Clinical and Prognostic Implications of Methods and Partition Values Used to Assess Left Atrial Volume by Two-Dimensional Echocardiography

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Background: The 2015 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations for chamber quantification suggest new abnormality threshold and severity partition values for left atrial (LA) volume that are equally valid for the biplane method of disk (MOD) summation and the area-length method (ALM). However, they have never been clinically validated. Thus, we compared the clinical and prognostic impact of LA volume assessed by MOD and ALM by using both the 2015 and 2005 abnormality thresholds.

Methods: In a retrospective study of 467 patients with sinus rhythm and various cardiac conditions (median age 61 years, 68% men), maximal LA volumes were measured with MOD and ALM. Patients were followed for 3.7 ± 1.1 years to record both all-cause mortality and cardiac death.

Results: Applying the 2015 cutoff values, 21% of patients with dilated LA according to the 2005 recommendations were reclassified as normal. Severity of LA dilatation was reclassified in 48% (222/467) patients. ALM provided significantly larger LA volumes than MOD (41 [32; 58] mL/m^2 vs 39 [30; 55] mL/m^2; P = .0150), reclassifying 18% (84/467) of patients. Patients who died had larger LA volumes measured with both MOD (57 [38; 77] mL/m^2 vs 37 [30; 51] mL/m^2; P < .0001) and ALM (58 [40; 82] mL/m^2 vs 40 [32; 54] mL/m^2; P < .0001). Regardless of the method used, LA volume was a significant factor associated with mortality, with both the 2015 and 2005 cutoff values providing similar prognostic power.

Conclusions: The use of 2015 partition values and different methods of LA volume measurement leads to significant changes in patients' clinical profiles. LA enlargement is an important prognostic indicator independent of cutoff values and methods used. Care should be taken to ensure consistent measurements and interpretation of two-dimensional echocardiography LA volume during patient follow-up. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Two-dimensional echocardiography, Left atrial volume index, Prognosis

Left atrial (LA) enlargement is an important risk factor and a powerful independent predictor of adverse cardiovascular events in various clinical scenarios, such as acute and chronic coronary artery disease,[1] dilated cardiomyopathy,[2] heart failure,[3] diabetes mellitus,[4] cohorts of unselected patients,[5,6] and healthy volunteers.[7]

Using the results of large normative studies,[8,9] the recently updated recommendations for cardiac chamber quantification issued jointly by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI)[10] proposed new abnormality threshold and severity partition values for LA maximum volume measured with two-dimensional echocardiography (2DE), which were significantly larger than those published in 2005.[11] Applying the higher abnormality threshold for LA volume index (34 vs 28 mL/m^2) is expected to lead to the reclassification of patients previously diagnosed with mildly or even moderately dilated LA as having normal LA. However, the actual extent of this change as well as its clinical and prognostic impact remain unknown.

Moreover, the coexistence of two different algorithms for the routine calculation of biplane LA maximum volume, such as the method of disks (MOD; Simpson disks summation method) and the area-length method (ALM),[10,11] which may yield slightly different measurements in the same patient, adds to the complexity of the LA quantification by 2DE. Despite the fact that some studies reported

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Abbreviations

2DE = Two-dimensional echocardiography

ALM = Area-length method

ASE = American Society of Echocardiography

EACVI = European Association of Cardiovascular Imaging

EAE = European Association of Echocardiography

LA = Left atrium/atrial

MOD = Method of disks

slightly larger LA volumes when measured by ALM in comparison with MOD,[8] there is a lack of method-specific reference values and evidence that these methods can actually be used interchangeably.

Accordingly, the present study was designed to (1) determine the clinical impact of different reference values and severity partition values (recommended by ASE/European Association of Echocardiography [EAE] in 2005 and ASE/EACVI in 2015) and methods of LA volume measurement (MOD and ALM) on diagnosis and reclassification of severity of LA enlargement in a cohort of patients with structural heart diseases undergoing clinically indicated routine 2DE; and (2) compare the prognostic value of LA enlargement assessed by MOD versus ALM and using 2015 versus 2005 abnormality thresholds and severity cutoff values.

METHODS

Study Design and Population

Between October 2010 and December 2012, patients with sinus rhythm and various cardiac conditions who underwent clinically indicated transthoracic echocardiography were enrolled into a single-center retrospective observational cross-sectional study aimed to assess the reference values[12] and the prognostic power of three-dimensional echocardiography LA volumes. For the present retrospective analysis, the following inclusion criteria were used: (1) recordings of both 2DE apical four- and two-chamber views allowing for LA quantification, (2) sufficient image quality to trace LA endocardium; (3) availability of follow-up data. Patients with more than 5 mm difference between LA lengths in the two apical views were excluded[10] (Figure 1). Demographic and clinical data (age, weight, height, body surface area, body mass index, cardiovascular risk factors, and comorbidities) were retrieved from the electronic clinical records of the hospital database. The study was approved by the local Ethics Committee.

Echocardiographic Analysis

Digitally stored data sets in raw-data format were analyzed offline using commercially available software (EchoPAC BT12, GE Vingmed, Horten, Norway). All measurements were performed according to the ASE/EACVI guidelines.[10]

Quantitative analysis of 2DE-derived LA volume was performed by a single experienced echocardiographer (E.S.) unaware of either clinical information or outcomes. LA maximal volume was measured at the end of ventricular systole (the last frame before the mitral valve opening) in the apical four- and two-chamber views. While tracing the LA endocardium, the LA appendage and the ostia of pulmonary veins were excluded. When dropout was encountered, a straight line joining the closest visualized structures completed the atrial outline. Mitral annulus was considered as LA atrioventricular border.[12] The length of LA was measured from the middle of the mitral annular plane to the posterior wall (Figure 2). The software package was set in order to calculate the LA maximal volume by both MOD and ALM using the same endocardial tracings. LA volumes were indexed to body surface area. Indexed maximal LA volumes were classified as normal, mildly, moderately, or severely dilated according to the abnormality thresholds and severity partition values recommended by both ASE/EAE in 2005[11] and ASE/EACVI in 2015[10] (Table 1).

In addition, left ventricular size and function parameters were obtained from the analysis of two-dimensional and three-dimensional echocardiography data sets of the left ventricle, as described elsewhere.[13]

Reproducibility Analysis

Intraobserver variability was tested on 45 good-quality apical four- and two-chamber images by an experienced echocardiographer (E.S.) who reanalyzed the same recordings one more time, being blinded to the first measurements. For interobserver variability, the same images were analyzed independently by a different experienced researcher (J.B.).

Follow-up

All patients were followed for occurrence of new outcome events, which included all-cause mortality and cardiac death (defined as death resulting from an acute myocardial infarction, heart failure, cardiovascular procedures, and sudden cardiac death). Follow-up data were collected by an investigator (D.G.), who was not involved in the echocardiographic measurements, through analysis of clinical records and telephone contacts to patients, physicians, or the next of kin when the patient was not available.

Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normal distribution of variables. Continuous variables were reported as the mean and SD for normally distributed variables, while nonnormally distributed variables were reported as the median and interquartile range. Statistical significance was tested using a χ^2 test for categorical variables. *T*-test or Mann-Whitney test was used to test the differences in the continuous variables according to the data distribution. Receiver-operator characteristic curves were generated to assess the overall performance and predictive value of the different cutoffs and methods of LA volume assessment. Kaplan-Meier survival analysis was used to plot all-cause mortality and cardiac death. Differences between survival curves were assessed by the log-rank test. Statistical analysis was performed using R (ver. 3.3.1) and GraphPad Prism (ver. 7.0a). A P value of $<.05$ was considered statistically significant.

RESULTS

A total of 467 patients were included into the study cohort. Demographic and clinical characteristics and echocardiographic data of the study patients are summarized in Table 2.

During a mean follow-up of 3.7 ± 1.1 years, 59 (12.6%) deaths, including 43 (9.2%) cardiac deaths, occurred. Patients who died were older, had larger LA maximal volume (irrespective of the method of calculation), lower left ventricular ejection fraction, and less negative global longitudinal strain (Table 3).

Clinical and Prognostic Impact of Abnormality Thresholds and Cutoff Values of LA Volumes

As expected, when applying the 2015 abnormality threshold, the number of patients with abnormal LA decreased significantly compared with those classified using the 2005 abnormality threshold

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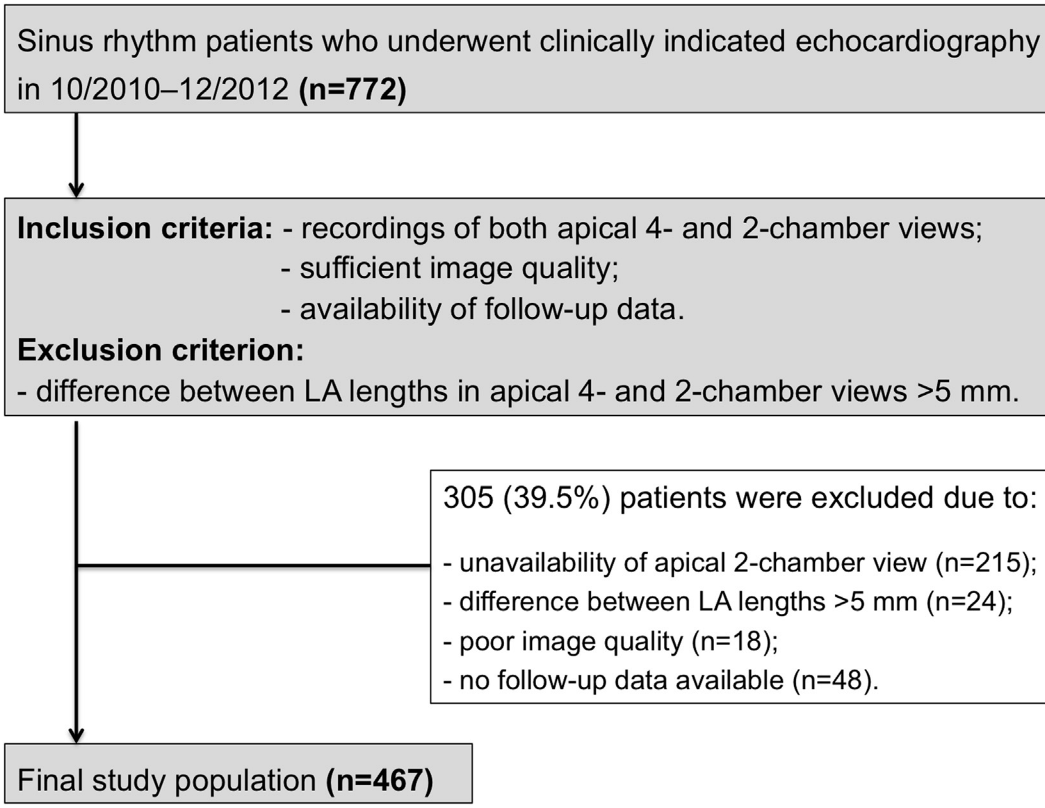

Figure 1 Study enrollment flow chart.

(292 [62.5%] vs 370 [79.2%]; $P < .0001$; Figure 3). In addition, the adoption of the new severity partition values determined a remarkable reclassification of the patients among the various degrees of LA enlargement. Using 2015 cutoff values, the number of patients with mild LA dilation increased from 65 (13.9%) to 103 (22.1%); $P = .0012$. Conversely, the number of patients with moderate or severe LA dilation decreased from 81 (17.3%) and 224 (50.0%) to 41 (8.8%) and 148 (31.7%), respectively, $P \leq .0001$. When applying 2015 partition values, a total of 222 (47.5%) patients were reclassified compared with the grouping based on 2005 partition values (Figure 3).

Figure 4 shows the Kaplan-Meier survival analyses of all-cause mortality (A-D) and cardiac death (E-H) applying LA volume index partition values suggested in 2005 versus 2015, as well as using different methods. Overall, there was a significant association between the degree of LA enlargement and mortality for both MOD and ALM (2015 criteria, all-cause mortality: $\chi^2 = 24.84$, $P < .0001$ vs $\chi^2 = 19.78$, $P = .0002$, respectively; cardiac death: $\chi^2 = 19.63$, $P = .0002$ vs $\chi^2 = 15.91$, $P = .0012$, respectively). There was a stepwise increase in the risk of both all-cause and cardiac mortality from moderately to severely dilated LA (2015 cutoff values: $\chi^2 = 5.901$, $P = .0151$ and $\chi^2 = 4.539$, $P = .0331$, respectively; 2005 cutoff values: $\chi^2 = 5.248$, $P = .022$ vs $\chi^2 = 5.902$, $P = .0151$, respectively) but not between other LA volume categories (from normal to mildly or moderately dilated).

The higher abnormality threshold suggested in 2015 ASE/EACVI recommendations demonstrated similar prognostic significance in comparison with the 2005 abnormality threshold, as demonstrated by receiver-operator characteristic analysis (Figure 5A-5B).

Clinical and Prognostic Impact of the Methods Used to Calculate LA Volumes

The 2DE LA maximum volumes obtained by MOD correlated tightly with those calculated with ALM (Figure 6A). LA maximal volumes measured using MOD were significantly smaller than those calculated by ALM (LA volume, 71 [55; 100] mL vs 76 [58; 106] mL, $P = .0215$; LA volume index, 39 [30; 55] mL/m^2 vs 41 [32; 58] mL/m^2, $P = .0150$). Bland-Altman analysis also demonstrated underestimation of LA volume when measured by MOD in comparison with ALM (negative bias of -5.41 mL) and the increase in the difference in parallel with the magnitude of measurements (Figure 6B).

Accordingly, the two different 2DE methods to calculate LA volume affected our patients' classification by the degree of LA enlargement. The number of patients with normal LA size was larger when LA volume was assessed using MOD ($n = 175$, 37.5%) than when applying ALM ($n = 140$, 30.0%; $P = .0155$). In total, 84 (18.0%) patients were upgraded in the severity of their LA enlargement when using ALM in comparison with MOD (Figure 3).

When the overall sensitivity and specificity of MOD and ALM as factors associated with mortality were compared using receiver-operator characteristic curves, the areas under the curve for indexed LA volumes measured by MOD and ALM were similar (0.6548 vs 0.6455, respectively), suggesting no differences in prognostic significance (Figure 5C).

