Relation of Left Atrial Volumes in Patients With Myocardial Infarction to Left Ventricular Filling Pressures and Outcomes

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The inter-relationships between minimal and maximal left atrial volume index (LAVI), left ventricular filling pressures and survival have not been well studied. This study aimed to compare LAVImin with LAVImax with respect to (1) relative prognostic value, and (2) correlation with left ventricular end-diastolic pressures (LVEDP), in patients with myocardial infarction (MI). A retrospective study involving consecutive patients with a first-ever MI (n = 419) was undertaken. LAVIs were determined using Simpson's biplane method from 2D echocardiography performed the day after admission. LAVmin ≥ 18 mls/m^2 and LAVImax ≥ 34 mls/m^2 were considered enlarged. The primary end point was composite major adverse cardiovascular events (MACE) (death/MI/heart failure). Correlation between LVEDP and LAVI was assessed in 120 patients who underwent echocardiography and cardiac catheterization either simultaneously (n = 30) or same-day (n = 90). At a median follow-up of 24 months, there were 61 MACE events. On Cox proportional hazards multivariate analysis incorporating significant clinical predictors and LVEF, whereas both LAVImin ≥ 18 mls/m^2 (hazard ratio 3.15 [95% confidence interval 1.70 to 5.54], p <0.001) and LAVImax ≥ 34 mls/m^2 (hazard ratio 1.79 [95% confidence interval 1.02 to 3.14], p = 0.041) were independent predictors of MACE, LAVImin showed a stronger association. Intermodel comparisons of the model chi-square and Harrell's C-statistic confirmed better prognostication with LAVImin. In the invasive cohort, because LAVImin and LAVImax had a similar correlation with LVEDP ≥ 15 mm Hg (r = 0.41 [p <0.001] vs r = 0.42 [p <0.001]), LAVmin ≥ 18 mls/m^2 had a greater sensitivity for LVEDP ≥ 15 mm Hg than LAVImax ≥ 34 mls/m^2 (sensitivity 59.4% vs 34.4%). In conclusion, utilizing thresholds of ≥18 and ≥34 mls/m^2, respectively, LAVImin was a better predictor of survival than LAVImax, the pathophysiologic basis of which relates to a better sensitivity for elevated left ventricular filling pressures with LAVImin at these thresholds. There may be incremental clinical value in measuring LAVImin alongside LAVImax. **(Am J Cardiol 2019;124:325−333)**

Left atrial volume indexed to body surface area (BSA) using the maximal volume (LAVImax) is a powerful predictor of survival in patients with cardiac disease.[1−5] Recent studies have shown that the minimal left atrial volume indexed to BSA (LAVImin) also has prognostic value, and may be better than LAVImax.[6] The pathophysiologic basis of any prognostic differences between LAVImax and LAVImin is not well delineated, but LAVImin may be a better correlate of instantaneous left ventricular filling pressures (LVFP).[7] This study sought to determine and compare (1) the relative prognostic value of LAVImin and LAVImax and (2) the correlation between LAVI measurements and invasively measured LVFP, in the same cohort of consecutive patients presenting with a first-ever MI. The study hypotheses were that (1) LAVImin would be a superior predictor of survival compared with LAVImax and (2) LAVImin would show a better correlation with LVFP compared with LAVImax. This study is an extension of a previous study from the present study group which examined outcomes associated with diastolic dysfunction assessed with current American Society of Echocardiography/European Association of Cardiovascular Imaging diastology guidelines.[8]

Methods

A total of 718 consecutive patients with MI (ST-elevation MI and non-ST-elevation MI) who underwent coronary angiography during the study period between January 2013 and December 2014 at a single tertiary level referral center

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were considered for inclusion in this study. Exclusion criteria included previous MI (n = 160), significant mitral valve disease (moderate or greater regurgitation or any stenosis; n = 32), atrial fibrillation (n = 33), paced rhythm (n = 12), prosthetic mitral valves (n = 6), and significant hemodynamic instability (shock, florid acute pulmonary edema, requirement for mechanical ventilation, inotropes, intra-aortic balloon pump, and those with ventricular tachyarrhythmia; n = 4) and insufficient image quality (n = 52), leaving a final study group of 419 patients. The default strategy for management of ST-elevation MI was primary percutaneous coronary intervention (PCI) with 24-hour catheterization laboratory activation, and an early invasive approach for non-ST-elevation MI, with the aim of angiography/PCI within 24 hours of admission. All patients were started on evidence-based medical therapy for MI on admission unless contraindications existed.

A comprehensive transthoracic echocardiogram was performed within 24 hours of admission for all patients. All echocardiograms were performed on either a General Electric Vivid E9 machine (Horten, Norway) or a Phillips IE33 machine (Andover, Massachusetts) with tissue Doppler imaging software and a 2.5 to 5 MHz variable frequency, phased array transthoracic transducer. The echocardiography protocol and assessment of systolic and diastolic function at the study institution were in accordance with contemporary American Society of Echocardiography guidelines and detailed descriptions of which have been published previously.[8,9] LAVI was assessed using a Simpson's biplane method with an inbuilt disk summation algorithm on the echo machines used in this study.[10] For LAVImax, LA endocardium was traced out in the apical 4- and 2-chamber views at ventricular end-systole just before mitral valve opening, with the left atrial appendage, the area under the mitral valve annulus and the inflow of the pulmonary veins excluded from the tracing. The height of the LA (h) was divided into 20 segments, with each segment, segment having a height of h/20, and, assuming an oval shape, a major and minor orthogonal diameter (D1 and D2) determined by the inbuilt disk summation algorithm. The total volume was determined using the formula $\pi/4$ (h)$\sum$(D1)(D2). The calculated volume was indexed to BSA to calculate LAVImax. LAVImin was determined in a similar fashion by tracing the LA endocardium coincident with the R wave on the electrocardiogram in the apical 4- and 2-chamber views at the end of atrial systole after atrial contraction to obtain the smallest volume.[6] LAVImin $\geq$ 18 mls/m^2 was considered enlarged.[6] Total LA reservoir volume was calculated using unidexed biplane LA volumes using the formula: LAVmax − LAVmin. Left atrial function was assessed using the rhythm independent left atrial function index (LAFI), which was calculated using the formula: LAFI = LA emptying fraction × LVOT VTI/LAVImax (LVOT VTI = left ventricular outflow tract velocity time integral,.[11] LAFI < 0.2 (unitless) was considered reduced as derived by Thomas et al.[11] LA emptying fraction was calculated as LAVmax − LAVmin/LAVmax.

