAVI), and LAVI were calculated. The end point was all-cause mortality. During a median follow-up of 3.3 years (interquartile range 1.8−4.6 years), 121 patients died (14.8%). Follow-up was 100%. In a final multivariable model adjusting for clinical and echocardiographic parameters, LAEF, but not MinLAVI or LAVI, was an independent predictor of all-cause mortality in HFrEF patients: LAEF: hazard ratio (HR) 1.11 ($P = .033$) per 5% decrease; MinLAVI: HR 1.03 ($P = .57$) per 5 mL/m^2 increase; LAVI: HR 1.06 ($P = .16$) per 5 mL/m^2 increase.

Conclusions: LAEF is an independent predictor of all-cause mortality in HFrEF patients after multivariable adjustment. LAEF provides incremental prognostic value over LAVI in risk stratification of HFrEF patients. (*J Cardiac Fail 2019;25:87−96*)

Key Words: Heart failure with reduced ejection fraction, left atrial function, prognosis, risk stratification, mortality, echocardiography.

Heart failure (HF) represents a large societal burden of disease and has recently been characterized as an emerging epidemic.[1] HF is associated with significant mortality, morbidity, and health care expenditures.[1] Echocardiography is an essential tool in the diagnosis, management, and risk stratification of HF patients.[2] Echocardiographic assessment of HFrEF patients may improve survival and overall prognosis with the use of better and more intensified medical treatment.[3]

Left atrial (LA) size and the LA volume index (LAVI) measured by means of echocardiography are established predictors of mortality in HF.[4,5] Accordingly, measurement of LAVI is included in contemporary echocardiographic guidelines.[6] However, the prognostic value of left atrial (LA) functional parameters in HFrEF patients has not been a major area of interest thus far.[7] In a study of 982 patients admitted with suspicion of HF, LA emptying fraction (LAEF) measured with the use of cardiac magnetic resonance imaging (CMRI), but not left ventricular ejection fraction (LVEF), was an independent predictor of death, and the prognostic value of LAEF in this population was superior to maximal LA volume.[8] These findings suggest that atrial functional measures, such as LAEF and the

From the [1]Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; [2]Institute of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Denmark and [3]Clinical Institute, Aalborg University, Aalborg, Denmark.

Reprint requests: Daniel Modin, MB Department of Cardiology, Herlev & Gentofte Hospital, University of Copenhagen, Niels Andersensvej 65, post 835, DK-2900, Copenhagen, Denmark, Tel: +45 4182 8993, Fax: +45 3977 7381. E-mail: danielmodin@live.dk

Funding: Daniel Modin was supported by a scholarship from the Medical Society in Copenhagen while preparing this paper. The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

See page 95 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2018.11.016

minimal LA volume calculated from the measurements of both maximal and minimal LA volume, may contribute incremental prognostic value in HFrEF. However, little is known about the prognostic value of LA functional parameters measured by means of 2-dimensional echocardiography in HFrEF.

The present study therefore aimed to investigate whether LA functional measures, such as LAEF and the minimal LA volume (indexed to body surface area [MinLAVI]), hold incremental prognostic value over LAVI and other established prognosticators in predicting all-cause mortality in HFrEF patients.

Methods

Data

Routine echocardiographic examinations are conducted at the Department of Cardiology, Herlev-Gentofte University Hospital, according to a standardized protocol.[9] Results have been stored on a local hard drive since 2005.

Study Sample

For this retrospective study, we identified 1102 nonacute consecutive HFrEF patients with LVEF <45% who were referred to the HF clinic of a large University Hospital in Copenhagen in the period of 2005−2013. The HFrEF population in the present study has previously been described in detail.[9] All patients had been diagnosed with HFrEF by a senior clinician according to contemporary guidelines,[10] and all patients had a history of angiography to determine coronary artery status. We searched the hospital database for echocardiograms pertaining to each patient. We considered echocardiograms recorded a maximum of 1 year before first admittance to the HF clinic (median 30 days before admittance, interquartile range [IQR] 6−56 days before admittance). A total of 22 patients did not have an examination within this window and were therefore excluded. Furthermore, 15 patients were excluded because of inadequate examination quality. This resulted in 1065 patients with echocardiograms of sufficient quality within the specified time frame. Then 247 patients were excluded owing to insufficient image quality for the measurement of LA functional parameters. This resulted in a final study sample of 818 HFrEF patients. Baseline clinical characteristics and medications were retrieved from the HF clinic database and were recorded on the first visit to the clinic. Mortality status was retrieved from the Danish National Registry of Mortality at follow-up, and follow-up was 100%.

Clinical Characteristics

Diabetes mellitus (DM) was defined as either fasting plasma glucose levels >7 mmol/L, nonfasting glucose >11.1 mmol/L, or the use of glucose-lowering medications. Ischemic cardiomyopathy (ICMP) was defined either as a history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery (CABG). Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg.

Echocardiography

Vivid 7 or 9 ultrasound machines (GE Healthcare, Horten, Norway) were used by experienced sonographers in all echocardiographic examinations. Echocardiograms were stored in a GE Healthcare Image Vault and underwent offline analysis by a single investigator, blinded to all patient data and outcomes, with the use of Echopac version 12 (GE Healthcare).

Conventional Echocardiography

The acquisition of conventional echocardiographic parameters has previously been described in detail.[9] We measured the maximum LA volume by means of the biplane area length method[6] from the apical 4-chamber and apical 2-chamber views in end-systole with the use of the frame just before mitral valve opening. We measured the minimal LA volume by means of the biplane area length method from the apical 4-chamber and apical 2-chamber views in end-diastole with the use of the frame just before mitral valve closure. LAEF was calculated as (maximal LA volume − minimal LA volume)/maximal LA volume. MinLAVI was calculated as minimal LA volume indexed to body surface area (BSA), and LAVI as maximal LA volume indexed to BSA. Our laboratory has previously demonstrated good inter- and intraobserver variability in the measurement of LAEF, minimal LA volume and maximal LA volume.[11] In this analysis, the intraobserver coefficients of variation (CVs) were as follows: LAEF CV 9.0%; minimal LA volume CV 10.7%; and maximal LA volume CV 10.7%. The interobserver CVs were as follows: LAEF CV 19.9%; minimal LA volume CV 29.3%; and maximal LA volume CV 24.6%. Tricuspid annular plane systolic excursion (TAPSE) was measured with the use of M-mode in the apical 4-chamber view. Pulsed-wave Doppler echocardiography in the 4-chamber view was used to assess mitral valve inflow patterns and thus E, A, deceleration time (DT), and E/A. In patients with atrial fibrillation, the LA does not contract in end-diastole and no measureable A-wave is present.[12] Therefore, we did not determine A or E/A in patients with atrial fibrillation. LVEF was obtained with the use of the modified Simpson rule.[6] LV end-diastolic dimensions were measured from the parasternal long-axis view at the level of the mitral valve leaflets. These dimensions include the interventricular septum thickness, the LV internal diastolic diameter (LVIDd), and the LV posterior wall thickness. These measurements were used to calculate the LV mass by means of the Devereux formula and the LV mass index (LVMI) by means of division with BSA.[6] The early diastolic peak tissue velocity (e′) was determined by placing the range gate in each side of the mitral annular plane in a pulsed-wave tissue Doppler recording of the apical 4-chamber view with subsequent averaging of values to obtain e′. The degree of mitral valve regurgitation was