Reproducibility

The intra- and interobserver reproducibility of 2DE measurements of LA maximum volume was excellent when analyses were repeated on the same good-quality images by experienced operators (Table 4).

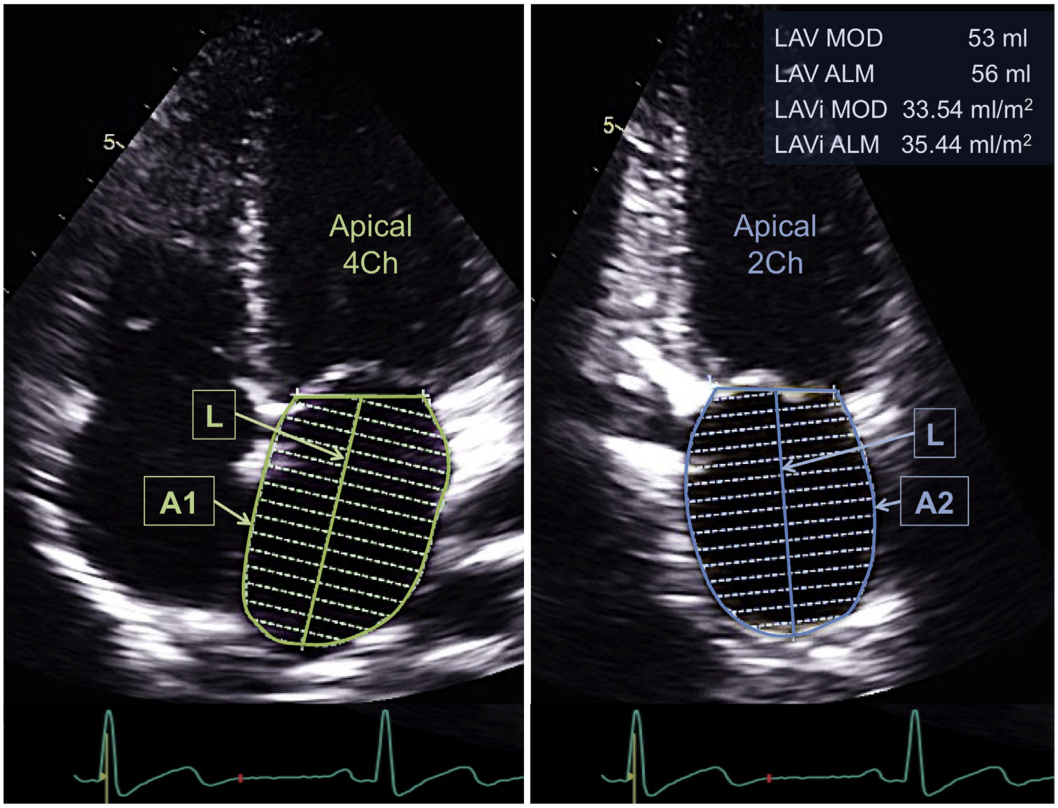

Figure 2 Two-dimensional echocardiographic assessment of LA maximal volume by MOD and ALM LA endocardium is traced in apical four-chamber and two-chamber views on the frame just prior to mitral valve opening, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins. Then using the same endocardial tracings, LA volume was calculated using two currently recommended methods: (1) MOD, applying the following equation: $\pi/4(h)\ \sum(D1)(D2)$,where h is the height of the disks and $D1$ and $D2$ are orthogonal minor and major transverse axes of each disk. (2) ALM, applying the following equation: $8/3\pi \cdot [(A1 \cdot A2)/L]$, where $A1$ and $A2$ are the LA areas measured in the apical two- and four-chamber views and L is the shortest of the two long axes. According to the 2015 ASE/EACVI recommendations, the LA volume index (body surface area = 1.58 m^2) should be classified as normal, when measured by MOD, and mildly dilated, when measured by ALM. Applying the previous cutoff values from 2005, LA is classified as moderately dilated. *2Ch*, two-chamber view; *4Ch*, four-chamber view; *LAV*, LA volume; *LAVi*, LA volume indexed to body surface area.

Table 1 Reference values and severity partition cutoff values for 2DE-derived LA volumes

	LA volume index (mL/m^2)			
Chamber quantification guidelines	Normal	Mildly abnormal	Moderately abnormal	Severely abnormal
Lang *et al*, 2005[11]	16-28	29-33	34-39	≥40
Lang *et al*, 2015[10]	16-34	35-41	42-48	>48

DISCUSSION

In the current study, we assessed the clinical and prognostic effects of the new abnormality threshold and severity partition cutoff values for 2DE-derived LA maximal volume introduced in the 2015 ASE/EACVI recommendations. In addition, we have also evaluated the clinical and prognostic effects of the different methods (MOD and ALM) included in the current guidelines for LA volume calculation. Our main findings can be summarized as follows: (1) applying the new abnormality threshold, one out of five patients who were previously diagnosed with an enlarged LA were reclassified as having normal LA volume; (2) using the new severity partition cutoff values led to reclassification of 48% of patients according to the degree of LA enlargement; (3) LA size classification using both the 2005 and 2015 cutoff values demonstrated similar prognostic power in predicting death; (4) a 5 mL (7%) difference in LA maximal volumes measured by MOD and ALM determined reclassification of 18% of our patients; and (5) LA volumes calculated with either MOD or ALM had similar prognostic significance.

Clinical and Prognostic Impact of Abnormality Thresholds and Partition Cutoff Values for LA Volumes

The 2005 abnormality threshold for 2DE-derived LA maximal volume[11] was based on normative studies performed in a limited number of individuals free from cardiovascular disease[14-16] and on population-based studies.[17,18] Accordingly, the normal value for LA volume index was established as 22 ± 6 mL/m^2 and LA volume

Table 2 Demographic, clinical, and echocardiographic characteristics of the patients

Variable	Overall (N = 467)
Age, years	61 (46; 72)
Gender, male	316 (67.7)
Height, m	1.70 (1.63; 1.76)
Weight, kg	73 (63; 83)
Body surface area, m^2	1.84 (1.70; 1.98)
Body mass index, kg/m^2	24.9 (22.8; 27.6)
Heart rate, bmp	68 (60; 76)
Systolic blood pressure, mm Hg	120 (110; 140)
Diastolic blood pressure, mm Hg	75 (70; 80)
Sinus rhythm	467 (100)
Smoking	170 (36.4)
Diabetes	67 (14.3)
Dyslipidemia	196 (42.0)
Family history of CAD	111 (23.8)
Hypertension	262 (56.1)
CAD	163 (34.9)
LA volume, MOD biplane, mL	71 (55; 100)*
LA volume, ALM biplane, mL	76 (58; 106)*
LA volume index, MOD, mL/m^2	38.55 (30.11; 55.15)†
LA volume index, ALM, mL/m^2	40.77 (32.33; 57.66)†
3DE LV end-diastolic volume index, mL/m^2	75 (62; 94)
3DE LV end-systolic volume index, mL/m^2	33 (25; 51)
3DE LV ejection fraction, %	55 (43; 62)
3DE LV mass, g	180.5 (146; 210)
2DE LV global longitudinal strain, %	−15.7 (−18.95; −11.8)

