Effect of Regional Upper Septal Hypertrophy on Echocardiographic Assessment of Left Ventricular Mass and Remodeling in Aortic Stenosis

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Background: Transthoracic echocardiography (TTE) is the reference method for evaluation of aortic stenosis (AS), and it is extensively used to quantitate left ventricular (LV) mass and volumes. Regional upper septal hypertrophy (USH) or septal bulge is a frequent finding in patients with AS and may lead to overestimation of LV mass when using linear measurements. The objective of this study was to compare estimates of LV mass obtained by two-dimensional transthoracic echocardiographic LV dimensions measured at different levels of the LV cavity with those obtained by cardiovascular magnetic resonance (CMR).

Methods: One hundred six patients (mean age, 63 ± 15 years; 68% men) with AS were included in this subanalysis of the PROGRESSA study. Two-dimensional transthoracic echocardiographic measurements of LV dimensions were obtained at the basal level (BL; as recommended in guidelines), immediately below the septal bulge (BSB), and at a midventricular level (ML). Regional USH was defined as a basal interventricular septal thickness ≥ 13 mm and >1.3 times the thickness of the septal wall at the ML. Agreement between transthoracic echocardiographic and CMR measures was evaluated using Bland-Altman analysis.

Results: The distribution of AS severity was mild in 23%, moderate in 57%, and severe in 20% of patients. Regional USH was present in 28 patients (26%). In the whole cohort, two-dimensional TTE overestimated LV mass (bias: BL, +60 ± 31 g; BSB, +59 ± 32 g; ML, +54 ± 32 g; $P = .02$). The biplane Simpson method slightly but significantly underestimated LV end-diastolic volume (bias −10 ± 20 mL, $P < .001$) compared with CMR. Overestimation of LV mass was more marked in patients with USH when measuring at the BL and was significantly lower when measuring LV dimensions at the ML ($P < .025$ vs BL and BSB).

Conclusions: Two-dimensional TTE systematically overestimated LV mass and underestimated LV volumes compared with CMR. However, the bias between TTE and CMR was less important when measuring at the ML. Measurements at the BL as suggested in guidelines should be avoided, and measurements at the ML should be preferred in patients with AS, especially in those with USH. (J Am Soc Echocardiogr 2020;■:■-■.)

Keywords: Upper septal hypertrophy, Aortic stenosis, Doppler echocardiography, Cardiovascular magnetic resonance, Left ventricular mass, Left ventricular remodeling

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Abbreviations

2D = Two-dimensional

AS = aortic stenosis

ASE = American Society of Echocardiography

BL = Basal level

BSB = Below the septal bulge

CH = concentric hypertrophy

CMR = Cardiovascular magnetic resonance

CR = concentric remodeling

EH = Eccentric hypertrophy

IVS = Interventricular septal

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVH = Left ventricular hypertrophy

LVID = Left ventricular internal diameter

ML = Midventricular location

MVR = Left ventricular mass/volume ratio

PW = Posterior wall

RWTR = Relative wall thickness ratio

TTE = Transthoracic echocardiography

USH = Upper septal hypertrophy

Aortic stenosis (AS) is characterized by progressive narrowing of the aortic valve orifice, which imposes a pressure overload on the left ventricle and therefore leads to left ventricular (LV) hypertrophy.[1,2] Accurate estimation of LV mass by transthoracic echocardiography (TTE) is key to assess the presence and severity of LV hypertrophy (LVH) and thereby enhance risk stratification in patients with AS.[3-5] Beyond simple estimates of LV mass, adverse LV remodeling has also shown to have an impact on prognosis.[6-8] The most frequently used method in clinical practice to calculate LV mass is the modified formula of the American Society of Echocardiography (ASE),[9,10] which incorporates the end-diastolic LV dimensions and septal and posterior wall (PW) thickness measured on two-dimensional (2D) or M-mode TTE in the parasternal long-axis view. The ASE guidelines recommend measuring the LV dimensions at the base of the left ventricle (i.e., at the tip of the mitral valve leaflets). The ASE formula, however, assumes that the left ventricle has an ellipsoid shape with a 2:1 long axis/short axis ratio and a symmetric distribution of hypertrophy.[9,11] However, patients with AS often harbor asymmetric LVH[12,13] with regional hypertrophy and bulging of the basal interventricular septum.[14,15] This feature, often also called subaortic ventricular septal bulge, sigmoid septum, or regional or discrete upper septal hypertrophy (USH),[16-18] is associated with hypertensive disease,[17] older age,[18] and AS.[14,15] Its prevalence varies according to the different definitions, and its prognostic value remains unclear.[16] When USH is present, measuring LV dimensions at the basal level (BL; i.e., at the tip of the mitral leaflets) as recommended in the ASE guidelines[9,10] may overestimate LV mass. Hence, in the presence of prominent USH, it may be preferable to measure LV dimensions immediately below the septal bulge (BSB) or even more apically (i.e., at a midventricular level [ML]), as recent evidence suggests.[19] Indeed, LV diameter may be much smaller and interventricular thickness much larger at the BL compared with BSB or the ML.

We hypothesized that measuring LV dimensions BSB or at the ML would improve agreement between 2D TTE and cardiac magnetic resonance (CMR) for measures of LV mass in patients with AS, especially in those with regional USH. The objective of this study was to compare the accuracy of LV mass obtained with LV dimensions measured on 2D TTE at the BL (as recommended in the guidelines) compared with more apical levels, using CMR as the reference method.