graded according to contemporary guidelines with the use of mitral valve morphology and Color Doppler imaging.[13]

Speckle-Tracking Echocardiography

Collection and calculation of strain parameters derived from speckle-tracking echocardiography have been previously described in detail.[9] Briefly, longitudinal speckle tracking was performed in the 3 apical views. A region of interest was defined and created by a semiautomated process, in which the operator placed 3 pointers at the endocardial-blood border, 2 in each side of the mitral annular plane and 1 at the apex of the LV, with the program subsequently detecting the endocardial border and the myocardial wall thickness. Global longitudinal strain (GLS) was calculated from a total of 18 heart wall segments obtained from the apical 4-chamber, apical 2-chamber, and apical long-axis views. Six segments were thereby averaged from each view to produce a single measurement from each view. Then values from each of the 3 apical views were averaged into a single GLS measure.

Ethics

This study was approved by a regional Scientific Ethics Committee and by the Danish Data Protection Agency. The study complies with the Second Declaration of Helsinki. Informed consent is not needed for studies involving the use of hospital record and registry data in Denmark as long as the study has been approved by the Danish Data protection Agency and a regional Ethics Committee.

Statistics

All statistical analyses were carried out with the use of Stata 13 for Mac OS. Statistical significance was defined as $P < .05$. Continuous variables exhibiting gaussian distribution were compared with the use of the Student 2-tailed t test. In Table 1, untransformed continuous variables not exhibiting gaussian distribution were reported as median with IQR and compared with the use of the Mann-Whitney U test. Proportions were compared through use of the chi-square test. Linear regression of means was used to analyze trend over tertiles of LAEF. In case of nongaussian distribution, the Cuzick test for nonparametric trend was used to asses trend over tertiles of LAEF.[14] Survival curves were constructed with the use of the Kaplan-Meier method. Poisson cubic spline regression was used to estimate mortality rates as a function of LAEF and MinLAVI. To determine the number of knots in these spline regression models, we calculated the Akaike information criterion (AIC) for each model and selected the number of knots that yielded the lowest AIC value. Cox proportional hazards regression models were used to assess the prognostic value of LA functional parameters. To determine whether LA functional parameters contributed with independent prognostic value, we constructed multivariable models adjusted for known clinical and echocardiographic predictors of outcome in HFrEF.

In model 1 we chose to adjust for important clinical variables (age, sex, mean arterial pressure [MAP], treatment with diuretics, DM, and atrial fibrillation). Then we evaluated the prognostic value of all echocardiographic variables available in our study when adjusted for the covariates specified in model 1. The results of these analyses are presented in Supplemental Table S1. The purpose of assessing the prognostic value of all available echocardiographic markers in model 1 was to determine which variables proved to be important in this model such that they could be selected for entry into model 2 with the use of a forward-selection approach. Using an entry criterion of $P \leq .15$, we chose all echocardiographic variables that fulfilled this significance criteria in model 1 and added these to the adjusting covariates from model 1 to obtain the covariate adjustment for model 2. In addition, we adjusted model 2 for mitral valve regurgitation severity, because this is a known prognosticator in HFrEF. Then we assessed the prognostic value of LAEF, MinLAVI, and LAVI when entered individually into model 2. Then, using an entry criterion of $P \leq .15$, we created model 3, which besides all the adjusting covariates from model 2 additionally included LAEF, MinLAVI, and LAVI in the same model (unless in model 2 they displayed a P value $>.15$, in which case they were considered to have "dropped out" per the forward selection criteria). Thus, in models 1 and 2, LAEF, minLAVI, and LAVI were tested individually, whereas in model 3, to determine which LA parameter was the strongest predictor of outcome, LAEF and minLAVI were entered simultaneously into the same model (LAVI was not included in this model because it was not significant in model 2). Harrell C-statistics were calculated for each predictor to quantify prognostic strength.

In this study we included HFrEF patients with LVEF <45%. However, in the newest heart failure guidelines, HFrEF is defined with LVEF <40%.2 Therefore, we conducted a sensitivity analysis restricting our final multivariable model to consider only patients with LVEF <40% to determine whether this would alter our results. Finally, because atrial fibrillation is very prevalent in HFrEF (in this study 15% had atrial fibrillation), we conducted a sensitivity analysis to determine whether atrial fibrillation modified the prognostic value of the LA functional measures (LAEF and MinLAVI). We conducted stratified analysis to analyze the association between LAEF and MinLAVI and outcome in patients with atrial fibrillation and in patients without atrial fibrillation. In these subgroup analyses, the extent of our multivariable adjustment was limited by the number of events in each subgroup (28 events occurred in patients with atrial fibrillation, 93 in patients without atrial fibrillation). Therefore, when considering only patients with atrial fibrillation we adjusted for age, sex and mean arterial pressure. When considering only patients without atrial fibrillation, we adjusted for age, sex, mean arterial pressure, body mass index, heart rate (HR), ischemic cardiomyopathy, CABG, DM, and LVEF, because the higher number of events in this subgroup allowed for more extensive adjustment without the

Table 1. Patients Stratified According to Tertiles of LAEF.