Values are reported as median (25th percentile; 75th percentile) or *n* (%). *3DE*, three-dimensional echocardiography; *CAD*, coronary artery disease; *LV*, left ventricular.
**P* = .0215.
†*P* = .0150.

beyond 1 SD of the mean (i.e., higher than 28 mL/m^2) was considered as enlarged.[11] The choice to use 1 SD of the mean value to define LA dilation was based on the results of previous prognostic studies showing that LA volume larger than 28 mL/m^2 predicted adverse cardiac events.[19,20] However, it was clear that the abnormality threshold of 28 mL/m^2 was very sensitive but showed suboptimal specificity.[21] Larger LA normal range, while being less sensitive, would be a stronger marker in distinguishing normal versus pathological LA. In fact, a different cutoff value (34 mL/m^2) was used to identify LA dilation in the algorithm proposed to evaluate diastolic function of the left ventricle and elevated filling pressure.[22]

The abnormality threshold suggested in the new 2015 ASE/EACVI recommendations for cardiac chamber quantitation[10] was obtained from the results of recent normative studies and large population databases including more than 2,500 subjects[8,9,23,24] with the mean calculated LA volume of 25 ± 4.5 mL/m^2 (previously, it was 22 ± 6 mL/m^2). An abnormality threshold value of 2 SD of the mean was adopted, which has resulted in an upper limit of normality for LA volume index of 34 mL/m^2.[10] The same upper limit of normality has been confirmed in a recent study performed on healthy volunteers too.[12] Additionally, the increase in mean LA volume and, consequently, the upper limit of normality might have been caused by the use of atrial-focused, rather than standard four- and two-chamber apical views in the majority of recent studies, which resulted in larger LA volumes.[25] Furthermore, in the 2015 ASE/EACVI recommendations, severity partition cutoff values to identify moderate and severe LA dilation were determined by experience-based consensus of expert opinions.[10] However, the prognostic power of the new cutoffs has never been tested. This aspect is particularly important since the larger threshold and partition cutoff values are expected to reduce the number of patients with enlarged LA and downgrade the degree of LA dilation.

Our data confirm the expected effect of larger abnormality thresholds and severity cutoff values of LA volume on patients' classification: an increase in the number of patients with normal LA and a downgrading of the severity in those with enlarged LA. By measuring LA volume with the MOD and using 2015 cutoff values[10] the severity of the LA enlargement was downgraded in 48% of the patients diagnosed with an enlarged LA according to 2005 recommendations.[11] All patients (65/65) who would have been diagnosed with mildly enlarged LA and 16% (13/81) of those who would have been diagnosed with moderately enlarged LA in 2005 were reclassified as normal using the 2015 cutoff values.[10]

In a number of previous studies, 2DE-derived maximal LA volume has been shown to be a powerful prognostic predictor in various cardiac disease states.[1,4-6,26] However, the methods used in these studies for measuring maximal LA volume were not uniform: some investigators used biplane MOD,[3,5,7] some applied biplane ALM,[4,6,26] and others used different formulas and the no-longer-recommended single-plane algorithms.[1,2] Similar variability can be found for the cutoff values of LA volume used to demonstrate the prognostic significance of LA enlargement in these studies: they varied widely from ≥24 mL/m^2 to ≥45 mL/m^2 to predict mortality[3,5] and up to >50 mL/m^2 to predict rehospitalization for heart failure.[27]

There have been conflicting views on the association between LA enlargement and increasing age.[12,16,28] In a large study, LA maximal volumes measured by 2DE were not significantly different in individuals of different ages, suggesting LA enlargement should not be considered a part of a normal aging process.[16] In healthy elderly individuals, observed minor changes in atrial size are likely to be caused by functional compensatory mechanisms aiming to overcome the normal age-related decrease in left ventricular relaxation. However, more significant changes are likely to be related to "subclinical" pathological processes.[29]

Our data show that the increased abnormality threshold and severity partition cutoff values for maximal LA volume index in the new 2015 ASE/EACVI recommendations[10] maintain prognostic significance, irrespective of the method used to calculate LA volume by 2DE. We did not document any significant stepwise increase in the risk of mortality with each increment of LA volume category from normal to mildly or moderately dilated. The relatively limited number of events and the small sample of patients with moderate enlargement of the LA according to the 2015 cutoff values (41 [8.8%]) and those with mild LA enlargement according to the 2005 cutoff values (65 [13.9%]) might not have provided sufficient power to detect an association between LA volume and outcomes in these subgroups. Larger studies with longer follow-up might be needed to prove a graded risk of mortality.

Clinical and Prognostic Impact of the Methods Used to Calculate LA Volume

In the current and the previous recommendations for chamber quantification, two different methods (MOD and ALM) for 2DE LA volume calculation have been suggested. Despite the fact that

Table 3 Clinical and echocardiographic characteristics of the patients according to outcome

Variable	Death of any cause	Survivors	*P* value
Number of patients	59 (12.6)	408 (87.4)	
Age, years	75 (62; 80)	59 (45; 70)	**<.0001**
Gender, male	36 (61.0)	280 (68.6)	.2440
Body surface area, m^2	1.79 (1.59; 1.99)	1.84 (1.71; 1.98)	.1817
Body mass index, kg/m^2	24.7 (22.1; 28.33)	25 (22.8; 27,6)	.5727
Systolic blood pressure, mm Hg	110 (102.5; 140)	120 (110; 138.5)	.2388
Diastolic blood pressure, mm Hg	70 (70; 80)	75 (70; 80)	.4263
Smoking	19 (32.2)	151 (37.0)	.4743
Diabetes	13 (22.0)	54 (13.2)	.0715
Dyslipidemia	26 (44.1)	170 (41.7)	.7273
Family history of CAD	8 (13.6)	103 (25.2)	.0505
Hypertension	35 (59.3)	227 (55.6)	.5929
CAD	26 (44.1)	137 (33.6)	.1142
LA volume index, MOD, mL/m^2	57.14 (37.5; 77.39)	37.43 (29.66; 50.51)	**<.0001**
LA volume index, ALM, mL/m^2	57.78 (40.48; 81.93)	39.61 (31.85; 53.91)	**<.0001**
3DE LV EDV index, mL/m^2	77 (62; 114.5)	75 (62; 93)	.1661
3DE LV ESV index, mL/m^2	40 (24.5; 74.5)	33 (25; 48)	.1040
3DE LV EF, %	50 (31; 61.5)	56 (45; 62)	**.0252**
3DE LV mass, g	170 (140.5; 224.5)	181 (146; 209)	.8729
2DE LV global longitudinal strain, %	−15 (−17.9; −9.5)	−15.8 (−19; −12.13)	**.0265**
3DE RV EDV index, mL/m^2	98.4 (75.8; 112.9)	77.7 (66.1; 93.7)	**.0007**
3DE RV ESV index, mL/m^2	58 (44.4; 76.3)	39.3 (32.5; 49.3)	**<.0001**
3DE RV EF, %	37.6 (29.7; 44.7)	48.8 (45; 52.5)	**<.0001**
Tricuspid annular plane systolic excursion, mm	14 (12.3; 19.8)	21 (18.5; 25)	**<.0001**
Systolic pulmonary artery pressure, mm Hg	43 (31; 52)	27 (21; 36)	**<.0001**