METHODS

Patient Population

We retrospectively reviewed the echocardiographic and CMR studies of 106 patients with AS and preserved LV ejection fraction (LVEF) who were prospectively recruited in the PROGRESSA study (NCT01679431) between 2008 and 2014. All patients underwent comprehensive Doppler echocardiographic studies and CMR within a period of ≤3 months. Detailed inclusion and exclusion criteria were previously reported.[20] Briefly, patients ≥18 years of age with peak aortic velocity >2.0 m/sec were included. Patients were excluded if they had symptomatic AS, moderate to severe aortic regurgitation or mitral valve disease (mitral stenosis or regurgitation), or LVEF < 50% or if contraindications to contrast-enhanced CMR were present. The study was approved by the ethics committee of the Quebec Heart and Lung Institute, and patients provided written informed consent at the time of inclusion.

Doppler Echocardiography

All Doppler echocardiographic examinations were acquired using commercially available ultrasound machines and according to current recommendations of the ASE.[9,10,21] Images were analyzed offline in a core laboratory using a commercially available software (TomTec Imaging Systems, Bayern, Germany) by experienced readers blinded to clinical and CMR data. Minor-axis dimensions (LV internal diameter [LVID] at end-diastole and end-systole and interventricular septal [IVS] thickness and PW thickness) were measured in parasternal long axis using 2D images at three different levels: (1) the BL (i.e., at the level of the mitral valve leaflet tips), (2) BSB (just apical to the septal bulge), and (3) the ML (Figure 1). The traditional BL was visually identified at the mitral leaflet tips. The BSB level was defined as the point immediately distal to the basal "septal bulge" (i.e., isolated USH). In patients in whom no USH was evident visually, measurement was made at the intersection between the basal and midventricular portions. Finally, the ML was identified as the true maximal diameter of the LV cavity.

LV mass was calculated using the modified ASE formula[9,22]:

$$LVM = 0.80 \times 1.04 \times \left[(\text{IVS thickness} + \text{LVID} + \text{PW thickness})^3 - \text{LVID}^3\right] + 0.6\ \text{g}.$$

HIGHLIGHTS

- Guidelines suggest TTE linear measurements be made at the basal level.
- USH in AS may overestimate LV mass measured at basal level.
- LV mass was measured at base, below septal bulge and mid-ventricular, and compared with CMR.
- Measurements at midventricular level showed best agreement with CMR.

LV volumes and LVEF were measured in apical four- and two-chamber views using the biplane Simpson method. Special care was taken to avoid apical foreshortening. LVH was defined as an indexed LV mass > 115 g/m^2 in men and >95 g/m^2 in women.[9] Relative wall thickness ratio (RWTR) was calculated using the formula RWTR = 2 × PW thickness/LVID. By taking into account both values of LV mass and RWTR, patients were classified into four different patterns using the following criteria[9]: (1) normal pattern: absence of LVH and RWTR ≤ 0.42; (2) eccentric hypertrophy (EH): presence of LVH and RWTR ≤ 0.42; (3) concentric remodeling (CR): absence of LVH and RWTR > 0.42; and (4) concentric hypertrophy (CH): presence of LVH and RWTR > 0.42. Discrete USH was defined as a basal IVS thickness ≥ 13 mm and >1.3 times the thickness of the septal wall at the ML.

Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance examinations were performed using a 1.5-T system (Achieva; Philips Healthcare, Best, the Netherlands). Standard cine images of cardiac morphology and function were acquired. Image analysis was performed offline in a core laboratory using standardized approaches and dedicated software (CMR[42]; Circle Cardiovascular Imaging, Calgary, AB, Canada), blinded to clinical and transthoracic echocardiographic data. LV volume, LV mass, and LVEF were measured by contour analysis of end-diastolic and end-systolic phases of complete short-axis stacks. Papillary muscles and trabeculations were included when measuring mass (equivalent to weighting the left ventricle) and excluded when measuring volumes (equivalent to blood-pool techniques). Basal and apical slices with only myocardium and no discernable ventricular pool were included for LV mass estimation only, in line with current recommendations.[23] LV mass was calculated as the difference between the total epicardial volume (sum of epicardial cross-sectional areas multiplied by the sum of slice thickness and gap between slices) minus the total endocardial volume (sum of endocardial cross-sectional areas multiplied by the sum of slice thickness and interslice gap) multiplied by the specific density of myocardium (1.05 g/mL).

LVH was defined as an indexed LV mass > 81 g/m^2 for women and >85 g/m^2 for men.[24] The LV mass/volume ratio (MVR) has been considered the conceptual equivalent of TTE-derived RWTR in patients with AS.[12,25] Thus, and analogous to classification using TTE, we categorized patients into four patterns of LV remodeling by CMR: (1) normal: normal LV mass and MVR < 1.16; (2) CR: normal LV mass and MVR ≥ 1.16; (3) CH: increased LV mass and MVR ≥ 1.16; and (4) EH: increased LV mass and MVR < 1.16.

Statistical Analysis

Normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous data are expressed as mean ± SD or median (interquartile range) according to their distribution and were compared using one-way analysis of variance or the Kruskal-Wallis test as appropriate. Categorical variables are expressed as percentages. Correlation and agreement (95% CIs) between transthoracic echocardiographic measurements compared with the referent method (CMR) were assessed using Spearman correlations and Bland-Altman comparisons, respectively. A paired Student's *t* test was used to test for any overestimation or underestimation. Comparisons between continuous variables were made using repeated-measures analysis of variance with post hoc Bonferroni