Variable	All Patients	1st Tertile (LAEF <28%)	2nd Tertile (LAEF 28%−43%)	3rd Tertile (LAEF >43%)	*P* for Trend
Demographics					
n	818	273	273	272	
Age (y)	66.4 ± 11.4	68.6 ± 9.9	66.0 ± 11.6	64.5 ± 12.2	<.001
Male	600 (73.4%)	205 (75.1%)	198 (72.5%)	197 (72.4%)	.48
Clinical characteristics					
Systolic BP (mm Hg)	129.9 ± 20.7	126.9 ± 20.3	131.3 ± 21.3	131.6 ± 20.3	.008
Diastolic BP (mm Hg)	74.7 ± 12.4	74.5 ± 12.2	74.9 ± 12.3	74.6 ± 12.7	.96
Pulse pressure (mm Hg)	55.2 ± 16.8	52.4 ± 16.1	56.4 ± 17.7	57.0 ± 16.3	.051
MAP (mm Hg)	93.1 ± 13.5	92.0 ± 13.4	93.7 ± 13.5	93.6 ± 13.6	.17
Hypertension	337 (41.2%)	107 (39.2%)	113 (41.4%)	117 (43.0%)	.66
BMI (kg/m^2)	26.4 ± 4.8	26.2 ± 4.1	26.4 ± 4.8	26.5 ± 5.3	.44
Diabetes mellitus	93 (11.4%)	33 (12.1%)	29 (10.6%)	31 (11.4%)	.80
Heart rate (beats/min)	74 ± 16	78 ± 17	73 ± 15	70 ± 13	<.001
Ischemic cardiomyopathy	457 (55.9%)	135 (49.5%)	161 (59.0%)	161 (59.2%)	.02
History of AMI	384 (46.9%)	111 (40.7%)	133 (48.7%)	140 (51.5%)	.011
CABG	159 (19.4%)	56 (20.5%)	60 (22.0%)	43 (15.8%)	.17
RAS blockade	647 (79.1%)	218 (79.9%)	222 (81.3%)	207 (76.1%)	.28
Beta-blocker	542 (66.3%)	183 (67.0%)	183 (67.0%)	176 (64.7%)	.57
Spironolactone	122 (14.9%)	44 (16.1%)	33 (12.1%)	45 (16.5%)	.89
Diuretics	412 (50.4%)	141 (51.6%)	141 (51.6%)	130 (47.8%)	.37
Antiarrhythmics	37 (4.5%)	12 (4.4%)	12 (4.4%)	13 (4.8%)	.83
Total cholesterol (mmol/L)	4.46 ± 1.14	4.44 ± 1.21	4.43 ± 1.07	4.51 ± 1.15	.49
Atrial fibrillation	125 (15.3%)	93 (34.1%)	25 (9.2%)	7 (2.6%)	<.001
Permanent atrial fibrillation	113 (13.8%)	87 (31.9%)	22 (8.1%)	4 (1.5%)	<.001
Paroxysmal atrial fibrillation	12 (1.5%)	6 (2.2%)	3 (1.1%)	3 (1.1%)	.47
Mitral regurgitation					.002
None	305 (37.3%	87 (31.9%)	109 (39.9%)	109 (40.1%)	
Mild	439 (53.7%)	148 (54.2%)	140 (51.3%)	151 (55.5%)	
Moderate	68 ± 8.3	35 (12.8%)	21 (7.7%)	12 (4.4%)	
Severe	6 (0.7%)	3 (1.1%)	3 (1.1%)	0 (0.0%)	
Echocardiography					
MinLAVI (mL/m^2)	21.1 ± 13.3	32.6 ± 15.3	18.8 ± 7.0	11.9 ± 5.1	<.001
LAVI (mL/m^2)	30.9 ± 13.8	39.0 ± 16.7	28.9 ± 10.1	25.0 ± 9.4	<.001
LVEF (%)	27.8 ± 9.1	23.9 ± 9.0	28.7 ± 8.6	30.7 ± 8.4	<.001
GLS (%)	9.7 ± 3.3	8.0 ± 2.8	10.0 ± 3.2	11.1 ± 3.3	<.001
TAPSE (cm)	1.9 ± 0.6	1.6 ± 0.5	1.9 ± 0.6	2.1 ± 0.5	<.001
LVIDd (cm)	5.6 ± 1.0	5.9 ± 1.0	5.6 ± 1.0	5.5 ± 0.9	<.001
LVMI (g/m^2)	120.9 ± 38.9	128.4 ± 36.4	120.2 ± 37.6	114.1 ± 41.5	<.001
E (m/s)	0.81 ± 0.2	0.94 ± 0.31	0.81 ± 0.27	0.71 ± 0.23	<.001
A (m/s)*	0.71 ± 0.26	0.56 ± 0.28	0.72 ± 0.28	0.77 ± 0.23	<.001
E/A*	1.02 (0.74−1.65)	1.93 (1.09−2.93)	1.03 (0.79−1.60)	0.84 (0.67−1.18)	<.001
DT (ms)	189 ± 79	168 ± 74	190 ± 72	210 ± 81	<.001
e′ (cm/s)	6.9 ± 2.5	7.1 ± 2.7	6.8 ± 2.3	6.7 ± 2.5	.15
E/e′	11.8 (8.9−15.9)	12.9 (9.5−17.6)	11.3 (9.0−15.7)	10.5 (7.9−14.3)	<.001

BP, blood pressure; MAP, mean arterial pressure; BMI, body mass index; BPM, beats per minute; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; RAS, renin-angiotensin system; MinLAVI, minimal left atrial volume indexed to body surface area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; LVIDd, left ventricular inner diameter at end-diastole; LVMI, left ventricular mass index; DT, deceleration time. Values are presented as mean ± SD, n (%), or median (interquartile range).

*Measured only in patients without atrial fibrillation, because no A-wave is present in atrial fibrillation rhythm

risk of overfitting the model. Also, in patients with atrial fibrillation, to assess whether the prognostic value of LA functional parameters was secondary to LV filling pressure, we assessed the prognostic value of LA functional parameters adjusting only for E, because E correlates well with LV filling pressure in patients with heart failure.[15]

Results

Outcome and Follow-Up

Median follow-up time was 3.3 years (IQR: 1.8−4.6 years), and follow-up was 100%. A total of 121 patients (14.8%) reached the end-point of all-cause mortality.