3DE, Three-dimensional echocardiography; *CAD*, coronary artery disease; *EDV*, end-diastolic volume; *EF*, ejection fraction; *ESV*, end-systolic volume; *LV*, left ventricular; *RV*, right ventricular.
Values are reported as median (25th percentile; 75th percentile) or *n* (%). The bold font indicates statistical significance.

biplane MOD incorporates fewer geometric assumptions, theoretically is more accurate, and is considered the preferred method to measure LA volume, biplane ALM is also acknowledged in the new guidelines as a reliable alternative that can be used in clinical practice.[10]

Our results are in agreement with the previous studies that have demonstrated that values of LA volume measured using ALM are slightly larger compared with those obtained using MOD within the same endocardial tracing.[8,30-32] Such discrepancies could be explained by differences between the geometric assumptions and the mathematical models on which these methods are based. There are two main geometrical assumptions included in both formulas. First, 2DE calculations are based on the fact that the four-chamber and the two-chamber views are orthogonal and that they are crossing the LA cavity through its center, which is not necessarily true in actual patients. Second, both methods assume an oval shape of the LA in the cross-sectional plane; however, in reality the LA may be quite irregular and asymmetrical both in normal and dilated atria.[12]

Biplane ALM calculated LA volume applying the following equation:

$$8/3\pi\ [(A1 \cdot A2)/L],$$

where $A1$ and $A2$ are the LA areas measured in the apical two- and four-chamber views and L is the distance from the midpoint of the mitral annulus plane to the superior margin (Figure 2).[10] In ideal circumstances, the LA lengths in both orthogonal apical views should be nearly equal. However, in real life a mild discrepancy may exist due to the variability of chamber orientation and foreshortening. The use of the longer, the shorter, and the average of the two lengths obtained from the four-chamber and two-chamber views has been studied.[33] Logically, using the longer of the two lengths will yield a slightly smaller volume, while the shorter length will result in a slightly larger LA volume calculation. Current guidelines have recommended the use of the shorter of the two lengths,[10] which minimizes the underestimation of LA volume by 2DE when compared with reference techniques.[31]

MOD (also known as the disk summation technique) is based on the premise that an LA cavity can be divided into a series of stacked oval disks with a known height and orthogonal minor and major axes derived from LA planimetry in two orthogonal views. MOD applies the following equation:

$$\pi/4(h) \sum (D1)(D2),$$

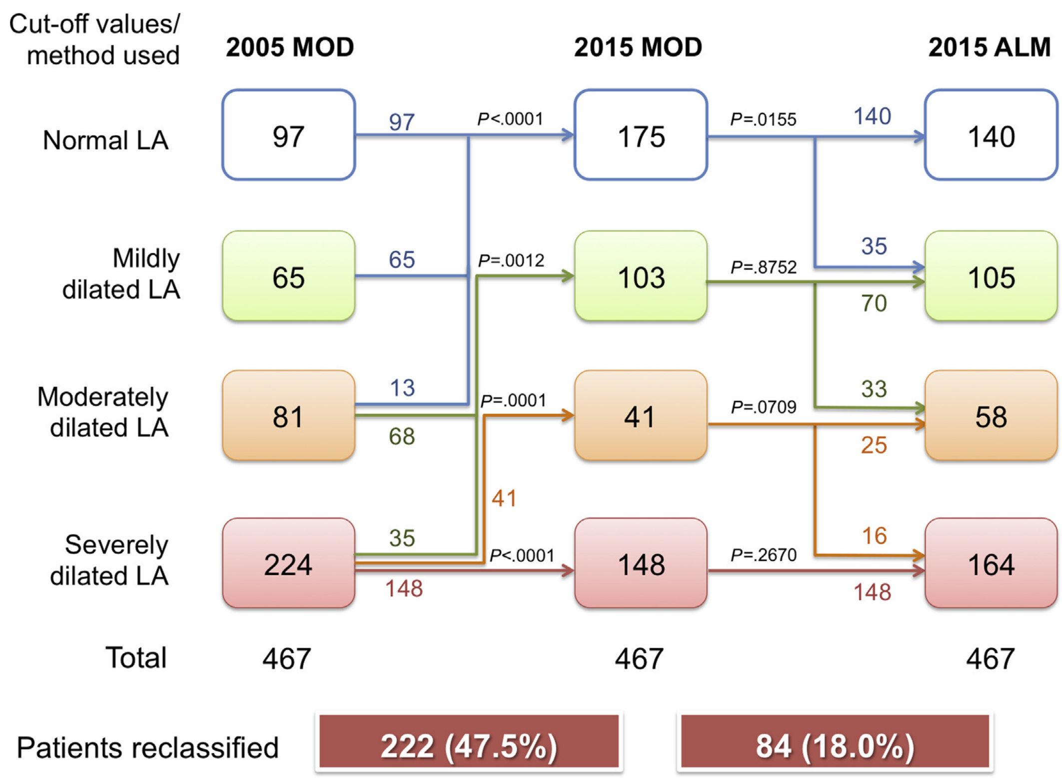

Figure 3 Reclassification of LA volume abnormality applying different cutoff values and different methods of its assessment. Use of abnormality thresholds and severity partition cutoffs suggested by ASE/EAE in 2005 (column 2005 MOD) and by ASE/EACVI in 2015 (column 2015 MOD) led to significant reclassification of all patient subgroups. Applying ALM caused a significant decrease in the number of patients with normal LA volume index (column 2015 ALM) in comparison with MOD (column 2015 MOD).

where h is the height of the disks and $D1$ and $D2$ are orthogonal minor and major transverse axes of each disk (Figure 2).[10]

Important advantages of the MOD are the facts that it is based on the computerized summation of disks' volumes for the total volume and that it does not require a specific linear dimension for LA volume calculation, such as the shortest LA length in the ALM.[33] The latter might be a source of systematic error in LA volume measured by these two methods since the input of the shortest length in the formula denominator may result in larger volumes.

Earlier studies reported a trend toward larger discrepancies between ALM and MPD with increasing LA volume.[34] However, in a recent study analyzing the determinants of discrepancies between different 2DE methods for the assessment of maximal LA volume, it was shown that the LA geometry, rather than LA size, was related to inconsistences between ALM and MOD results.[32] In multivariable analysis, the LA geometry index (calculated as the ratio between the LA area measured in the four-chamber view and that of a theoretical regular ellipse having the same diameters) remained the only independent predictor of the difference between LA volumes calculated by two methods. Only after exclusion of this index from analysis did average LA volume emerge as the only independent predictor.[32]

Importantly, LA volumes assessed by 2DE are different from those provided by three-dimensional echocardiography, computed tomography, and cardiac magnetic resonance and cannot be used interchangeably.[12,35,36] Since ALM tends to provide greater LA volumes compared with MOD, it was shown to have a better agreement with LA volumes obtained from reference techniques. Thus, underestimation of LA volume measured by ALM was less evident than that measured by MOD in comparison with three-dimensional echocardiography (mean relative difference −10% vs −16%, respectively),[32] computed tomography (−33% vs −39%, respectively),[31] and cardiac magnetic resonance (−19% vs −24%, respectively).[37] It was also demonstrated that underestimation of LA volume by both 2DE methods in comparison with three-dimensional echocardiography was more significant in patients with LA shape that deviates from that of a regular ellipse, supporting a strong influence of LA geometry on accuracy of LA assessments by 2DE.[32]

Although ALM has been reported to provide larger values of LA volume, abnormality threshold and severity cutoff values for LA volume are not specified according to the 2DE method used to calculate it. Our results confirm that ALM provides slightly (however, statistically significant) larger LA volumes than MOD and are in agreement with the results of the NORRE study suggesting a higher upper limit of normal for LA volume index measured using ALM (41.9 mL/m^2 in men and 41.5 mL/m^2 in women with ALM vs 37.0 mL/m^2 in men and 36.9 mL/m^2 in women with MOD).[8] Nevertheless, our data show that, irrespective of the method used to calculate LA volume by 2DE, its association with adverse outcomes is maintained, and it is similar for LA volumes measured with MOD and ALM.