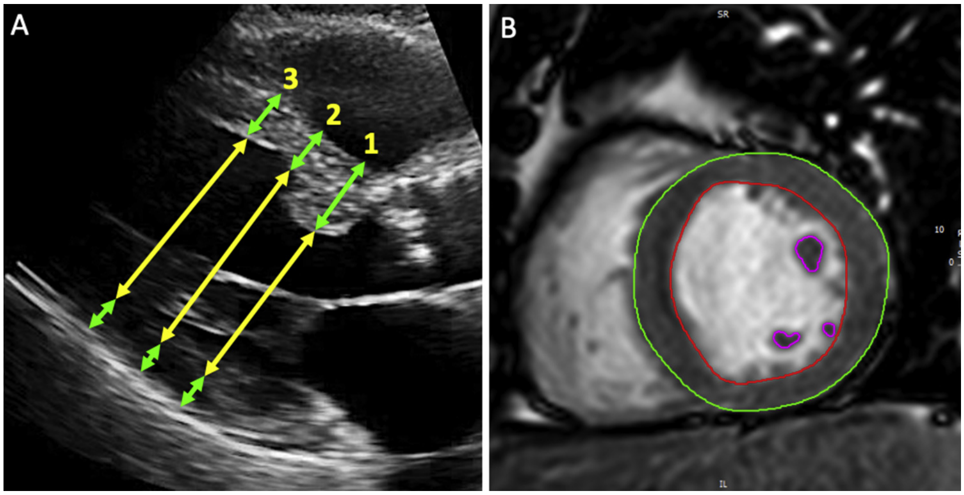

Figure 1 Different methods for LV mass measurement. **(A)** The three different locations for bidimensional LV wall thickness and diameter measurement: (1) BL, (2) BSB, and (3) ML. LV mass was calculated using the ASE formula. **(B)** A midventricular slice from CMR. The *green line* represents the epicardium, the *red line* the endocardium, and the *purple line* the papillary muscle contour (included in LV mass calculation and excluded from the left ventricle).

adjustment for multiple comparisons. Prevalence of LVH according to different methods was analyzed using Cochran's *Q* test. Comparisons of remodeling patterns was made using symmetry and marginal homogeneity tests with Bonferroni adjustment for multiple comparisons (P values < .01 were considered to indicate significance). Multivariate linear regression analysis was performed to identify the variables independently associated with LV mass estimation by each of four different methods (three TTE and one CMR). We performed two models, with and without the presence of USH, to test its influence on different methods of LV mass measurement. Logistic regression analysis was also performed to assess the characteristics associated with the presence of a septal bulge. The variables that were entered in multivariate analyses were those with clinical relevance and/or P values < .10 after univariate analysis. Intraobserver and interobserver variability of TTE and CMR measurements was evaluated by two blinded readers in a subset of 10 randomly selected patients using a two-way mixed-effects model with intraclass correlation coefficients. Statistical analyses were performed using Stata version 15.1 (StataCorp LP, College Station, TX) and SPSS Statistics version 25 (IBM, Armonk, NY). A two-sided P value < .05 was considered to indicate significance.

RESULTS

Baseline Characteristics

One hundred six patients were included. The mean age was 63 ± 15 years, and 72 (68%) were men. Mean body surface area was 1.86 ± 0.20 m^2, mean systolic blood pressure was 132 ± 19 mm Hg, and mean diastolic blood pressure was 75 ± 10 mm Hg. Systemic hypertension was present in 60 patients (57%), dyslipidemia in 66 (62%), and diabetes in 17 (16%). The mean LVEF was 66 ± 6%. Using aortic valve area to assess severity, AS was classified as mild in 24 (23%), moderate in 61 (57%), and severe in 21 (20%) patients. Other baseline characteristics are detailed in Supplemental Table 1.

LV Dimensions

End-diastolic LVID was smallest at the BL, intermediate BSB, and largest at the ML ($P < .001$). There were no significant differences in LVID at end-systole among the three levels. IVS thickness was largest at the BL, intermediate BSB, and lowest at ML (12.2 ± 2.0, 10.7 ± 1.6, and 9.58 ± 1.5 mm, respectively, $P < .001$; Table 1), whereas LV PW thickness was comparable at all three measurement levels (9.5 ± 1.3, 9.6 ± 1.3, and 9.5 ± 1.4 mm, respectively, $P = .47$).

LV Mass

In the whole cohort, LV mass was comparable when calculated at the BL compared with BSB (179.3 ± 42.1 vs 178.4 ± 43.2 g, respectively, $P > .99$), but significantly lower at the ML (173.5 ± 44.4 g, $P = .04$ vs BL; Table 1). Even though correlation with CMR was good, all three transthoracic echocardiographic measurements systematically and markedly overestimated LV mass (BL: bias +60 ± 31 g/m^2, $r = 0.70$; BSB: bias +59 ± 32, $r = 0.71$; ML: bias +54 ± 32, $r = 0.70$; $P < .001$ vs CMR for all). However, overestimation was less pronounced when measured at the ML ($P = .022$ vs BL and $P = .007$ vs BSB; Figures 2 and 3). The prevalence of LVH was comparable between BL and BSB measurements (both 23%), and there was a trend toward a lower prevalence at the ML (17%, $P = .063$). Using CMR criteria, the prevalence of LVH was very low and significantly lower than with TTE (4%, $P < .001$).

LV Volume

Compared with CMR, the biplane Simpson method yielded lower end-diastolic volumes (134 ± 29 vs 124 ± 30 mL, respectively; bias −10 ± 22 mL; $P < .001$) and slightly higher end-systolic volumes (40 ± 17 vs 43 ± 15 mL, respectively; bias +3 ± 14 mL; $P = .037$). Thus, LVEF was higher by CMR than by TTE (71 ± 7% vs 66 ± 6%, respectively, $P < .001$; Figure 3B, Supplemental Figure 1).

