Ultrasound Enhancing Agents with Transthoracic Echocardiography for Maximal Wall Thickness in Hypertrophic Cardiomyopathy

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Abstract

Objectives: To determine whether ultrasound enhancing agent (UEA) changes maximal wall thickness (WT) in hypertrophic cardiomyopathy (HCM), and if it improves correlation with magnetic resonance imaging (MRI).

Patients and Methods: A total of 107 patients with HCM were prospectively enrolled at a single tertiary referral center between July 10, 2014, and August 31, 2017, and underwent transthoracic echocardiography (TTE) with and without UEA and MRI. Maximal WT measurements were compared, and variability among the 3 modalities was evaluated using a simple linear regression analysis and paired t tests and Bland-Altman plots. Interobserver variability for each technique was assessed.

Results: Most (63%) of cardiac imagers found UEA helpful in determining maximal WT by TTE, with 49% reporting change in WT. Of 52 patients where UEA changed WT measurement, 32 (62%) reported an increase and 20 (38%) reported a decrease in WT. The UEA did not alter the median discrepancy in WT between MRI and TTE. However, where UEA increased reported WT, the difference between MRI and TTE improved in 79% of cases ($P=.001$) from 2.0-0.5mm. In those with scar on MRI, UEA improved agreement of WT between TTE and MRI compared with that of TTE without UEA (79% vs 39%; $P=.011$). Interclass correlation coefficient for WT for TTE without UEA, with UEA, and MRI was 0.84; (95% CI, 0.61-0.92), 0.88; (95%CI, 0.82-0.92), and 0.97; (95%CI, 0.96-0.98), respectively.

Conclusion: Although use of UEA did not eliminate differences in WT discrepancy between modalities, the addition of UEA to TTE aided in WT determination and improved correlation with MRI in those with greater WT and in all patients with myocardial scars.

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy, characterized by left ventricular (LV) hypertrophy without a secondary underlying hemodynamic cause. Recent advances in genetic testing, and imaging techniques, have likely contributed to the rising prevalence of HCM, from originally 1 in 500 to now 1 in 200 persons.[1] Accurate assessment of maximal LV wall thickness (WT) in HCM is essential, as it has diagnostic,[2] prognostic,[2,3] and therapeutic[2,3]

implications, and may help guide clinical decision for defibrillator implant.

In a previous study of 618 HCM patients, we found that clinically reported maximal WT differs between transthoracic echocardiography (TTE) and magnetic resonance imaging (MRI), with MRI reporting larger WT measures more frequently than TTE.[4] A Subsequent multicenter study has shown marked variation in WT measures by TTE and MRI in patients with HCM.[5] Ultrasound enhancing agent (UEA) has been shown to improve

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cardiac chamber assessment, including septal WT measurement in the general population[6] and has been suggested to improve WT assessment compared with that of MRI in a cohort of patients with HCM.[7]

This study sought to prospectively determine the clinical value of the use of an UEA in TTE assessment of WT in HCM. In addition, we sought to further assess and independently validate whether the use of UEA changed the reported LV maximal WT measurement and hypothesized that the LV maximal WT measurement with UAE would better correlate with measures by MRI.

METHODS

Patients were prospectively enrolled at a single tertiary referral center between July 10, 2014, and August 31, 2017. All patients provided informed consent before enrollment and underwent clinical evaluation in our HCM subspecialty clinic to confirm the diagnosis of HCM.[8] Patients were included in the study if they were aged 18 years or older and reported clinically indicated TTE and MRI as part of their medical evaluation. Patients were excluded from the study if they were pregnant, refused consent, and exhibited contraindication to the administration of UEA,[9] or underwent intervention that would potentially change LV WT between the dates of the TTE and the MRI studies (ie, septal reduction by myectomy or alcohol ablation). Patients with atrial fibrillation were included if the irregularity of the R-R intervals was not variable enough to degrade MRI image quality. The MRI sequence protocol was the same for those in sinus rhythm and those with atrial fibrillation. Patients with MRI compatible pacemakers or implantable cardioverter defibrillators were included. Clinical variables from the time of imaging were abstracted from health records. Mayo Clinic Institutional Review Board approved the study. Funding for the study was provided by a grant from GE Healthcare, Milwaukee, WI.