Baseline Characteristics of the Population Stratified According to Tertiles of LAEF

Decreasing LAEF was significantly associated with increasing age, decreasing systolic blood pressure, and increasing HR (Table 1). Increasing prevalence of previous pacemaker implantation, previous intracardiac defibrillator implantation, previous acute myocardial infarction (AMI), and previous episodes of angina pectoris were all significantly associated with decreasing LAEF (Table 1). Finally, increasing severity of mitral regurgitation was significantly associated with decreasing LAEF (Table 1).

Decreasing LAEF was significantly associated with increasing values of LAVI, MinLAVI, LVIDd, LVMI, E-

wave, E/A, and E/e′ (Table 1). Decreasing values of LVEF, GLS, TAPSE, A-wave, and DT were all associated with decreasing LAEF (Table 1).

Prediction of All-Cause Mortality

LAEF, MinLAVI, and LAVI were all significant predictors of outcome according to univariable Cox regression (Table 2). LAEF and MinLAVI both displayed significantly higher C-statistics than LAVI ($P < .001$; Table 2). Patients in the first (worst) tertile of LAEF displayed ∼4 times greater risk of death from any cause compared with patients in the third (best) tertile of LAEF (Fig. 1). Patients in the third (worst) tertile of MinLAVI displayed ∼3 times greater risk of death from any cause compared with patients in the 1st (best) tertile (Fig. 2). Patients in the third (worst) tertile of LAVI displayed ∼2.5 times greater risk of death from any cause compared to patients in the first (best) tertile (Fig. 3). In unadjusted analysis, we found that the risk of death increased continuously as a function of LAEF, particularly at low values of LAEF (Fig. 4). The same was true for the unadjusted relationship between MinLAVI and the risk of death (Fig. 4).

LAEF, MinLAVI, and LAVI all remained significant in a multivariable model adjusting for age, sex, mean arterial pressure, treatment with diuretics, DM, and atrial fibrillation (model 1; Table 2). In a multivariable model adjusted for the same parameters as model 1 with the addition of mitral regurgitation, LVEF, GLS, TAPSE, DT, E/e′, and left ventricular end-systolic volume index, LAEF and MinLAVI were the only independent echocardiographic predictors of all-cause mortality (model 2; Table 2). Finally, in a final multivariable model to determine which variable was the strongest predictor of outcome, we added both LAEF and MinLAVI to model 2, obtaining model 3, and only LAEF remained a significant predictor of outcome: LAEF: hazard ratio (HR) 1.11, 95% CI 1.01−1.23 ($P = .033$), per 5% decrease; MinLAVI: HR 1.03, 95% CI 0.93−1.15 ($P = .57$), per 5 mL/m^2 increase (model 3; Table 2). Also, because LVEF <40% is used to diagnose HFrEF in the latest guidelines, we analyzed whether restricting our final multivariable model to consider only patients with LVEF <40% altered our results. We found that this did not significantly alter our results: LAEF: HR 1.10, 95% CI 1.02−1.17 ($P = .041$), per 5% decrease; MinLAVI: HR 1.02, 95% CI 0.91−1.14 ($P = .59$), per 5 mL/m^2 increase.

We also assessed whether atrial fibrillation modified the prognostic value of LAEF and MinLAVI. There was no statistically significant interaction between atrial fibrillation and LAEF (P for interaction .41) or MinLAVI (P for interaction .051). In a model considering only patients with atrial fibrillation adjusting for age, sex, and MAP, LAEF and MinLAVI both remained independent predictors of outcome: LAEF: HR 1.31, 95% CI 1.07−1.60 ($P = .008$), per 5% decrease; MinLAVI: HR 1.10, 95% CI 1.02−1.19 ($P = .019$), per 5 mL/m^2 increase. In a model adjusting only for E, only LAEF, not MinLAVI or LAVI, remained an independent predictor of outcome (LAEF: HR 1.27, 95% CI 1.03−1.55 ($P = .023$), per 5% decrease; MinLAVI: HR 1.09, 95% CI 0.97−1.24 ($P = .15$), per 5 mL/m^2; LAVI: HR 1.06, 95% CI 0.94−1.20 ($P = .35$), per 5 mL/m^2 increase). In a model considering only patients without atrial fibrillation adjusting for age, sex, MAP, body mass index (BMI), HR, ICMP, CABG, DM, and LVEF, LAEF and MinLAVI remained independent predictors of outcome: LAEF: HR 1.09, 95% CI 1.01−1.17 ($P = .032$), per 5% decrease; MinLAVI: HR 1.11, 95% CI 1.03−1.20($P = .009$), per 5 mL/m^2 increase).

Table 2. Prediction of All-Cause Mortality With the Use of Cox Regressions

Variable	Hazard Ratio (95% CI)	*P* Value
Unadjusted (818 patients, 121 events)		
LAEF (per 5% decrease)	1.21 (1.14−1.29); C-statistic = 0.675	<.001
MinLAVI (per 5 mL/m^2 increase)	1.16 (1.12−1.21); C-statistic = 0.661	<.001
LAVI (per 5 mL/m^2 increase)	1.14 (1.09−1.19); C-statistic = 0.620	<.001
Model 1 (817 patients, 121 events)		
LAEF (per 5% decrease)	1.17 (1.1.10−1.25)	<.001
MinLAVI (per 5 mL/m^2 increase)	1.13 (1.07−1.18)	<.001
LAVI (per 5 mL/m^2 increase)	1.10 (1.05−1.16)	<.001
Model 2 (727 patients, 106 events)		
LAEF (per 5% decrease)	1.13 (1.05−1.23)	.002
MinLAVI (per 5 mL/m^2 increase)	1.11 (1.02−1.21)	.0018
LAVI (per 5 mL/m^2 increase)	1.06 (0.98−1.16)	.16
Model 3 (727 patients, 106 events)		
LAEF (per 5% decrease)	HR 1.11, 95CI 1.01−1.23	.033
MinLAVI (per 5 mL/m^2 increase)	HR 1.03, 95CI 0.93−1.15	.57

Abbreviations as in Table 1. Model 1 is adjusted for age, sex, diabetes, MAP, treatment with diuretics, and atrial fibrillation.

Model 2 is adjusted for the same variables as model 1 with the addition of mitral regurtitation, LVEF, GLS, TAPSE, DT, E/e′, and LV end-systolic volume index.

Model 3 is identical to model 2 with the addition that LAEF and MinLAVI were entered simultaneously into the same model.

Discussion

In this study, we found in addition to LAVI, both MinLAVI and LAEF were significant predictors of all-cause mortality in HFrEF patients; however, after adjusting for clinical and echocardiographic parameters, LAEF emerged as the strongest predictor of outcome.