Table 1 Echocardiographic and CMR measurements

	TTE					
	BL	BSB	ML	Biplane simpson	CMR	*P*
LVID (diastole), mm	45.4 ± 4.4*,†	47.8 ± 4.4†,‡	49.3 ± 5.0*,‡	—	—	<.001
LVID (systole), mm	27.3 ± 5.0	27.0 ± 5.2	26.9 ± 5.2	—	—	.08
IVS thickness (diastole), mm	12.2 ± 2.0*,†	10.7 ± 1.6†,‡	9.6 ± 1.5*,‡	—	—	<.001
PW thickness (diastole), mm	9.5 ± 1.3	9.6 ± 1.3	9.5 ± 1.4	—	—	.47
LV end-diastolic volume, mL	—	—	—	124 ± 30	134 ± 29	<.001
LV end-systolic volume, mL	—	—	—	43 ± 15	40 ± 17	.037
Absolute LV mass, g	179.3 ± 42.1†	178.4 ± 43.2†	173.5 ± 44.4*,‡		119.5 ± 29.6*,†,‡	<.001
Indexed LV mass, g/m^2	95.9 ± 18.6†	95.3 ± 18.5†	92.6 ± 19.1*,‡		63.7 ± 12.1*,†,‡	<.001
LVH	24 (23)	24 (23)	18 (17)		5 (5)*,†,‡	<.001
RWTR	0.42 ± 0.07*,†	0.41 ± 0.06†,‡	0.39 ± 0.07*,‡		—	<.001
LVM bias (vs CMR)	+60 ± 31†	+59 ± 32†	+54 ± 32*,‡		—	.004
LVEDV bias (vs CMR)	−39 ± 25*,†	−27 ± 25†,‡	−18 ± 27*,‡		—	<.001

LVM, LV mass; *LVEDV*, LV end-diastolic volume.
Data are expressed as mean ± SD or as number (percentage).
*$P < .05$ vs BSB.
†$P < .05$ vs ML.
‡$P < .05$ vs BL.

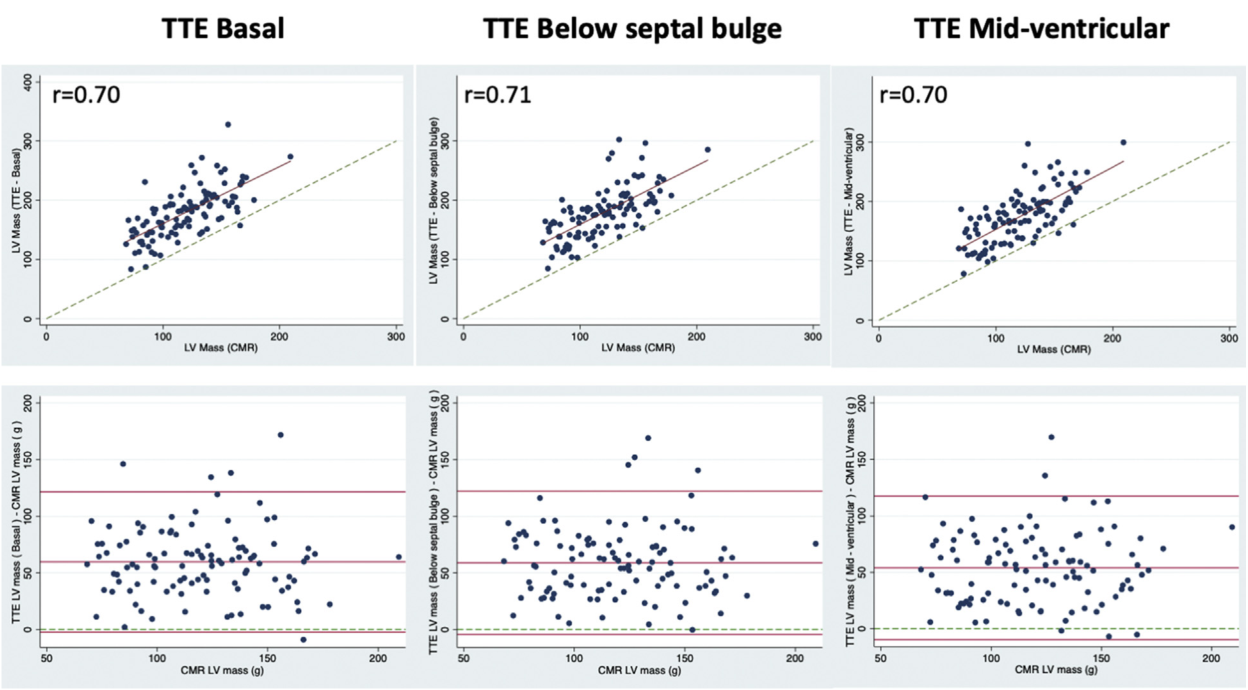

Figure 2 Correlation and agreement between LV mass derived by different transthoracic echocardiographic methods and CMR. **(Top)** Correlation between LV mass derived by different transthoracic echocardiographic methods and CMR-derived LV mass (the reference method). The *red solid line* represents the regression line, and the *green dashed line* represents the identity line. *R* represents the Spearman correlation coefficient. **(Bottom)** Bland-Altman plots of LV mass calculated using different transthoracic echocardiographic methods and CMR. The *solid red lines* are the mean bias and ±1.96 SD. The *dashed green line* represents the level of zero bias.