The primary outcome measurement was a composite of major adverse cardiovascular events (MACE) comprising all-cause death, MI, and heart failure (HF) during the follow-up period. All-cause mortality was assessed as a secondary end point. Outcomes data were obtained from federal government maintained databases, including the national death registry, where each patient is tracked through a unique Medicare number for hospital admissions and death.

The correlation between LVFP and LAVI were studied in 2 subsets of patients. An initial subset of unselected patients (n = 30) underwent simultaneous echocardiography and cardiac catheterization with measurement of both LAVI and left ventricular end-diastolic pressures (LVEDP) on the cardiac catheterization table. A further subset of patients who underwent echocardiography and cardiac catherization with measurement of LVEDP on the same day (n = 90) were also identified and analyzed for the correlation between LVEDP and LAVI. For the simultaneous cohort, cardiac catheterization was performed immediately after echocardiography was performed on the cardiac catheterization table. Measurements obtained during the on-table echocardiogram included dedicated views for the measurement of LA size, as well as mitral inflow, pulmonary venous inflow, tissue Doppler imaging, and tricuspid regurgitation velocity. Measurements were obtained over 3 cardiac cycles and averaged. Cardiac catheterization was performed via 6 French femoral approach in all patients in the simultaneous cohort. Heparin 5,000 IU was given immediately upon successful insertion of the femoral sheath. LVEDP measurements were performed through a fluid-filled 6 French pigtail catheter with side holes after careful flushing of the catheter prior to coronary angiography before injection of any contrast media. The pigtail catheter was carefully balanced to 0 at the midaxillary level before measurements. Pressure waveforms for 6 to 10 beats were recorded at end expiration. An LVEDP $\geq$15 mm Hg was considered elevated. For the same day cohort, measurements were obtained during the same working day, with patients fasted for 4 hours before the procedure and infused with maintenance intravenous saline (80 to 125 mls/h) during the fasting period.

Intraobserver variability for LAVI measurements were determined by an experienced sonographer performing measurements on 20 randomly selected cases from the same dataset 1-month apart. Interobserver variability was determined by a second sonographer performing measurements on the same 20 cases.

Continuous variables are expressed as mean ± SD and compared using an unpaired *t* test if data were normally distributed or the Mann-Whitney *U* test if data were not normally distributed. Categorical variables are presented as n (%) and compared with Fisher's exact test. Correlation between LAVI and LVEDP were studied with Pearson's correlation coefficients. Diagnostic performance of LAVI thresholds for LVFP was examined by constructing receiver-operating curves with determination of area under the curve. Correlations between factors of interest and outcomes were tested with Cox proportional hazards analysis. Factors significant at a level of 0.1 on univariate analysis were considered for inclusion in a multivariable Cox proportional hazards analysis. A series of nested models for prediction of MACE and all-cause mortality were undertaken. Intermodel comparisons for increase in predictive power were performed by a comparison of the model chi-squared at each step by calculating change in overall

log-likelihood ratio chi-square. Harrell's C-statistic was also calculated for each model as an analogous overall measurement of discrimination for predicting survival. Survival was also expressed using Kaplan-Meier Curves, with a log-rank test used to assess for significance between curves. Retrospective power calculations for sample size calculations were determined using sampling survival analysis (log-rank test).[12] A $p < 0.05$ was considered significant. All statistical analyses were carried out using SPSS version 23 (SPSS Inc, Chicago, Illinois). The study was approved by the institutional Human Research Ethics committee.

Results

The final study group consisted of 419 patients: 196 (46.8%) with LAVImin $\geq$ 18 mls/m^2 and 80(19.1%) with LAVImax $\geq$ 34 mls/m^2. Baseline clinical and angiographic characteristics are shown in Table 1 and echocardiographic data are summarized in Table 2. Clinically, patients with LAVImin $\geq$ 18 mls/m^2 were older, and had a higher prevalence of diabetes and chronic kidney disease. Echocardiographically, univariate comparisons showed that patients with enlarged LAVImin had a larger LV size with a lower LVEF, lower e' velocities (septal, lateral, and average), higher corresponding E/e' ratios, and evidence of reduced atrial function with a lower LAEF and LAFI. In a multivariate model to identify independent correlates of enlarged LAVImin incorporating clinical factors (age, diabetes, and chronic kidney disease) and echocardiographic characteristics (LVEDVI, wall thickness, LVEF, and average E/e'), age (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.01 to 1.06, p = 0.004), LVEDVI (OR 1.03, 95% CI 1.01 to 1.05, p = 0.019), LVEF (OR 0.96, 95% CI 0.94 to 0.98, p = 0.003), and average E/e' (OR 1.11, 95% CI 1.04 to 1.20, p = 0.003) were identified as independent correlates of enlarged LAVImin.