Consistent with methodology previously reported and clinical practice,[4] all patients underwent comprehensive 2-D TTE evaluation. All studies were interpreted by experienced, level 3 National Board of Echocardiography certified echocardiographers at the time of image acquisition. LV WT was measured in end-diastole on 2-D imaging in accordance with current guidelines.[10,11] All myocardial segments were interrogated from multiple imaging windows, including apical 2-chamber, 3-chamber, and 4-chamber planes and parasternal long axis and short-axis views at base, mid, and apex, and the measurements reported were from the thickest segment identified.

Left atrial volume index was calculated from the biplane method of disks at the end of LV systole using ventricular end-systolic apical 4-chamber and apical 2-chamber views.[10] As previously reported, continuous-wave Doppler was implemented to interrogate both the resting and provoked (either with the Valsalva maneuver or amyl nitrite use) LV outflow tract gradient.[12] Resting obstruction was defined as a maximum instantaneous gradient of ≥30 mm Hg and provoked obstruction as a gradient of ≥50 mm Hg in those patients not meeting the criteria for resting obstruction.[13]

The pulmonary artery systolic pressure was estimated through the tricuspid regurgitant velocity, size, and the collapsibility of the inferior vena cava.[14] The severity of mitral regurgitation was assessed using standard techniques[15]; in patients with severely eccentric jets, semi-quantitative evaluation was used.

TTE with UEA was performed in all patients immediately after the non-UEA TTE examination. Perflutren Protein Type A Microsphere (Optison; GE Healthcare) was the UEA agent used for all patients and was stored and administered according to product guidelines.[16] The UEA was subsequently administered by trained, registered nurses. Contrast echocardiography was performed by diagnostic sonographers familiar with the use of UEA TTE and in accordance with clinical practice and accepted guidelines.[9]

A dedicated group of cardiac radiologists interpreted all cardiac MRI studies, as reported in the methodology of a similar previous study.[4] All cardiac MRI studies were performed on a 1.5-T system (GE Healthcare). Electrocardiography-gated cine-balanced steady-state free precession images of the LV were obtained in the short-axis and 2-chamber, 3-chamber, and 4-chamber long-axis planes and were used for measuring the

maximum LV WT. The MRI short-axis images were reviewed at the apical, mid, and basal levels. The thickest wall segment was determined by visual assessment of these images, and this segment was measured in end-diastole excluding trabeculations and reported by the interpreting physician at the time of image acquisition.

Evaluation for myocardial late gadolinium enhancement was performed after administration of an intravenous bolus of a gadolinium-based contrast agent, either gadodiamide (Omniscan; GE Healthcare) or gadobenate dimeglumine (Multihance; Bracco Diagnostics Inc). Late gadolinium enhancement images covering the left ventricle in short-axis and long-axis views were obtained between 8 and 20 minutes after contrast administration using vendor-provided inversion recovery sequences. A short-axis multiple inversion time cine fast gradient echo sequence at the mid-ventricular level was used to select the inversion time with optimal myocardial nulling for late gadolinium enhancement images. The HCM septal morphologic characteristics were classified as sigmoid, reverse curve, neutral, or apical, using the cine-balanced steady-state free precession long-axis (3-chamber) images at end-diastole.[17]

Six patients reported with MRI studies performed before undergoing TTE assessment at our institution; these outside MRI images were assessed by a cardiac radiologist and interpreted using the same methodology as for studies performed at the study institution.