Prognostic Value of Atrial Volumes and Function

Several studies have demonstrated increased LA size to be a consistent predictor of outcome in HF.[4,16] Thus, it is well documented that the maximal LA volume conveys significant prognostic information in HFrEF, and assessment of maximal LA volume is included in current guidelines.[6] In the present study, we also found LAVI to be a significant univariable predictor of all-cause mortality in HFrEF. The prognostic value of the maximal LA volume relies on the

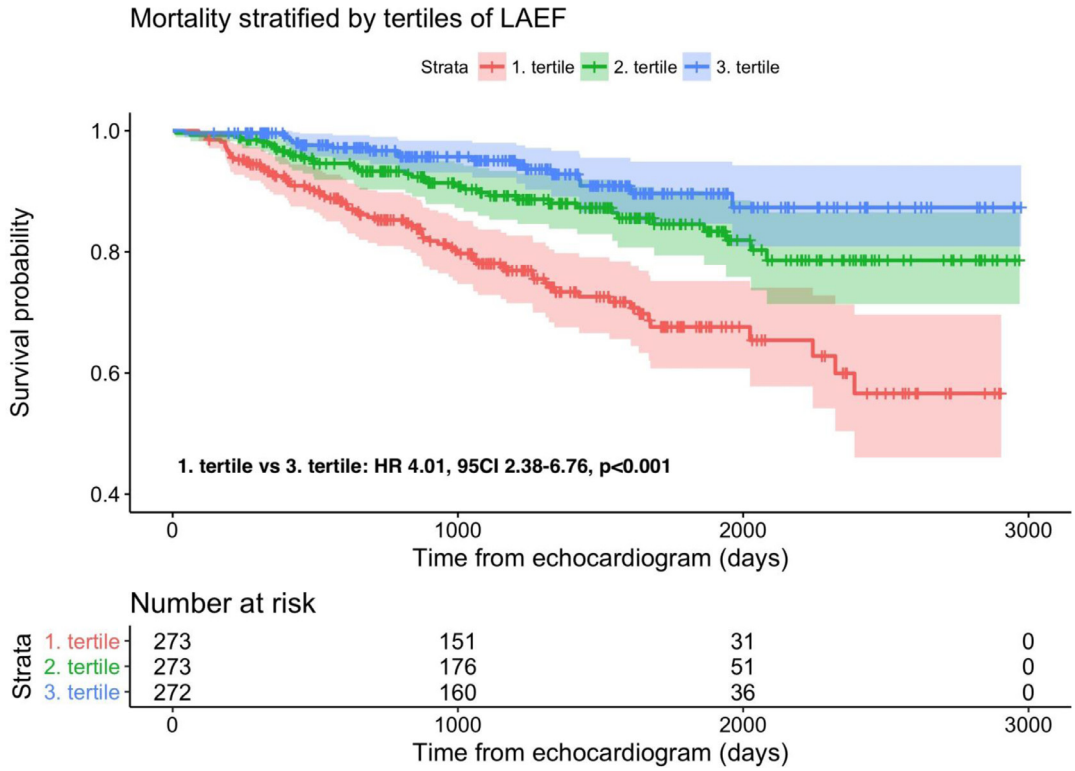

Fig. 1. Mortality of the population stratified according to tertiles of left atrial emptying fraction (LAEF). The tertile cutoffs are LAEF <28%, 28%−43%, and >43%.

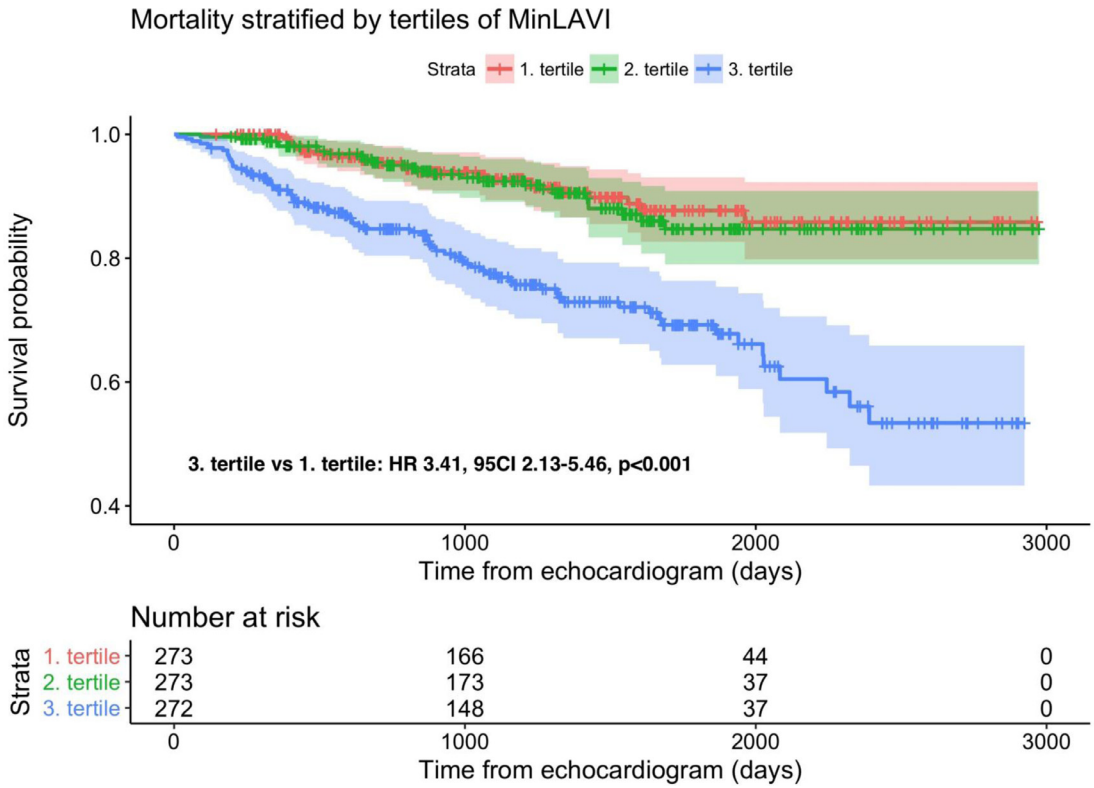

Fig. 2. Mortality of the population stratified according to tertiles of end-diastolic (minimal) left atrial volume indexed to body surface area (MinLAVI). The tertile cutoffs are MinLAVI <14 mL/m^2, 14−23 mL/m^2, and >23 mL/m^2.