The distribution of patients according to pattern of LAVI enlargement is shown in Figure 1. The predominant pattern of LAVI enlargement was that of normal LAVIs by both measurements (n = 218 [52.0%]) and dilated LAVIs by both measurements (n = 75 [17.9%]) at the 2 extremes, with a third group with dilated LAVImin but normal LAVImax (n = 121 [28.9%]) in between, suggesting progressive LA dilatation with enlargement of LAVImin preceding LAVImax, with dilated LAVImax likely representing end-stage LA dilatation.

At a median follow-up of 24 months, there were a total of 61 MACE events (37 deaths). Kaplan-Meier analysis for the

Table 1
Baseline clinical and angiographic characteristics

Characteristic	Overall group (n = 419)	Minimum LA volume index (ml/m^2) ≥18 (n = 196)	Minimum LA volume index (ml/m^2) < 18 (n = 223)	p*
	A	B	C	*B vs C
Age (years)	61.3 ± 13.7	64.6 ± 11.9	58.4 ± 12.1	<0.001
Men	310 (74.2%)	146 (74.4%)	144 (72.4%)	0.659
Body mass index (kg/m^2)	28.2 ± 7.7	28.2 ± 7.2	28.2 ± 5.6	0.980
Diabetes	82 (19.6%)	50 (25.5%)	32 (14.8%)	0.007
Hypertension	179 (42.7%)	89 (45.4%)	90 (40.4%)	0.198
Dyslipidemia	189 (45.2%)	86 (43.9%)	103 (46.2%)	0.694
Smoker	219 (52.3%)	92 (46.9%)	127 (57.0%)	0.064
Family history IHD	82 (19.6%)	32 (17.2%)	50 (22.5%)	0.176
Chronic kidney disease	45 (10.7%)	29 (14.8%)	16 (7.2%)	0.017
STEMI	130 (31.1%)	59 (30.1%)	71 (31.8%)	0.751
Culprit coronary artery				0.268
LM	5 (1.1%)	2 (1.0%)	3 (1.3%)	
LAD	171 (41.1%)	91 (46.4%)	80 (38.1%)	
LCx	102 (24.4%)	40 (20.4%)	62 (26.9%)	
Right	127 (30.4%	55 (28.1%)	72 (31.4%)	
Coronary artery assessment				0.217
None	21 (5.0%)	12 (6.1%)	9 (4.0%)	
1	271 (64.8%)	122 (62.2%)	149 (66.4%)	
2	70 (16.7%)	29 (14.8%)	41 (18.4%)	
3	57 (13.5%)	33 (16.8%)	24 (10.8%)	
Proximal culprit	138 (32.9%)	68 (34.7%)	70 (31.9%)	0.465
LAD	176 (42.0%)	91 (46.4%)	85 (38.1%)	0.092
Management strategy				0.254
PCI	316 (75.3%)	144 (73.7%)	172 (77.1%)	
Coronary bypass	55 (13.2%)	25 (12.6%)	30 (13.4%)	
Medical therapy	48 (11.4%)	27 (13.6%)	21 (9.4%)	
Peak troponin I (ng/ml)	19.31 ± 23.91	28.58 ± 21.10	17.71 ± 25.30	0.198
Discharge medications				
Aspirin	403 (96.1%)	188 (95.9%)	215 (96.6%)	0.712
Beta blocker	352 (84.2%)	164 (83.8%)	188 (84.3%)	0.743
ACE-inhibitor/ARB-blocker	381 (91.1%)	178 (90.8%)	203 (91.4%)	0.701
Statin	403 (96.2%)	188 (95.8%)	215 (96.3%)	0.798
Dual antiplatelet therapy	356 (85.1%)	166 (84.6%)	190 (85.6%)	0.764