Consistent with current clinical practice, cardiologists, and cardiac radiologists involved with performance and interpretation of the second WT assessment were not blinded to the results of the first WT assessment and were able to review the reports of the other imaging modality if they had been completed. Cardiac imagers completed a questionnaire to assess whether UEA aided the assessment of WT measures by TTE for each study, and noted WT measures by TTE with and without UEA. A threshold of 1 mm difference in WT measures was used (any difference in clinically reported WT). To assess interobserver variability, blinded independent measure of WT was performed for TTE (with and without UEA) and MRI.

Statistical Analyses

A power calculation of 0.80 performed before the initiation of the study suggested that a total patient population of greater than 100 would be needed to assess a WT difference of 1.5 mm (with a SD of 5 mm) between the different imaging techniques. Clinically significant hypertrophy is considered $\geq$15mm, and a 10% variation in measurements would be 1.5 mm. Continuous variables were presented as the mean $\pm$ SD and compared between groups using a 2-sample t test. When data was not normally distributed on the basis of visual inspection of histogram, median and interquartile ranges were reported. Categorical variables were noted as the number and percentage of total and compared among groups using the χ^2 test or Fisher exact test, as appropriate.

Correlation of continuous variables was performed with simple linear regression analysis. To assess variability of the reported LV WT among the 3 imaging modalities, Bland-Altman plots were constructed with 2 SD limits shown, and paired t tests were used for comparison. Interclass correlation coefficient (ICC) was used to assess maximal WT on a blinded second read compared with the clinical reads. Statistical significance was set a priori as $P>$.05. All statistical analysis was performed using SAS version 9.4 (SAS Institute Inc).

RESULTS

Of the 146 patients who consented to the study, 107 were included in the final analysis. None of these patients experienced an adverse event related to UEA. Of the 39 patients not included, 21 did not have an MRI performed within 6 months of the study TTE, 9 withdrew consent, and 9 reported an alternative diagnosis to HCM (3 subaortic membrane, 3 hypertensive heart disease, 1 Fabry disease, 1 LV noncompaction, and 1 cardiac amyloidosis). The median time interval between the TTE and the MRI assessment was 7.2 hours (IQR, 3.6-22.1 hours). Table 1 presents the baseline characteristics of the study population. All patients with atrial fibrillation were able to be scanned with an MRI.

The HCM morphology types included: sigmoid morphology 53 (50%), neutral septal

TABLE 1. Baseline Characteristics of the Study Population[a]	
Characteristic[b]	Value (n=107)
Age (y), mean ± SD	56.0±14.2
Male	61 (57)
Vital signs	
Body mass index (kg/m^2), mean ± SD	31.7±6.6
Heart rate (beats/min), mean ± SD[c]	62.2±9.6
Systolic blood pressure (mm Hg), mean ± SD[c]	125.4±18.4
Family history	
HCM	22 (21)
SCD	21 (20)
Symptoms	
NYHA function class III/IV	66 (62)
Presyncope	42 (40)
Syncope	13 (12)
Comorbidity	
AF (chronic or paroxysmal)	15 (14)
Ventricular tachycardia/fibrillation	9 (8)
Hypertension	49 (46)
COPD	4 (4)
Obesity	59 (55)
Medication	
β-Blocker	84 (79)
CCB	31 (29)
Disopyramide	6 (6)
Antiarrhythmics	4 (4)
Race	
White	98 (92)
Black	2 (2)
Other/unknown	4 (4)/3 (3)
Transthoracic Echocardiography	
LV mass (g), mean ± SD	238.9±131.3
LV mass index (g/m^2), mean ± SD	113.59±55.97
LA volume index (mL/m^2), mean ± SD	43.4±17.0
Obstruction (resting ≥30 mm Hg or provoked ≥50 mm Hg)	72 (67)
Mitral systolic anterior motion	78 (73)
PASP (mm Hg), mean ± SD	37.0±14.4
Moderate or greater mitral regurgitation	37 (25)
Presence of delayed enhancement on MRI	73 (68)
Morphologic subtype	
Sigmoidal	53 (50)

Continued on next column

TABLE 1. Continued	
Characteristic[b]	Value (n=107)
Morphologic subtype, continued	
Reverse curve	10 (9)
Apical	12 (11)
Neutral	32 (30)

[a]Abbreviations: AF, atrial fibrillation; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SCD, sudden cardiac death.