However, the discrepancies in the calculations provided by the two methods and the differences in partition values between the new and previous recommendations for cardiac chamber quantitation may cause some degree of confusion. Figure 2 illustrates an example of a patient whose LA, according to the 2015 ASE/EACVI recommendations, would have been classified as normal when measured by MOD, mildly dilated when measured by ALM, and moderately dilated if the 2005 ASE/EAE cutoff values were applied. This potential inconsistency of disease staging may negatively affect the clinical

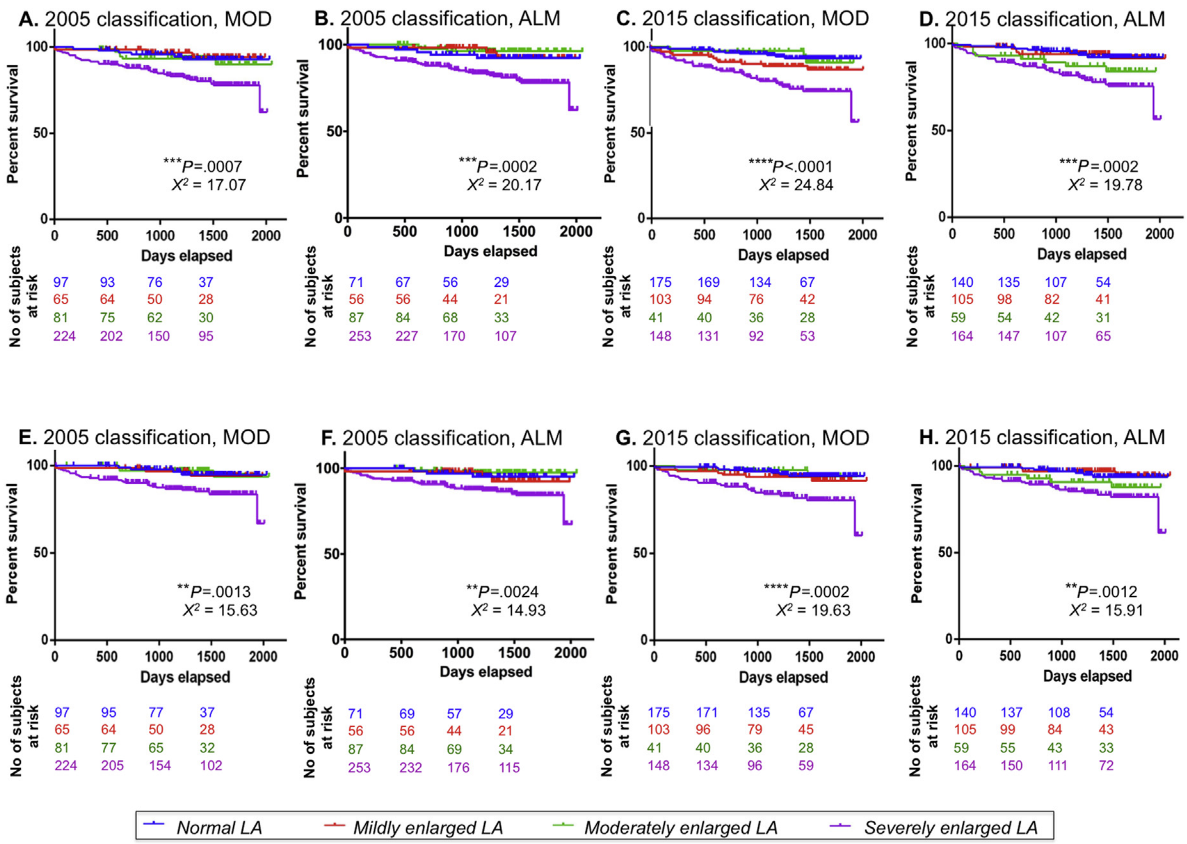

Figure 4 Kaplan-Meier survival analysis for all-cause mortality **(A-D)** and cardiac death **(E-H)**. Graded relationship between Kaplan-Meier cumulative event-free survival and categorical increment of indexed LA volume classified using cutoff values recommended in 2005 versus 2015 and measured by MOD versus ALM. The colors of the numbers of subjects at risk correspond to the relevant groups.

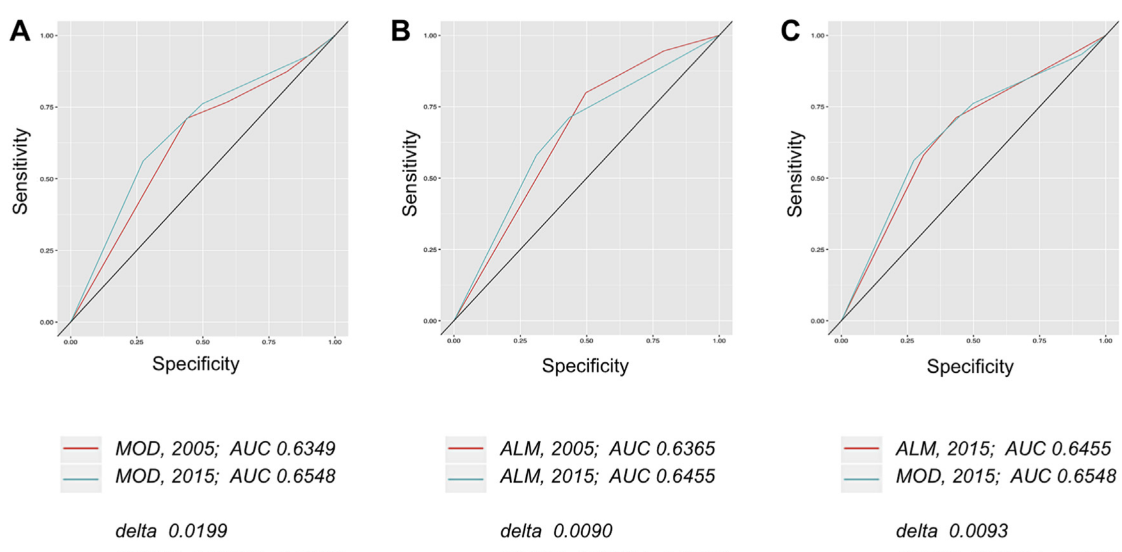

Figure 5 Comparison of receiver-operator characteristic curves for the overall performance of LA volume for the prediction of all-cause mortality using different abnormality thresholds (recommended in 2005 vs 2015, panels **A** and **B**) and measured by different methods (MOD vs ALM, panel **C**). *AUC*, Area under the curve.