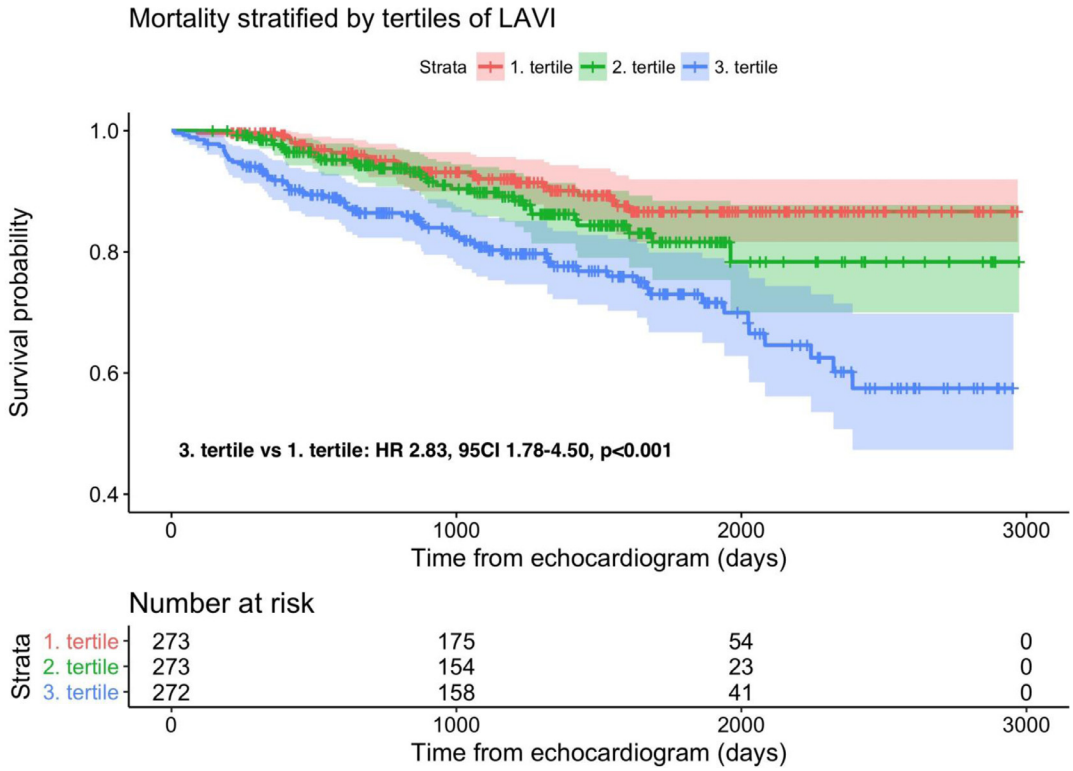

Fig. 3. Mortality of the population stratified according to tertiles of left atrial volume index (LAVI). The tertile cutoffs are LAVI <24 mL/m^2, 24−34 mL/m^2, and >34 mL/m^2.

assumption that LA size is a marker of chronically elevated LV filling pressure.[17] A restrictive LV filling pattern, determined with the use of Doppler echocardiography, has previously been shown to predict all-cause mortality in HFrEF.[18] However, because mitral filling patterns are very dependent on loading conditions during examination and can vary widely, especially with volume depletion, the LA size may represent a more consistent marker of LV filling pressures.[19] The LA responds to increased LV filling pressures with dilation and fibrotic accumulation,[19] and, accordingly, significant enlargement of the LA is often found in HFrEF.[20] Thus, LA volume is both an established and biologically plausible marker of the severity of HF. Recently, however, in a study of 664 HF patients, LAEF measured with the use of CMRI was a superior predictor of survival compared with LVEF.[8] Furthermore, in a study of 982 patients admitted with suspicion of HF, LAEF measured with the use of CMRI, but not LVEF, was an independent predictor of death, and the prognostic value of LAEF in this population was superior to maximal LA volume.[8] This indicates that LA functional measures may offer more prognostic value than LAVI. This is supported by the results of the present study, where we found LAEF to offer incremental prognostic value over LAVI in HFrEF.

Why LA function may offer more prognostic value than LAVI has not been fully elucidated. One explanation may be that LAEF is a stronger correlate of LV filling pressure than maximal LA volume. The LA is directly exposed to the LV filling pressure in end-diastole during the LA contraction. Therefore, the minimal LA volume, which is included in the calculation of LAEF, is a balance between atrial afterload (LV filling pressure) and atrial contractile function. In a CMRI study of patients undergoing clinically indicated left heart catheterization, LAEF and the LA minimal volume were superior to maximal LA volume in identifying increased LV filling pressure.[21] Furthermore, the minimal LA volume measured by means of 3-dimensional echocardiography has been shown to display a stronger association with diastolic function than the maximal LA volume.[22] The minimal LA volume has also been shown to be more strongly correlated to natriuretic peptide levels in a community-based sample compared with LAVI.[23] These considerations along with our results suggest that LAEF may be a better marker of LV filling pressure and congestion than LAVI and, as a result, may offer prognostic value over LAVI in predicting outcome in HFrEF.

It is also possible that part of the prognostic value of LA functional measures found in the present study is due to an ability to quantify primary myocardial disease independently from the relation to LV filling pressure. A study of ischemic cardiomyopathy and idiopathic dilated cardiomyopathy patients found that patients with idiopathic dilated cardiomyopathy had significantly lower LAEF even though they had similar systolic and diastolic function.[24] Likewise, in a study comparing patients with dilated cardiomyopathy and patients with aortic stenosis, atrial systolic function as determined by atrial active emptying fraction was significantly lower in patients with dilated cardiomyopathy even though there was