Table 2
Echocardiographic data

Variable	Overall group (n = 419) A	Minimal LA volume index ≥18 ml/m^2 (n = 196) B	Minimal LA volume index <18 ml/m^2 (n = 223) C	p* *B vs C
LV size and LVEF				
Biplane LV ejection fraction (%)	53.2 ± 11.4	51.6 ± 11.4	56.0 ± 9.8	<0.001
Interventricular septum thickness (mm)	11.2 ± 2.4	11.6 ± 2.0	10.9 ± 2.8	0.006
LV posterior wall thickness (mm)	10.1 ± 1.8	10.4 ± 1.8	9.8 ± 1.7	0.002
LV end-diastolic volume index (ml/m^2)	46.0 ± 13.0	49.6 ± 13.6	43.9 ± 12.9	<0.001
LV end-systolic volume index (ml)	25.8 ± 11.0	24.1 ± 12.2	19.2 ± 10.6	<0.001
Diastolic parameters				
Mitral E-wave velocity (cm/s)	7.0 ± 2.2	7.3 ± 2.5	6.6 ± 1.7	0.002
Mitral A-wave velocity (cm/s)	6.3 ± 2.1	6.7 ± 2.2	6.6 ± 1.8	0.299
Mitral E/A ratio (unitless)	1.1 ± 0.5	1.1 ± 0.5	1.1 ± 0.7	0.827
Septal E' velocity (cm/s)	6.4 ± 1.9	6.1 ± 1.9	6.9 ± 1.7	<0.001
Lateral E' velocity (cm/s)	7.4 ± 1.0	7.9 ± 3.0	9.0 ± 3.5	0.001
Average E' velocity (cm/s)	7.2 ± 2.2	7.0 ± 2.2	7.9 ± 2.3	<0.001
Septal E/E' ratio (unitless)	11.8 ± 5.6	13.1 ± 6.9	10.1 ± 3.0	<0.001
Lateral E/E' ratio (unitless)	8.5 ± 4.4	11.0 ± 11.3	8.2 ± 3.3	0.002
Average E/E' ratio (unitless)	10.5 ± 5.2	11.5 ± 6.1	8.9 ± 2.8	<0.001
Diastolic function grade				0.005
Normal or Grade 1	321 (76.6%)	139 (70.9%)	182 (81.6%)	
Grade 2	43 (10.2%)	30 (15.3%)	13 (5.8%)	
Grade 3	55 (13.1%)	27 (13.8%)	28 (12.6%)	
LA parameters				
LA maximum volume index (cm^3/m^2)	30.5 ± 14.4	33.8 ± 9.0	23.4 ± 4.6	<0.001
LA minimum volume index (cm^3/m^2)	18.7 ± 7.1	24.9 ± 7.9	13.9 ± 2.4	<0.001
LA reservoir volume (mls)	18.5 ± 9.5	17.8 ± 9.8	19.4 ± 8.6	0.100
LA ejection fraction (%)	33.1 ± 10.9	26.1 ± 10.7	39.5 ± 11.0	<0.001
LA function index (unitless)	0.24 ± 0.10	0.16 ± 0.08	0.33 ± 0.11	<0.001
Right heart parameters				
Tricuspid regurgitation velocity (m/s)	2.5 ± 0.5	2.6 ± 0.5	2.4 ± 0.3	0.001
Right atrial pressure (mm Hg)	5.5 ± 3.5	5.7 ± 3.3	4.6 ± 2.9	0.009
Right ventricular systolic pressure (mm Hg)	30.5 ± 9.8	32.9 ± 11.1	27.0 ± 7.5	<0.001
RV annulus (S') velocity (cm/s)	18.3 ± 6.3	12.0 ± 2.8	11.5 ± 2.4	0.104

primary end point of MACE showed that LAVImin appeared to have the best association with the highest log-rank chi-square statistic. Table 3 summarizes the results of Cox univariate proportional hazards analysis to identify significant clinical predictors for MACE (Figure 2). The results of a Cox multivariable proportional hazards analysis involving the separate addition of LAVImin and LAVImax to significant clinical predictors (age, diabetes mellitus [DM], chronic kidney disease [CKD], and number of diseased vessels) and LVEF showed that because both LAVImax (hazard ratio [HR] 1.79, 95% CI 1.02 to 3.14, p = 0.041) and LAVImin (HR 3.15, 95% CI 1.70 to 5.84, p <0.001) were independent predictors of MACE, LAVImin had the better association with a higher OR, more significant p value and the highest model chi-square value. The addition of LAVImin to multivariate models resulted in a greater increase in model power compared with LAVImax (Figure 3). Harrel's C calculations showed that the model containing LAVImin produced the highest Harrell's C value.

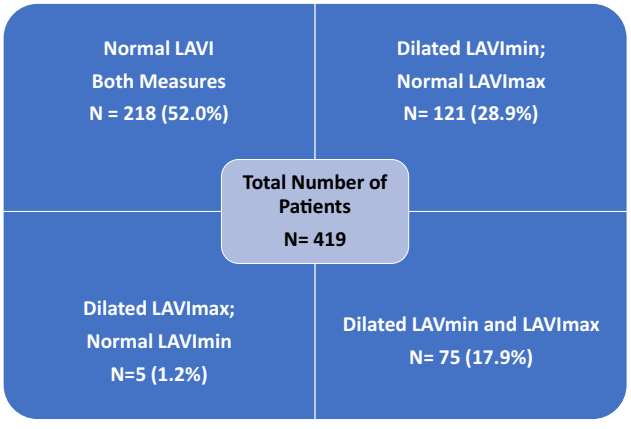


Figure 1. Diagram illustrating distribution of patients according to pattern of LAVI enlargement. Distribution of patients according to pattern of LA enlargement is shown with patients with normal LAVIs by both measurements *(top left)*, normal LAVImax but dilated LAVImin *(top right)*, dilated LAVImax but normal LAVImin *(bottom left)*, and dilated LAVIs by both measurements *(bottom right)*. LA = left atrial; LAVI = left atrial volume index.

For the secondary end point of all-cause mortality, on Kaplan-Meier analysis, LAVImin had the best association with the highest log-rank chi-squared statistic (log-rank chi-square value 20.2 [p <0.001] vs 14.2 [p <0.001]). On Cox multivariable proportional hazards analysis involving the separate addition of LAVImin and LAVImax to significant clinical predictors (age, CKD, and number of diseased vessels) and LVEF, LAVImin (HR 3.61, 95% CI 1.55 to 8.39, p = 0.003), but not LAVImax (HR 1.47, 95% CI 0.73 to 2.94, p = 0.177), was an independent predictor of

Table 3
Cox univariate analysis to identify significant predictors for major adverse cardiovascular events