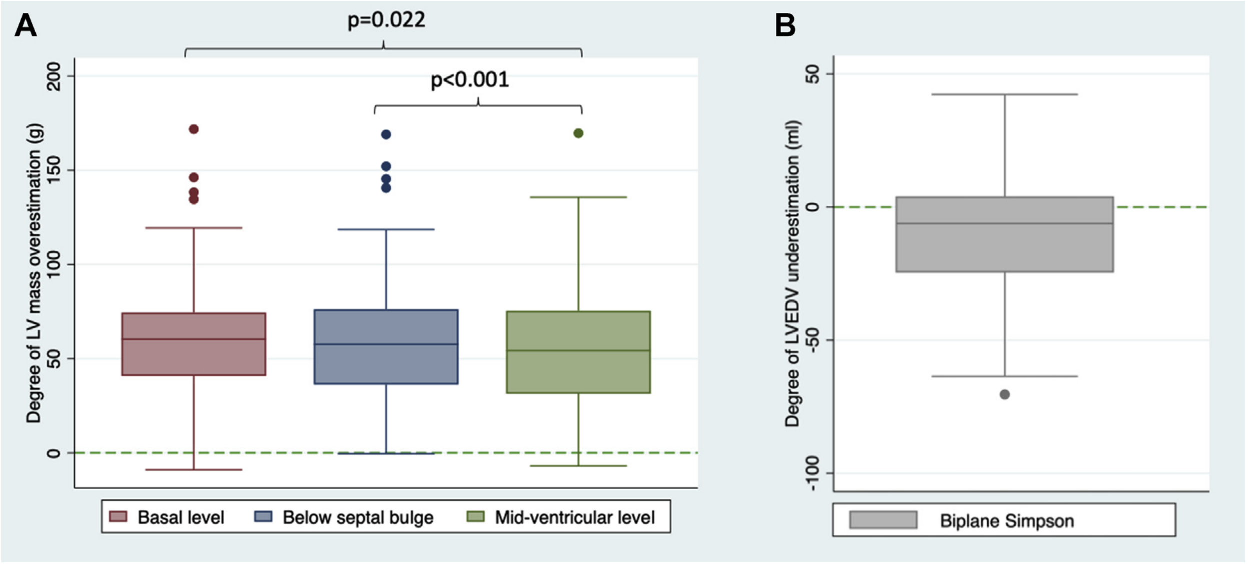

Figure 3 Agreement of LV mass and LV volume between TTE and CMR according to site of measurement. **(A)** Box plot showing the degree of LV mass overestimation (vs CMR) according to site of measurement. **(B)** Box plot showing the degree of LV end-diastolic volume (LVEDV) underestimation (vs CMR) of the biplane Simpson method. *Boxes* are presented with median (*central line*) and percentiles 25 (*lower line*) and 75 (*upper line*). *Whiskers* represent the upper and lower adjacent values.

LVH and Remodeling

RWTR was highest (i.e., more pronounced CR) at the BL (0.42 ± 0.07), intermediate BSB (0.41 ± 0.06), and lowest at the ML (0.39 ± 0.07; $P < .001$; Table 1).

Hence, the prevalence of the patterns of LV remodeling significantly and markedly differed depending on the method of measurement (Figure 4A). Using TTE, the prevalence of abnormal LV remodeling patterns was highest at the BL (CR, 41%; CH, 11%;

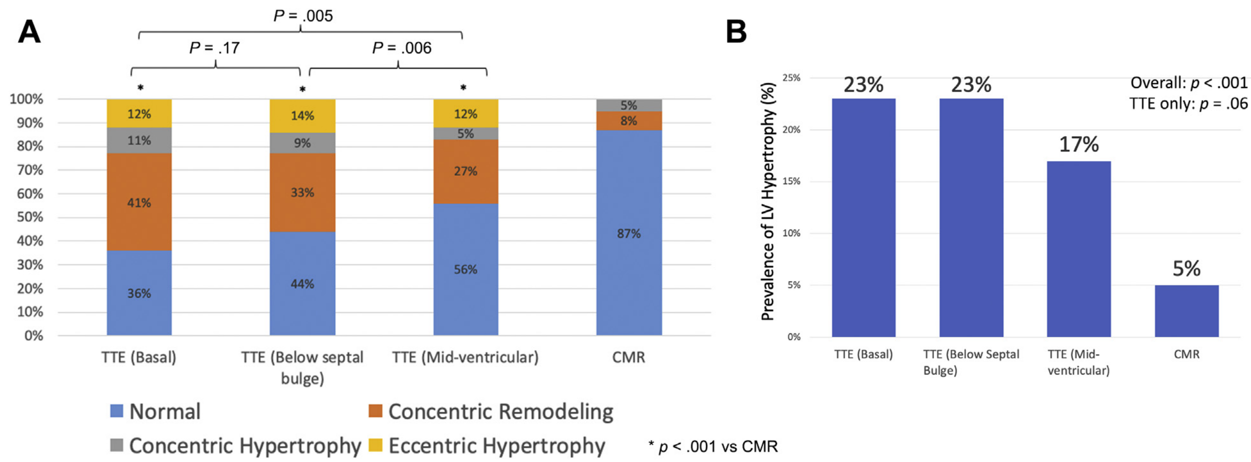

Figure 4 Prevalence of LV remodeling patterns according to measurement method. **(A)** LV remodeling patterns by TTE according to site of measurement compared with CMR. *P* values represent the symmetry and marginal homogeneity test. **(B)** Prevalence of LVH by TTE according to site of measurement compared with CMR.

EH, 12%), intermediate BSB (CR, 33%; CH, 9%; EH, 14%), and lowest at the ML (CR, 27%; CH, 5%; EH, 12%). The prevalence of abnormal patterns was markedly lower using CMR (CR, 8%; CH, 5%; EH, 0%).

The prevalence of LVH according to measurement technique is presented in Table 1 and Figure 4B.