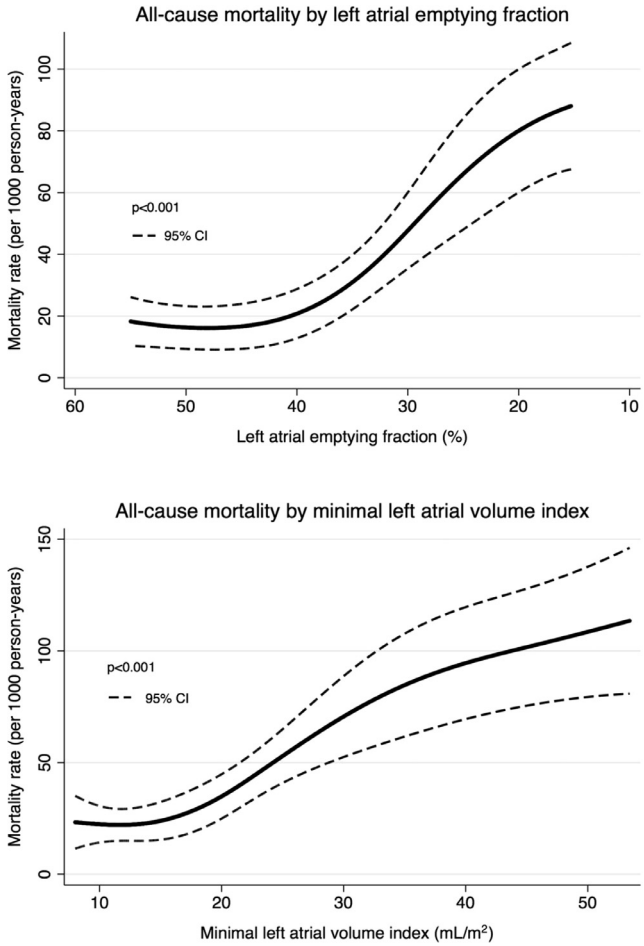

Fig. 4. The association between all-cause mortality and measures of left atrial function. The curves display the unadjusted mortality rate with 95% confidence intervals as a function of (top) the left atrial emptying fraction and (bottom) the minimal left atrial volume index. A Poisson regression model was used to estimate incidence rates.

no difference in maximal LA volume or in hemodynamically assessed LV filling pressure.[25] This difference in LA function can not be explained by differences in LA maximal volume or LV filling pressure. In the present study, we corrected our multivariable model for E/e′, a marker of LV filling pressure, yet LAEF remained a strong predictor of outcome. Therefore, it is possible that at least part of the prognostic value conveyed by LAEF in HFrEF may stem from an ability to quantify generalized myocardial disease.

LAEF and MinLAVI

As discussed above, it is likely that some of the prognostic value of LAEF is due to the strong correlation with LV filling pressure.[21] However, an interesting finding was the lack of prognostic value of MinLAVI when both LAEF and MinLAVI were entered into the final multivariable model. This suggests that the prognostic value of LAEF is not only carried by the minimal LA volume and its relation to LV filling pressure, not only determined by LA contractile function, but also by LA reservoir and conduit functions.[26,27] The LA has 3 important functions throughout the cardiac cycle, and all contribute to optimal cardiac performance:[26–30] (1) during the reservoir phase in systole, the LA acts as a reservoir for pulmonary venous return while the mitral valve is closed;(2) during the conduit phase in early diastole, the LA acts as a conduit for blood entering the left ventricle; and (3) during end-diastole, the LA acts as a booster pump augmenting LV filling immediately before ventricular systole. Aging is associated with reduced LA compliance, reduced LA reservoir function, and reduced conduit function, partly owing to accumulation of LA fibrosis and increased LA stiffness.[31–33] This reduction in reservoir and conduit function associated with normal aging is compensated for by an increase in LA booster pump function.[26,30,33] Similarly, in early heart failure, increased LA pump function compensates for impaired LV function.[26,30,33,34] However, as LV function deteriorates further with progression of heart failure, the workload imposed on the LA exceeds its reserve capacity and LA pump failure ensues.[35,36] To maintain LV filling and stroke volume, the reservoir and conduit functions must compensate for decreased LA pump function.[26,30,35,36] Thus, because LAEF represents all 3 functions of the LA, LAEF may be able to identify patients with advanced disease in whom LA reservoir and conduit function can not compensate for LA failure. This notion is supported by our finding that LAEF, but not MinLAVI, also predicted mortality in patients with atrial fibrillation. In atrial fibrillation, LA contractile function is absent, and therefore LAEF does not represent LA systolic function and booster pump function in atrial fibrillation rhythm. LA compliance is reduced and LA stiffness is increased in patients with atrial fibrillation owing to LA fibrosis and impaired LA relaxation (due to constant fibrillation),[37] and because especially LA reservoir function is determined by LA compliance, this may result in impaired reservoir function.[26,27,30] Therefore, the prognostic value of LAEF in patients with atrial fibrillation may stem from an ability to quantify reservoir and conduit function, allowing the identification of patients with poor LA compliance and high LA stiffness, who can not compensate for the loss of contractile function. Alternatively, invasive hemodynamic studies have demonstrated that the irregular ventricular rate and the loss of atrial filling caused by atrial fibrillation significantly increase pulmonary capillary wedge pressure and contribute to diastolic dysfunction.[8] In HF patients with atrial fibrillation, pronounced diastolic dysfunction could potentially antagonize LA emptying during diastole and lead to reduced LAEF. This may also explain part of why LAEF was a strong predictor of mortality in patients with atrial fibrillation in our study. However, these considerations should be confirmed in future experimental studies.

Study Limitations

Some limitations to this study must be acknowledged. None of the patients were suspected of restricted cardiac

amyloidosis. However, as is the case for all other HFrEF studies, as well as for HFpEF studies, the presence of cardiac amyloidosis as a cause of HF symptoms can never be excluded completely. Furthermore, we did not have information on whether some patients may have developed HFrEF because of specific genetic mutations, rare conditions, or viral infections. These considerations are important because myocarditis, amyloidosis, and other infiltrative diseases may cause atrial myopathy and affect LA function independently from other disease mechanisms. Also, we did not have information on important clinical variables such as natriuretic peptide levels or New York Heart Association functional class. Because these variables contribute valuable prognostic information in HFrEF,[38,39] this is another limitation. In this study we did not have access to information regarding the specific cause of death, and as a result we could not analyze the association between LA functional parameters and cardiovascular mortality. However, when considering that ~80% of HFrEF patients die from cardiovascular causes,[40] we think that our results remain valid even though our outcome was all-cause mortality. Furthermore, we did not have information on heart failure hospitalizations during follow-up. Because heart failure hospitalization is associated with significant health care costs,[41] this would have been useful information. Multiple statistical tests were performed in this study, but no adjustment for multiple comparisons was made. Owing to a high degree of multicollinearity between LAEF and MinLAVI, these variables were tested separately in the multivariable models. Therefore, it was difficult to assess whether one was superior to the other. However, because LAEF and MinLAVI remained independent predictors of outcome when tested separately in the final multivariable model but LAVI did not, we may still conclude that LAEF and MinLAVI are superior to LAVI in predicting outcome in HFrEF. Finally, the study population was mainly of European race, and therefore our results can not be applied to other races.