Variable	Hazard ratio	95% CI	p Value
Clinical/angiographic variables			
Age	1.04	1.02-1.06	<0.001
Men	1.01	0.57-1.79	0.971
Body mass index (kg/m^2)	0.99	0.95-1.02	0.372
Smokers	1.73	1.04-2.90	0.035
Hypertension	1.67	1.01-2.75	0.047
Dyslipidemia	0.93	0.56-1.54	0.780
Diabetes	2.09	1.23-3.54	0.006
Chronic kidney disease	2.97	1.66-5.33	<0.001
Post-PCI TIMI flow	1.40	0.66-3.22	0.411
Successful revascularization	1.32	0.57-3.07	0.517
No of diseased vessels	1.90	1.43-2.52	<0.001
Infarct type (STEMI)	0.83	0.47-1.46	0.511
LV and RV size and function			
LV ejection fraction	0.97	0.95-0.99	0.009
LV end-diastolic volume index	1.03	1.02-1.04	0.031
LV end-systolic volume index	1.01	0.99-1.03	0.562
LV mass index (g/m^2)	1.70	1.03-2.81	0.040
RV annular (S') velocity (cm/s)	0.95	0.87-1.04	0.246
Diastolic parameters			
Mital E/A ratio >2	1.84	0.74-4.59	0.192
Deceleration time (ms)	1.00	0.99-1.04	0.855
Average E/e' ratio >14	3.20	1.87-5.46	<0.001
Tricuspid regurgitation velocity	1.61	0.82-3.15	0.165
LA parameters			
LA function index < 0.2 (unitless)	2.35	1.36-4.07	0.002
LA ejection fraction (%)	4.63	0.56-38.4	0.153
LA area (cm^2)	1.06	1.02-1.10	0.003
Maximum LA volume index (mls/m^2)	2.90	1.74-4.83	<0.001
Minimum LA volume index (mls/m^2)	3.97	2.21-7.12	<0.001
Discharge medications			
Aspirin	0.78	0.19-3.18	0.728
Beta-blocker	1.03	0.51-2.08	0.927
ACE-inhibitor/ ARB blocker	0.50	0.22-1.10	0.085
Statin	0.88	0.22-3.33	0.574
Dual antiplatelet therapy	0.50	0.28-0.98	0.030

all-cause mortality. Finally, when patients were categorized by the 3 predominant patterns of LAVI enlargement (Group 1: normal LAVIs by both measurements, Group 2: dilated LAVImin + normal LAVI max, and Group 3: dilated LAVIs by both measurements) there was a graded association with MACE as shown in Figure 4, with patients in Group 2 having a survival curve intermediate between Groups 1 and 3 (log-rank chi-square statistic 33.22, p <0.001).

In the hemodynamic substudy, both LAVImin and LAVImax were similarly correlated with LVEDP: LAVImin r = 0.41 (p <0.001) versus LAVImax r = 0.42 (p <0.001). LVEDP was elevated in patients with dilated LAVIs by both measurements: mean LVEDP in the LAVImin ≥ 18 mls/m^2 group was 16.9 ± 6.5 mm Hg versus 13.5 ± 6.1 mm Hg in the nondilated group (p = 0.004); mean LVEDP in LAVImax ≥ 34 mls/m^2 was 18.7 ± 6.3 mm Hg versus 14.1 ± 6.2 mm Hg in the nondilated group (p = 0.001). Linear regression curves for the correlation between LVEDP and LAVI measurements are shown in Figure 5. The diagnostic performance of LAVI cutoffs for LVEDP ≥ 15 mm Hg is summarized in Table 4. LAVImin ≥ 18 showed a significantly greater sensitivity for LVEDP ≥ 15 mm Hg than LAVImax ≥ 34 (59.4% vs 34.4%), whereas LAVImax had a significantly higher specificity (87.3% vs 58.2%). Area under the curves for LAVIs and elevated LVEDP were similar for both measurements (0.64 vs 0.63, p <0.05). Finally, when the invasive cohort was stratified according to the pattern of LA enlargement using the 3 groups specified above, there was a graded increase in LVEDP (Figure 6).

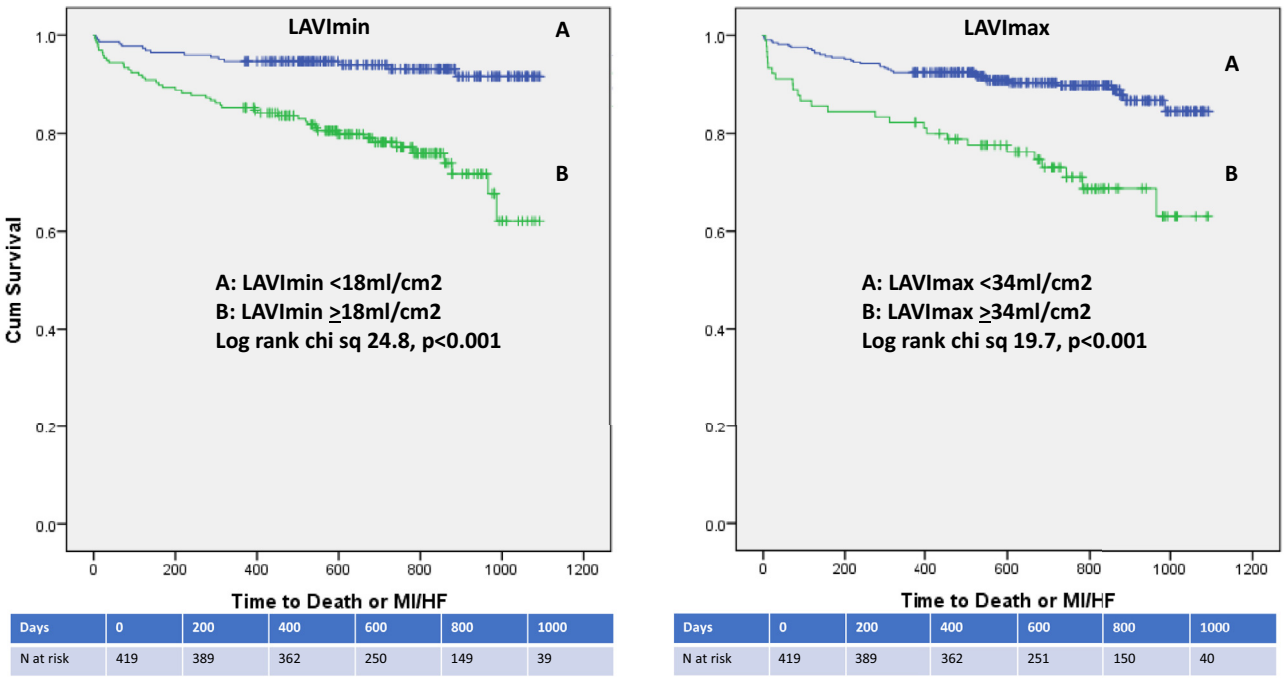
Retrospective power analyses (sample size calculations) for MACE showed that the minimal required sample sizes for LAVImin were n = 352 ($\alpha = 0.05$, $\beta = 0.01$) and n = 364 for LAVImax ($\alpha = 0.01$, $\beta = 0.01$). Bland-Altman analysis for intra- and interobserver variabilities for LAVImax and LAVImin and demonstrated satisfactory reproducibility for both measurements.