Influence of USH on LV Mass and Volume Estimation

Discrete USH was present in 28 patients (26%). However, 91 patients (86%) had larger septal thickness at the BL than BSB or at the ML, even though not fulfilling our pre-specified isolated USH criteria. Clinical, echocardiographic, and CMR characteristics of patients with and without USH are shown in Supplemental Table 2.

Compared with CMR, the degree of overestimation of LV mass by TTE was significantly more important in patients with USH than in those without USH (Figures 5 and 6, Supplemental Figure 2). This overestimation was, however, less marked when measuring at the ML than at the BL. Furthermore, in patients without USH, LV mass measurement bias was comparable independently of the measurement position ($P = .19$). On the other hand, in patients with USH, bias was significantly different depending on the position of measurement (highest bias at the BL, intermediate BSB, and lowest at the ML, $P < .001$).

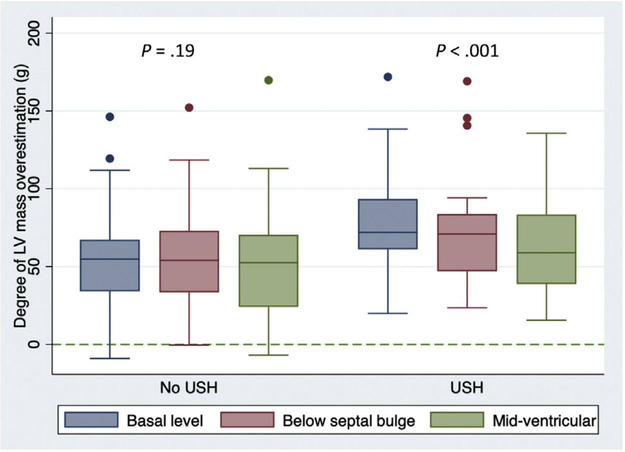

Figure 5 Agreement of LV mass between TTE and CMR according to site of measurement in patients with and without USH. Box plot showing the degree of LV mass overestimation (vs CMR) according to site of measurement in patients without USH (*left*) and with USH (*right*). *Boxes* are presented with median (*central line*) and percentiles 25 (*lower line*) and 75 (*upper line*). *Whiskers* represent the upper and lower adjacent values. *P* values represent repeated-measures analysis of variance.

Multivariate Analyses of Predictors of LV Mass Index by Different Methods

Using CMR measurements (the reference method), after adjusting for age, sex, body mass index, systolic blood pressure, and mean gradient (Table 2, model 1), male sex and systolic blood pressure were significantly associated with higher LV mass index ($P \leq .015$ for both), whereas age showed an inverse correlation (i.e., older age associated with smaller mass, $P = .011$). Mean transvalvular pressure gradient was not associated with LV mass in univariate or multivariate analyses. The addition of USH as a dichotomous variable (model 2) did not change the results, and this variable was not associated with LV mass in univariate or multivariate analyses.

On the other hand, the presence of discrete USH was independently associated with LV mass in transthoracic echocardiographic measurements at the BL and BSB ($P < .01$ for both), and there was a borderline trend toward significance at the ML ($P = .06$; model 2). The only variable that remained independently associated with LV mass in all three transthoracic echocardiographic measurements aside from the presence of USH was male sex in both models (with and without adjusting for USH).

Reproducibility

Intraobserver and interobserver reproducibility were excellent at both the BL and ML for LV mass (intraclass correlation coefficients: intraobserver 0.96, interobserver 0.94; and intraobserver 0.98, interobserver 0.93, respectively) and lowest at the BSB level (intraobserver 0.86, interobserver 0.85). Interobserver reproducibility for LV end-diastolic volume using Simpson method was 0.87 (Supplemental Table 4).