Conclusion

LAEF is an independent predictor of all-cause mortality in HFrEF patients after multivariable adjustment. LAEF provides incremental prognostic value over LAVI in risk stratification of HFrEF patients.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cardfail.2018.11.016.

References

1. Roger VL. Epidemiology of heart failure. Circ Res 2013;113:646–59.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.
3. Tribouilloy C, Rusinaru D, Mahjoub H, Goissen T, Lévy F, Peltier M. Impact of echocardiography in patients hospitalized for heart failure: a prospective observational study. Arch Cardiovasc Dis 2008;101:465–73.
4. Rossi A, Cicoira M, Bonapace S, et al. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MERGE Heart Failure). Eur J Heart Fail 2009;11:929–36.
5. Ramu B, Elwan AM, Coleman CI, Silverman DI, Gluck JA. The association between baseline left atrial volume index and all-cause mortality in patients with heart failure: a meta-analysis. Conn Med 2015;79:469–75.
6. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–71.
7. Fang F, Lee AP-W, Yu C-M. Left atrial function in heart failure with impaired and preserved ejection fraction. Curr Opin Cardiol 2014;29:430–6.
8. Pellicori P, Zhang Z, Lukaschuk E, et al. Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value. Eur Heart J 2015;36:733–42.
9. Sengeløv M, Jørgensen PG, Jensen JS, et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. JACC Cardiovasc Imaging 2015;8:1351–9.
10. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388–442.
11. Olsen FJ, Møgelvang R, Jensen GB, Jensen JS, Biering-Sørensen T. Relationship between left atrial functional measures and incident atrial fibrillation in the general population: the Copenhagen City Heart Study. JACC Cardiovasc Imaging 2018.
12. Kim T-S, Youn H-J. Role of echocardiography in atrial fibrillation. J Cardiovasc Ultrasound 2011;19:51–61.
13. Zoghbi WA, Enriguez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
14. Cuzick J. A Wilcoxon-type test for trend. Stat Med 1985;4:87–90.
15. Park JH, Marwick TH. Use and limitations of e/e′ to assess left ventricular filling pressure by echocardiography. J Cardiovasc Ultrasound 2011;19.
16. Dini FL, Cortigiani L, Baldini U, et al. Prognostic value of left atrial enlargement in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. Am J Cardiol 2002;89:518–23.
17. Tsang TSM, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284–9.
18. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F. Heart Muscle Disease Study Group. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by

Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. J Am Coll Cardiol 1993;22:808–15.
19. Douglas PS. The left atrium. J Am Coll Cardiol 2003;42: 1206–7.
20. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail 2015;8:295–303.
21. Posina K, Mclaughlin J, Rhee P, et al. Relationship of phasic left atrial volume and emptying function to left ventricular filling pressure: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2013;15:99.
22. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL. Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: impact of left ventricular systolic function. Heart 2012;98:813–20.
23. Hedberg P, Selmeryd J, Leppert J, Henriksen E. Left atrial minimum volume is more strongly associated with N-terminal pro−B-type natriuretic peptide than the left atrial maximum volume in a community-based sample. Int J Cardiovasc Imaging 2016;32:417–25.
24. Sheng Cao, Qing Zhou, Jin−ling Chen, Bo Hu, Rui−qiang Guo. The differences in left atrial function between ischemic and idiopathic dilated cardiomyopathy patients: a two−dimensional speckle tracking imaging study. J Clin Ultrasound 2016;44:437–45.
25. Triposkiadis F, Pitsavos C, Boudoulas H, Trikas A, Toutouzas P. Left atrial myopathy in idiopathic dilated cardiomyopathy. Am Heart J 1994;128:308–15.
26. Olsen FJ, Bertelsen L, de Knegt MC, et al. Multimodality cardiac imaging for the assessment of left atrial function and the association with atrial arrhythmias. Circ Cardiovasc Imaging 2016;9:e004947.
27. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol 2014;63:493–505.
28. Blume GG, McLeod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM. Left atrial function: physiology, assessment, and clinical implications. Eur J Echocardiogr 2011;12:421–30.
29. Suga H. Importance of atrial compliance in cardiac performance. Circ Res 1974;35:39–43.
30. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. Eur Heart J 2001;22:22–36.
31. Abou R, Leung M, Tonsbeek AM, et al. Effect of aging on left atrial compliance and electromechanical properties in subjects without structural heart disease. Am J Cardiol 2017;120:140–7.
32. Gramley F, Lorenzen J, Knackstedt C, et al. Age-related atrial fibrosis. Age 2009;31:27–38.
33. Meel R, Khandheria BK, Peters F, Libhaber E, Nel S, Essop MR. Effects of age on left atrial volume and strain parameters using echocardiography in a normal black population. Echo Res Pract 2016;3:115–23.
34. Matsuda Y, Toma Y, Matsuzaki M, et al. Change of left atrial systolic pressure waveform in relation to left ventricular end-diastolic pressure. Circulation 1990;82:1659–67.
35. Dernellis JM, Stefanadis CI, Zacharoulis AA, Toutouzas PK. Left atrial mechanical adaptation to long-standing hemodynamic loads based on pressure-volume relations. Am J Cardiol 1998;81:1138–43.
36. Prioli A, Marino P, Lanzoni L, Zardini P. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. Am J Cardiol 1998;82:756–61.
37. Dzeshka MS, Lip GYH, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications. J Am Coll Cardiol 2015;66: 943–59.
38. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ 2005;330 (7492):625.
39. Criteria Committee of the New York Heart Association. p 253, 9th ed. Boston: Little Brown and Co.; 1994. p. 253–6.
40. Rickenbacher P, Pfisterer M, Burkard T, et al. Why and how do elderly patients with heart failure die? Insights from the TIME−CHF study. Eur J Heart Fail 2012;14: 1218–29.
41. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? EP Eur 2011;13(Suppl 2). ii13−7.