Discussion

The present study contains a number of important findings: (1) although both LAVI measurements were independent predictors of outcome after MI, LAVImin using a cutoff of ≥18 mls/m^2 had a better correlation with survival compared with LAVImax using a cutoff of ≥34 ml/m^2; (2) LAVImin had a robust correlation with invasively and noninvasively measured LVFP, and LAVImin using a cutoff of ≥18 mls/m^2 has a greater sensitivity for elevated LVFP than LAVImax using a cutoff of ≥34 mls/m^2; (3) patients with normal LAVImax but dilated LAVImin represent an intermediate group with a distinct hemodynamic and prognostic profile compared with patients with dilated LAVImax, whose risk may be underestimated based on measurements of LAVImax alone; and which therefore (4) delineates the incremental clinical value of measuring LAVImin alongside LAVImax.

This study highlights that the cutoffs currently employed for LAVImax and LAVImin have varying correlations with LVFP and outcomes. LAVImax cutoff of 34 mls/m^2 is based on a number of high-quality studies with a large number of patients and this value has accordingly been endorsed by guidelines on chamber quantification as well as assessment of diastolic function.[13–21] LAVImin reference ranges used in the present study were principally based on the study by Wu et al, which defined a normal range cutoff for 2D LAVImin of 18 mls/m^2 (based on a sample of 124 normal subjects; mean LAVImin 11.8 ± 3.3 mls/m^2), which is in keeping with reference ranges defined by other smaller studies.[6,22–24]

The data to date regarding the prognostic value of LAVImin is based on a small number of studies.[6,7,25–28] Fatema et al showed that LAVImin but not LAVImax was an independent predictor of a first episode of atrial tachyarrhythmia in a population-based study in Minnesota.[25] Caselli et al showed that LAVImin was the best independent predictor of MACE when compared with other measurements of LV and LA size and function.[26] Russo et al showed that LAVImin was a better predictor of silent cerebral infarcts than LAVImax in a stroke-free community cohort.[27] Finally, Wu et al showed that LAVImin is a better predictor of MACE than LAVImax in a group of patients with a



Days	0	200	400	600	800	1000
N at risk	419	389	362	250	149	39

Days	0	200	400	600	800	1000
N at risk	419	389	362	251	150	40

Figure 2. Kaplan-Meier survival curves for MACE for LAVImin and LAVImax. Kaplan-Meier survival curves for MACE is shown, with comparison of curves with log-rank test (chi-squared values and p values shown as above). MACE = major adverse cardiovascular events.

stable cardiac disease.[6] The clinical significance of the growing body of evidence for LAVImin, to which this study is additive, is a potential change in practice with respect to assessment of left atrial size in the future. An important consideration is that LAVImin is simple to obtain and can be obtained from standard echocardiography, making it easy to adopt in clinical practice.

This study has a number of limitations. The sample size recruited represents a moderate sample size. Measurement of systolic function in the early phase after MI may underestimate LVEF due to myocardial stunning. Administration of medications such as glyceryl trinitrate, β blockers, and angiotensin-converting enzyme inhibitors in the periinfarction period would influence loading conditions and heart rate and thus potentially confound measurements. However, both LAVImin and LAVImax were measured under the same loading conditions for all patients mitigating this factor. Data on left atrial strain measurements were not available and therefore its relative prognostic value in relation to LAVImin could not be studied.

In conclusion, this study demonstrates that LAVImin, utilizing a cutoff of $\geq$18 mls/m^2, is superior to LAVImax utilizing a cutoff of $\geq$34 mls/m^2 for the prediction of survival after MI. The hemodynamic basis of this relates to a better sensitivity for elevated LVEDP. Moreover, the group of patients with normal LAVImax but dilated LAVImin, who comprise around 30% of patients after a first-ever MI, are identified as a distinct group of patients whose risk