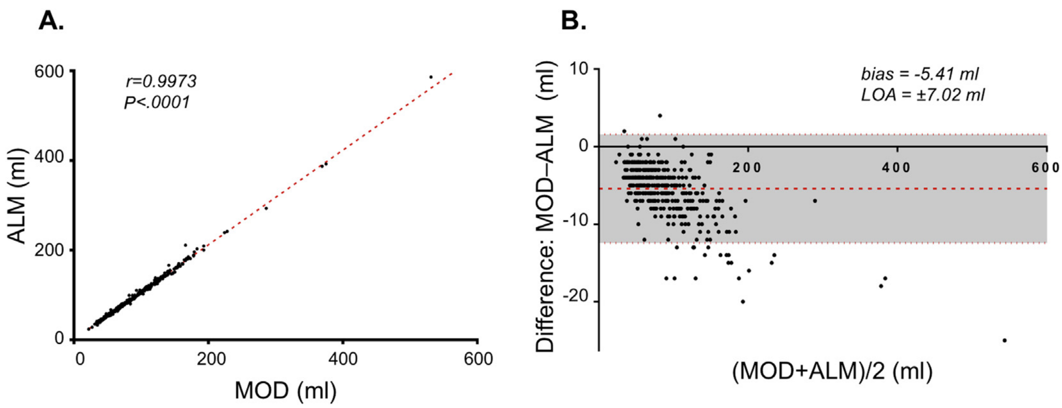

Figure 6 Comparisons of maximum LA volume measured by MOD versus ALM using Spearman correlation **(A)** and Bland-Altman **(B)** analyses. *LOA*, Limits of agreement.

management of the patients, especially when precise LA size assessment is clinically relevant (during follow-up after transcatheter interventions; in patients with atrial arrhythmias, heart failure, or arterial hypertension; and for the assessment of patients' prognosis).[38-40]

Finally, the new ASE/EACVI recommendations for the evaluation of left ventricular diastolic function by echocardiography included LA dilation (maximal LA volume index >34 mL/m^2) in a list of four recommended variables for identifying diastolic dysfunction,[41] without specifying which method should be used to calculate LA volume by 2DE. According to our results, using the same LA tracing and just switching from MOD to ALM will change the LA volume index from <34 mL/m^2 to >34 mL/m^2 in 20% of patients (35/175). This may have a significant impact in a clinical setting as diastolic dysfunction of the left ventricle may prompt additional investigations or influence clinical management.

A standardized approach to LA volume calculation by 2DE would be crucial for reproducible LA measurements and consistent communication regarding LA size among different echocardiographic laboratories and between the echocardiographic laboratory and clinicians. Meanwhile, we would suggest clearly stating the method used to calculate maximal LA volume in the echocardiographic report to allow physicians better interpretation of data. When clinically significant differences in the LA volume are noted between echocardiographic studies performed in different laboratories or by different operators during patients' follow-up, in the absence of clinical changes, it would be advisable to perform side-by-side comparison of the LA views and remeasure LA volume using the same method and technique.

Study Limitations

Our study cohort was referral based, and because the study protocol required the acquisition of three-dimensional echocardiography data sets of the cardiac chambers, it included only patients with regular sinus rhythm at the time of echocardiographic exam (including those with history of arrhythmias), so the extent to which the results can be extrapolated to other patient groups is not known. Additionally the areas under the curves for LA performance in prediction of mortality were only moderately strong, suggesting that other factors may contribute to the patients' outcomes. However, since the aim of this study was to assess neither the absolute accuracy of LA volume calculations by 2DE nor the independent prognostic value of LA enlargement (which had been extensively studied before), but rather

Table 4 Results of reproducibility analysis of repeated measurements evaluated using intraclass correlation (two-way mixed, single, absolute agreement model) and Bland-Altman plot

	Intraobserver	Interobserver
LA volume, MOD, mL	0 ± 2.6 (0.999; 0.998-0.999)	0.5 ± 3.3 (0.998; 0.997-0.999)
LA volume, ALM, mL	0.7 ± 3.1 (0.999; 0.998-0.999)	0.1 ± 4.1 (0.998; 0.996-0.998)

Values are expressed as bias ± SD (intraclass correlation; 95% CI).

was to compare in the same patient the clinical and prognostic effects of the new abnormality threshold and severity partition cutoff values for 2DE-derived LA maximal volume introduced in the 2015 ASE/EACVI recommendations for chamber quantitation and of the different methods (MOD and ALM) for LA volume calculation, our conclusions maintain their clinical relevance.

For the same reasons stated above, we did not make any attempt to assess the relative accuracy of MOD and ALM methods to measure LA volumes by comparing the echocardiographic measurements with measurements performed with a reference modality such as cardiac magnetic resonance. The accuracy of the two methods was not the aim of our study. Our study was designed to assess the clinical and prognostic effects of changing the upper limit of normality and partition values for LA dilation severity using clinically established and routinely used 2DE algorithms.

Patient prognosis was assessed in terms of all-cause mortality and cardiac deaths in order to have easily identifiable and unequivocal end points. Although it would have been interesting to assess also the predictive power of LA volumes versus incidence of new episodes of atrial fibrillation and/or rehospitalization for heart failure, the latter are more difficult to be unequivocally identified retrospectively.

CONCLUSIONS

In a cohort of patients with various cardiac conditions, the application of the new abnormality threshold and severity partition values recommended by ASE/EACVI in 2015 has led to significant reclassification

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of half of the patients, with a larger number of those having normal left atrium (LA) and a downgrade of the severity of the LA enlargement in the others.

The ALM provided significantly larger LA volumes than the MOD, increasing the degree of LA enlargement in 18% of patients and highlighting the fact that the two methods cannot be used interchangeably during the patient's follow-up.

The 2DE-derived LA volume index was confirmed to be a significant factor associated with mortality, regardless of the method used to calculate it, with the 2015 partition values providing noninferior prognostic significance in predicting patients' outcome when compared with the 2005 values.