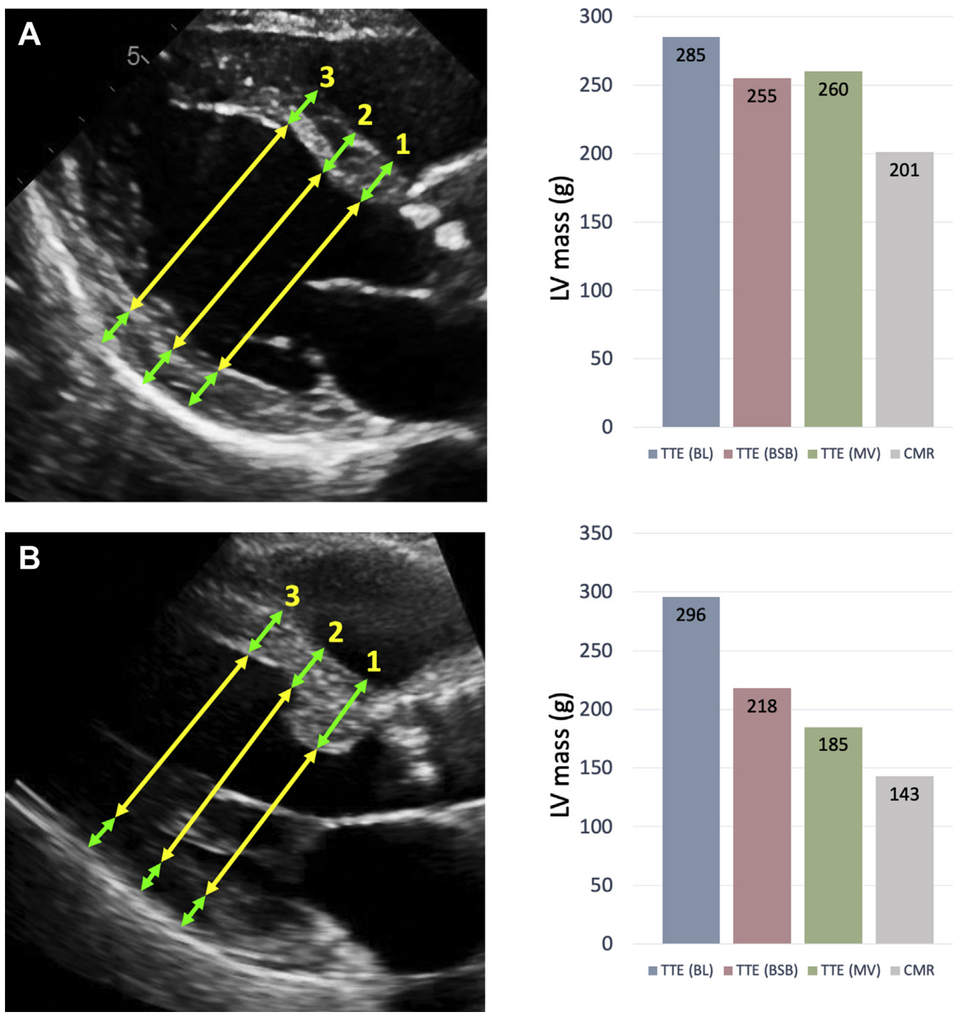

Figure 6 Examples of LV mass calculations in patients with and without USH. **(A)** A 76-year-old man without USH. At the *left*, the three levels of measurement (BL, BSB, and ML) are depicted. At the *right*, results for LV mass are shown. Transthoracic echocardiographic overestimation of LV mass (compared with CMR) was +84 g at the BL, +54 g BSB, and +59 g at the ML. **(B)** An 80-year-old woman with USH. In this case, TTE overestimation of LV mass was +153 g at the BL, +74 g BSB, and +42 g at the ML.

DISCUSSION

The main finding of this study in patients with AS is that, compared with CMR, 2D TTE overestimates LV mass to a larger extent when LV dimensions are measured at the BL, as recommended in the ASE guidelines,[9,10] compared with the ML. This issue is more frequent and pronounced in patients with discrete USH, who represented approximately one quarter of patients with AS in this series. Interestingly, recent guidelines suggest that in the presence of a septal bulge, linear measurements should be made immediately BSB[9,10] to avoid LV mass overestimation. Our results, along with the elegant study recently published by Chetrit *et al.*,[19] demonstrate that ML dimensions (which represent the true maximal diameter of the LV ellipsoid cavity) showed the best agreement with CMR, the established noninvasive volumetric gold standard for LV mass and LV end-diastolic volume.

This is, to our knowledge, the first study to evaluate the influence of discrete USH on the accuracy of 2D TTE for the measurement of LV mass compared with CMR. Discrete USH or septal bulge or sigmoid septum is a frequent finding in patients with AS and/or hypertension. In our series of patients with mild to severe AS, 26% had evidence of discrete USH, which is consistent with previous studies.[14] It is likely that in populations with higher proportions of severe AS, the prevalence of discrete USH would be higher. Furthermore, the criteria we used in this study for the definition of discrete USH captured the subset of patients with the most severe USH phenotype. However, the vast majority of the patients in the present series had different LV dimensions at the BL compared with BSB or the ML, which may have a significant effect on the measures of LV mass and the determination of the presence and severity of LVH and LV remodeling patterns.

Influence of LV Measurement Position on the Transthoracic Echocardiographic Estimation of LV Mass

ASE guidelines for cardiac chamber quantification recommend measuring LV dimensions at the BL to estimate LV mass on 2D TTE using the modified ASE formula.[9] This method provides good accuracy when the LV geometry is elliptic with relatively uniform and symmetric hypertrophy of LV walls. However, as shown

Table 2 Univariate and multivariate analyses of correlates with LVMi estimated by different methods

	Univariate		Multivariate			
			Model 1		Model 2	
	Standardized $\beta \pm$ SE	*P*	Standardized $\beta \pm$ SE	*P*	Standardized $\beta \pm$ SE	*P*
LVMi (CMR)			R^2 = 0.38, adjusted R^2 = 0.35		R^2 = 0.38, adjusted R^2 = 0.34	
Age, y	−0.02 ± 0.08	.80	−0.22 ± 0.07	**.011**	−0.22 ± 0.07	**.011**
Sex, male	0.55 ± 2.10	<.001	0.56 ± 2.14	**<.001**	0.56 ± 2.16	**<.001**
Body mass index, kg/m²	0.22 ± 0.26	.02	0.05 ± 0.24	.59	0.05 ± 0.24	.57
SBP, mm Hg	0.23 ± 0.06	.02	0.22 ± 0.06	**.015**	0.22 ± 0.06	**.017**
Mean gradient, mm Hg	0.06 ± 0.14	.52	0.06 ± 0.11	.43	0.06 ± 0.11	.46
USH	0.07 ± 2.68	.49	—	—	0.02 ± 2.22	.82
LVMi (TTE, BL)			R^2 = 0.10, adjusted, R^2 = 0.06		R^2 = 0.22, adjusted R^2 = 0.19	
Age, y	0.13 ± 0.12	.18	0.03 ± 0.13	.81	−0.01 ± 0.12	.93
Sex, male	0.27 ± 3.75	.005	0.23 ± 3.95	**.024**	0.19 ± 3.68	**.04**
Body mass index, kg/m²	0.19 ± 0.40	.051	0.09 ± 0.44	.41	0.13 ± 0.41	.18
SBP, mm Hg	0.18 ± 0.09	.07	0.11 ± 0.10	.33	0.08 ± 0.09	.45
Mean gradient, mm Hg	−0.05 ± 0.21	.63	−0.03 ± 0.21	.75	−0.09 ± 0.20	.33
USH	0.38 ± 3.82	<.001	—	—	0.37 ± 3.79	**<.001**
LVMi (TTE, BSB)			R^2 = 0.15, adjusted R^2 = 0.10		R^2 = 0.19, adjusted R^2 = 0.17	
Age, y	0.13 ± 0.12	.19	−0.02 ± 0.13	.84	−0.04 ± 0.12	.66
Sex, male	0.27 ± 3.72	.006	0.21 ± 3.82	**.034**	0.18 ± 3.70	**.019**
Body mass index, kg/m²	0.26 ± 0.39	.006	0.14 ± 0.43	.17	0.17 ± 0.41	.08
SBP, mm Hg	0.27 ± 0.09	.005	0.19 ± 0.02	.07	0.17 ± 0.10	.10
Mean gradient, mm Hg	−0.08 ± 0.21	.42	−0.06 ± 0.20	.54	−0.10 ± 0.20	.28
USH	0.27 ± 3.94	.006	—	—	0.26 ± 3.81	**.005**
LVMi (TTE, ML)			R^2 = 0.16, adjusted R^2 = 0.12		R^2 = 0.19, adjusted R^2 = 0.14	
Age, y	0.17 ± 0.12	.07	0.05 ± 0.13	.61	0.04 ± 0.13	.72
Sex, male	0.34 ± 3.8	<.001	0.28 ± 3.92	**.005**	0.26 ± 3.88	**.007**
Body mass index, kg/m²	0.26 ± 0.41	.008	0.14 ± 0.44	.18	0.16 ± 0.43	.12
SBP, mm Hg	0.21 ± 0.09	.03	0.10 ± 0.10	.33	0.09 ± 0.10	.39
Mean gradient, mm Hg	−0.01 ± 0.22	.92	0.01 ± 0.21	.89	−0.02 ± 0.21	.87
USH	0.20 ± 4.1	.04	—	—	0.18 ± 4.00	**.06**