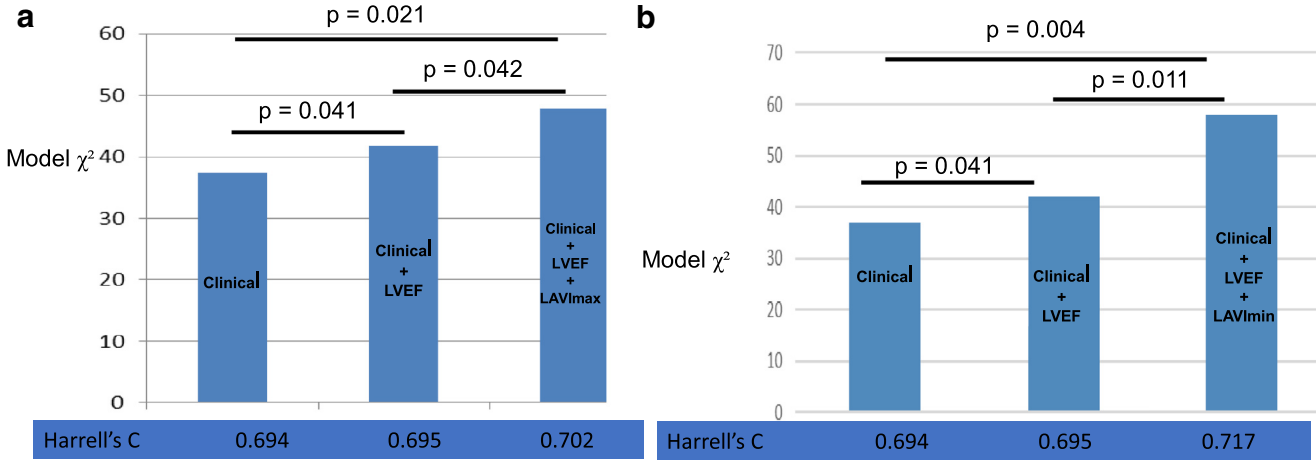


Figure 3. Incremental Value of LAVImin *(top)* and LAVImax *(bottom)* for MACE in Nested Cox proportional hazards models. Comparison of the model chi-squared values is shown in bar graphs; p values for intermodel comparisons summarized above bar graphs. LAVI = left atrial volume index; MACE = major adverse cardiovascular events.

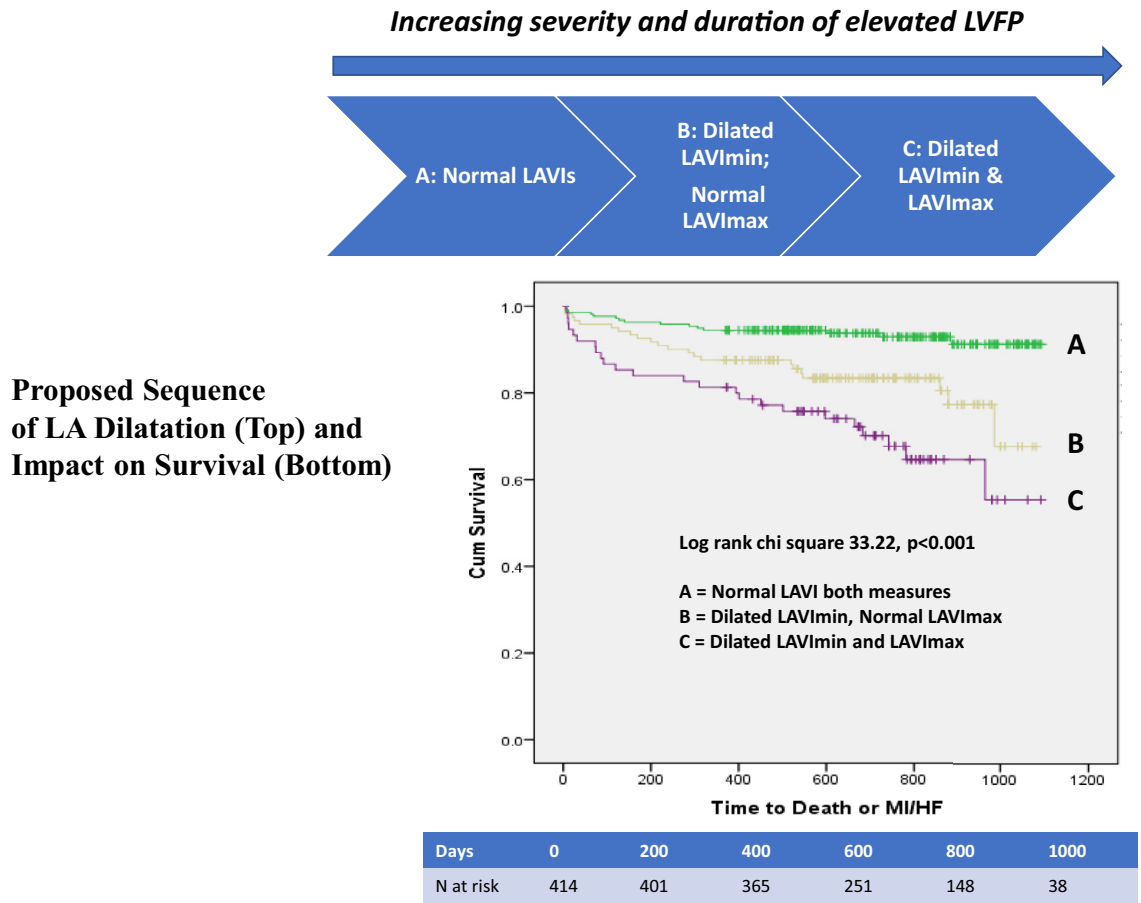


Figure 4. Proposed sequence of LA dilatation *(top)* and impact on survival *(bottom)*. Proposed sequence of LAVI dilatation with its consequent impact on survival is shown. Survival curves show patients with dilated LAVImin but normal LAVImax represent an intermediate group with a distinct prognostic profile compared with patients with dilated LAVImax. LAVI = left atrial volume index.