REFERENCES

1. Sabharwal N, Cemin R, Rajan K, Hickman M, Lahiri A, Senior R. Usefulness of left atrial volume as a predictor of mortality in patients with ischemic cardiomyopathy. Am J Cardiol 2004;94:760-3.
2. Rossi A, Cicoira M, Zanolla L, Sandrini R, Golia G, Zardini P, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 2002;40:1425.
3. Carluccio E, Dini FL, Biagioli P, Lauciello R, Simioniuc A, Zuchi C, et al. The "Echo Heart Failure Score": an echocardiographic risk prediction score of mortality in systolic heart failure. Eur J Heart Fail 2013;15:868-76.
4. Poulsen MK, Dahl JS, Henriksen JE, Hey TM, Hoilund-Carlsen PF, Beck-Nielsen H, et al. Left atrial volume index: relation to long-term clinical outcome in type 2 diabetes. J Am Coll Cardiol 2013;62:2416-21.
5. Leung DY, Chi C, Allman C, Boyd A, Ng AC, Kadappu KK, et al. Prognostic implications of left atrial volume index in patients in sinus rhythm. Am J Cardiol 2010;105:1635-9.
6. Tsang TSM, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018-23.
7. Wu VC-C, Takeuchi M, Kuwaki H, Iwataki M, Nagata Y, Otani K, et al. Prognostic value of LA volumes assessed by transthoracic 3D echocardiography: comparison with 2D echocardiography. JACC Cardiovasc Imaging 2013;6:1025-35.
8. Kou S, Caballero L, Dulgheru R, Voilliot D, De Sousa C, Kacharava G, et al. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. Eur Heart J Cardiovasc Imaging 2014;15:680-90.
9. Aurigemma GP, Gottdiener JS, Arnold AM, Chinali M, Hill JC, Kitzman D. Left atrial volume and geometry in healthy aging: the Cardiovascular Health Study. Circ Cardiovasc Imaging 2009;2:282-9.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, 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. J Am Soc Echocardiogr 2015;28:1-39.
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiograph. J Am Soc Echocardiogr 2005;18:1440-63.
12. Badano LP, Miglioranza MH, Mihaila S, Peluso D, Xhaxho J, Marra MP, et al. Left atrial volumes and function by three-dimensional echocardiography: reference values, accuracy, reproducibility, and comparison with two-dimensional echocardiographic measurements. Circ Cardiovasc Imaging 2016;9:e004229.
13. Muraru D, Badano LP, Peluso D, Dal Bianco L, Casablanca S, Kocabay G, et al. Comprehensive analysis of left ventricular geometry and function by three-dimensional echocardiography in healthy adults. J Am Soc Echocardiogr 2013;26:618-28.
14. Gutman J, Wang YS, Wahr D, Schiller NB. Normal left atrial function determined by 2-dimensional echocardiography. Am J Cardiol 1983;51:336-40.
15. Wang Y, Gutman JM, Heilbron D, Wahr D, Schiller NB. Atrial volume in a normal adult population by two-dimensional echocardiography. Chest 1984;86:595-601.
16. Thomas L, Levett K, Boyd A, Leung DYC, Schiller NB, Ross DL. Compensatory changes in atrial volumes with normal aging: is atrial enlargement inevitable? J Am Coll Cardiol 2002;40:1630-5.
17. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. J Am Coll Cardiol 2003;41:1036-43.
18. Vasan RS, Larson MG, Levy D, Evans JC, Benjamin EJ. Distribution and categorization of echocardiographic measurements in relation to reference limits: the Framingham Heart Study: formulation of a height- and sex-specific classification and its prospective validation. Circulation 1997;96:1863-73.
19. 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.
20. Takemoto Y, Barnes ME, Seward JB, Lester SJ, Appleton CA, Gersh BJ, et al. Usefulness of left atrial volume in predicting first congestive heart failure in patients > or = 65 years of age with well-preserved left ventricular systolic function. Am J Cardiol 2005;96:832-6.
21. Tsang MYC, Barnes ME, Tsang TSM. Left atrial volume: clinical value revisited. Curr Cardiol Rep 2012;14:374-80.
22. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.
23. Nistri S, Galderisi M, Ballo P, Olivotto I, D'Andrea A, Pagliani L, et al. Determinants of echocardiographic left atrial volume: implications for normalcy. Eur J Echocardiogr 2011;12:826-33.
24. Yamaguchi K, Tanabe K, Tani T, Yagi T, Fujii Y, Konda T, et al. Left atrial volume in normal Japanese adults. Circ J 2006;70:285-8.
25. Kebed K, Kruse E, Addetia K, Ciszek B, Thykattil M, Guile B, et al. Atrial-focused views improve the accuracy of two-dimensional echocardiographic measurements of the left and right atrial volumes: a contribution to the increase in normal values in the guidelines update. Int J Cardiovasc Imaging 2016;33:209-18.
26. AlJaroudi W, Alraies MC, Halley C, Rodriguez L, Grimm RA, Thomas JD, et al. Effect of age, gender, and left ventricular diastolic function on left atrial volume index in adults without known cardiovascular disease or risk factors. Am J Cardiol 2013;111:1517-22.
27. Ristow B, Ali S, Whooley MA, Schiller NB. Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul Study). Am J Cardiol 2008;102:70-6.
28. Nikitin NP, Witte KKA, Thackray SDR, Goodge LJ, Clark AL, Cleland JGF. Effect of age and sex on left atrial morphology and function. Eur J Echocardiogr 2003;4:36-42.
29. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J 2008;156:1056-64.
30. Ujino K, Barnes ME, Cha SS, Langins AP, Bailey KR, Seward JB, et al. Two-dimensional echocardiographic methods for assessment of left atrial volume. Am J Cardiol 2006;98:1185-8.
31. Al-Mohaissen MA, Kazmi MH, Chan KL, Chow BJW. Validation of two-dimensional methods for left atrial volume measurement: a comparison of echocardiography with cardiac computed tomography. Echocardiography 2013;30:1135-42.
32. Ballo P, Nistri S, Galderisi M, Mele D, Rossi A, Dini FL, et al. Determinants of discrepancies between two-dimensional echocardiographic methods for assessment of maximal left atrial volume. Eur Heart J Cardiovasc Imaging 2017;18:584-602.
33. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size. Physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357-63.

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34. Jiamsripong P, Honda T, Reuss CS, Hurst RT, Chaliki HP, Grill DE, et al. Three methods for evaluation of left atrial volume. Eur J Echocardiogr 2008;9:351-5.
35. Avelar E, Durst R, Rosito GA, Thangaroopan M, Kumar S, Tournoux F, et al. Comparison of the accuracy of multidetector computed tomography versus two-dimensional echocardiography to measure left atrial volume. Am J Cardiol 2010;106:104-9.
36. Kuhl JT, Lonborg J, Fuchs A, Andersen MJ, Vejlstrup N, Kelbaek H, et al. Assessment of left atrial volume and function: a comparative study between echocardiography, magnetic resonance imaging and multi slice computed tomography. Int J Cardiovasc Imaging 2012;28:1061-71.
37. Rodevand O, Bjornerheim R, Ljosland M, Maehle J, Smith HJ, Ihlen H. Left atrial volumes assessed by three- and two-dimensional echocardiography compared to MRI estimates. Int J Card Imaging 1999;15:397-410.
38. Toprak C, Kahveci G, Kilicgedik A, Pala S, Kirma C, Tabakci MM, et al. Left atrial remodeling in patients undergoing percutaneous mitral valve repair with the MitraClip system: an advanced echocardiography study. Echocardiography 2016;33:1504-11.
39. Casaclang-Verzosa G, Gersh BJ, Tsang TSM. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. J Am Coll Cardiol 2008;51:1-11.
40. Gerdts E, Wachtell K, Omvik P, Otterstad JE, Oikarinen L, Boman K, et al. Left atrial size and risk of major cardiovascular events during antihypertensive treatment: losartan intervention for endpoint reduction in hypertension trial. Hypertension 2007;49:311-6.
41. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.