LVMi, Indexed LV mass; *SBP*, systolic blood pressure.
Beta coefficients are standardized regression coefficients. The multivariate analysis was adjusted for age, sex, systolic blood pressure, and mean transvalvular pressure gradient (model 1) and for the same variables adding the presence of USH (model 2). Bold values represent those with $P < .05$.

in the present study, an important proportion of patients with AS do not fulfill these LV geometric assumptions, and they often have irregular LV geometry with sigmoid septum and localized or asymmetric hypertrophy. In such patients, transthoracic echocardiographic measurement of LV dimensions at the BL produces important overestimation of LV mass and adverse LV remodeling compared with measurements performed more apically in the LV cavity. The magnitude of overestimation of LV mass was modest (mean bias +32%) but significant. This may be explained by the fact that the ASE formula for LV mass includes both LV diameter and wall thickness. Measurements at the BL likely overestimate the actual average septal thickness, especially in patients with USH, but underestimate the average LV diameter, which attenuates the overestimation of LV mass. The results of this study therefore suggest that the best method to estimate LV mass by 2D TTE in patients with AS is the one using the LV dimensions measured at the ML in the ASE formula. However, even when using measures at the ML (which provide the best agreement), 2D TTE still overestimates LV mass compared with CMR. Three-dimensional TTE provides a more accurate estimation of LV mass and better agreement with CMR but is less often used and feasible in routine practice.[7,11,26]

The results of this study also suggest that CMR, which was used as the referent method, may underestimate LV mass or, more likely, that the CMR criteria to identify LVH may be too severe. Indeed, CMR identified only 5% of patients with LVH and 8% with LV CR in this series of patients with AS. In such a population, one would expect that the majority of patients have LVH or CR.

For assessment of LV volume by 2D TTE, biplane Simpson method, which is the ASE-recommended approach,[9,10] showed excellent correlation and agreement with CMR. This might have been influenced by the fact that our echocardiograms were obtained by highly trained sonographers with special care to avoid foreshortening and analyzed in a core laboratory by experienced readers in the context of an observational clinical study. However, it provides further evidence that the Simpson summation-of-disks method should be the recommended 2D echocardiographic method, as supported by the ASE guidelines.[9]

Limitations

Even though CMR is the reference method for the measurement of LV mass, the accuracy of this method may be affected by several pitfalls, including the inclusion or exclusion of papillary muscles, and/or of the most basal slices, as well as the specific CMR sequence used.[11] In our study, we included both papillary muscles and the most basal slices in LV mass calculation, which should have reduced but not eliminated the potential for LV mass underestimation. We only used 2D TTE and did not assess the feasibility, accuracy, and reproducibility of three-dimensional TTE, which is known to improve agreement with three-dimensional methods such as CMR.

Regarding reproducibility, we only analyzed repeated readings of the same set of images, whereas test-retest comparisons might have more relevance in the clinical setting.

Finally, we did not evaluate the associations of different measurements with clinical outcomes, which should be the ultimate goal of cardiovascular imaging. The hypothesis that 2D transthoracic echocardiography measurements at the ML compared with the BL will improve the prediction of clinical outcomes in patients with AS remains unproven and warrants further investigations.

CONCLUSION

The present study demonstrates that in patients with AS, TTE systematically overestimates LV mass and underestimates LV volumes compared with CMR. Transthoracic echocardiographic measurement of LV dimension at the ML instead of at the tip of the mitral valve leaflets as currently recommended in the ASE guidelines significantly reduces but does not suppress these biases. Hence, in patients with AS, especially in those with USH, linear measurements should preferably be made at the ML to improve accuracy of the measurements. However, the impact of this change of methodology on the prognostic value of LVH and remodeling patterns for clinical outcomes warrants further study.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2020.08.022.

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