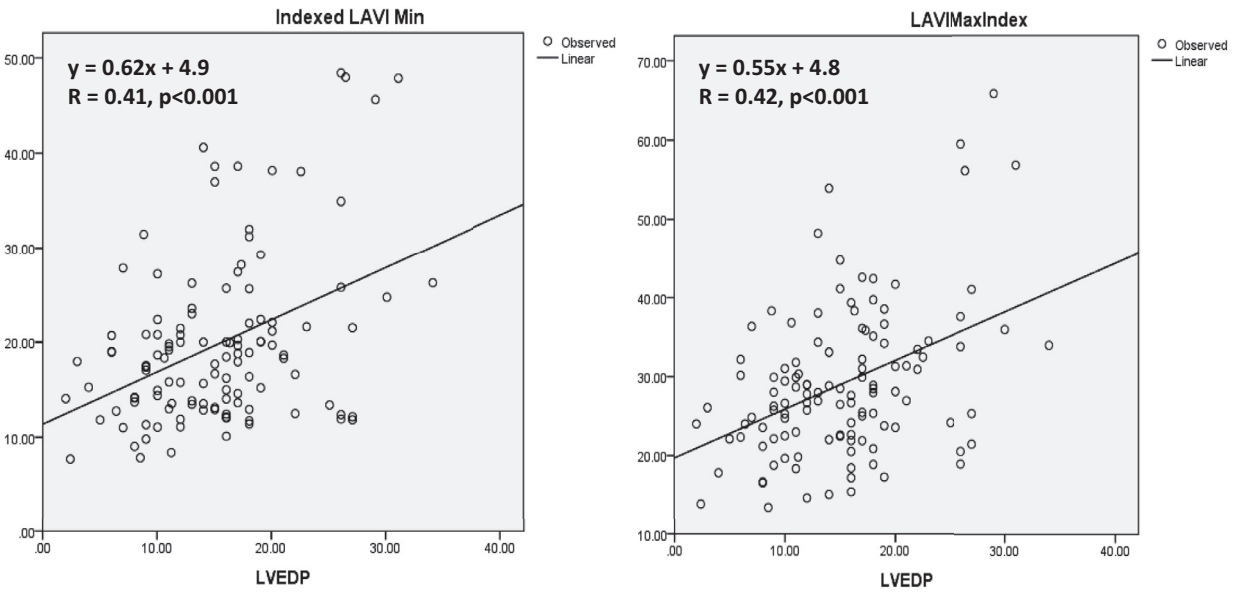


Figure 5. Correlation between LAVI measurements and LVEDP. Linear regression models for the correlation between LAVI measurements and LVEDP, with r values and p values as shown. LAVI = left atrial volume index; LVEDP = left ventricular end-diastolic pressure.

Table 4
Diagnostic performance of LA volume index measurements for elevated LV end-diastolic pressure ≥ 15 mm Hg

LA volume measure	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Area under curve
Minimum LA volume index ≥ 18 mls/m^2	59.4	58.2	62.3	55.2	0.64 (p = 0.011)
Maximum LA volume index ≥ 34 mls/m^2	34.4	87.3	75.9	53.3	0.63 (p = 0.012)

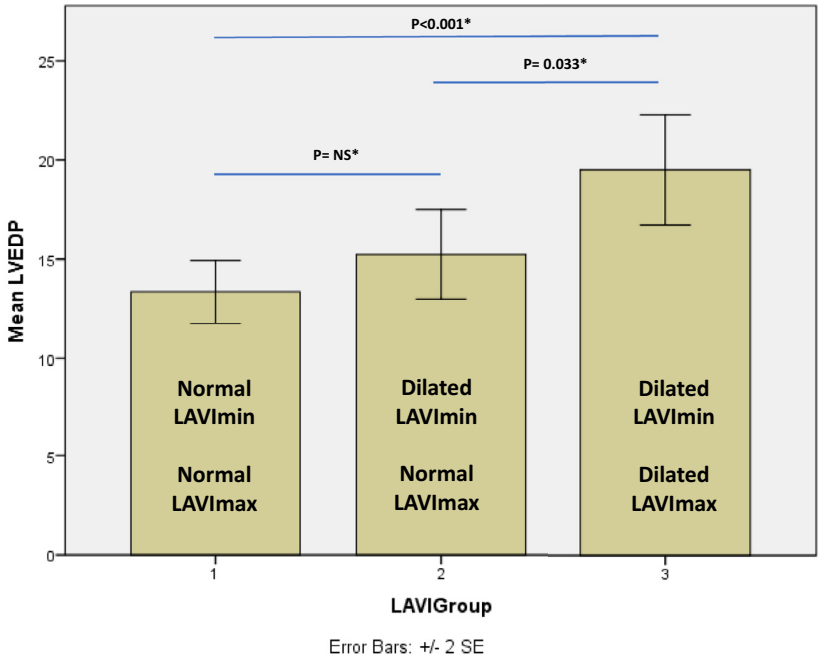


Figure 6. Comparison of LVEDP according to pattern of LAVI enlargement. Comparison of LVEDP according to pattern of LAVI enlargement: normal LAVIs by both measurements versus dilated LAVImin but normal LAVImax versus dilated LAVIs by both measurements; *p values from one-way ANOVA with post hoc Tukey hsd test. LAVI = left atrial volume index.

would be underestimated by measuring LAVImax alone, highlighting the incremental clinical value of measuring LAVImin alongside LAVImax.

Disclosures

The authors have no conflict of interest to disclose.

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