[b]Values are expressed as number (percentage) of patients, normally distributed variables as mean ± SD and non-normally distributed variables as median (IQR).

[c]Heart rate and blood pressure were obtained at the time of echocardiography.

morphology 32 (30%), reverse curve morphology 10 (9%), and apical hypertrophy 12 (11%). Left ventricular outflow tract (LVOT) obstruction was present in 72 patients (67%), with 34 patients reporting resting LVOT obstruction and 38 reporting dynamic provocable LVOT obstruction (with either the Valsalva maneuver or administration of amyl nitrite). The mean ± SD for LV mass index g/m^2 was 147.3±47.7 on 2D TTE without UEA, 135.8±46.4 with UEA, and 94.1±38.4 by MRI, *P*<.01.

In 67 (63%) patients, echocardiographers found that the use of an UEA aided in assessment of LV WT. In 52 (49%) patients, echocardiographers reported that the use of UEA led to a change in reported maximal LV WT. Of the 52 patients where UEA resulted in a change in LV WT measurement, 32 (62%) increased reported LV WT, whereas 20 (38%) decreased reported LV WT (Table 2). The use of an UEA improved agreement of TTE derived maximal LV WT with MRI in 33 (31%) patients, whereas it worsened agreement in 18 patients (17%).

Although the overall discrepancy of reported LV WT between MRI and TTE was the same with and without the use of UEA (a mean difference 2.0 mm) (Figure 1A), in the 32 patients in whom the use of UEA increased reported WT, the difference between the MRI and TTE was reduced to 0.5 mm (Figure 1B). Conversely, when UEA resulted in a decrease in reported WT (Figure 1C),

agreement with MRI worsened in 60% of the cases (P=.001). In general, in patients with less hypertrophy (WT <21 mm by unenhanced TTE), the application of UEA resulted in an increased WT measure than compared with 2D TTE, and in those with WT ≥21 mm, the use of UEA resulted in a decreased WT measure (Figure 2).

In 26 (81%) of the 32 patients (or 24% of the entire cohort) where UEA lead to an increased reported WT, there was greater agreement with MRI (P=.001, Table 3, Figure 3). In patients with scars as defined by abnormal delayed enhancement on MRI, UEA was more likely to improve agreement of reported WT between TTE and MRI than was TTE without UEA (79% vs 39%, P=.011). There was no significant difference in agreement between TTE with and without the use of UEA and MRI on the basis of morphologic subtypes of HCM (Table 3).

The TTE window used to detect maximal WT without UEA was parasternal long axis in 36 (33.6%), apical 4 chamber view in 31 (29.0%), short-axis view in 22 (20.6%), and apical 3-chamber view in 18 (16.8%). With the use of UEA, the window for the detection of maximal WT was parasternal long axis in 40 (37.4%), short-axis view in 29 (27.1%), apical 4-chamber view in 25 (23.4%), and apical 3-chamber view in 13 (12.1%). Maximal WT was most frequently observed in the basal anteroseptum on TTE without and with UEA (n=42 and n=45 respectively), followed by the mid inferoseptum (n=23 in both), the mid anteroseptum (n=20 and n=21, respectively), and the basal inferoseptum (n=12 and n=10, respectively).

Three patients were identified as having massive LV hypertrophy (WT ≥30 mm) both with and without the use of UEA. The MRI also identified these 3 patients reporting a massive HCM. The MRI also identified an additional 2 patients with WT ≥30 mm; the first reported a WT of 36 mm by MRI, 21 mm by UEA, and 23 mm by 2D, and the other patient reported a WT of 31 mm by MRI, 28 mm by UEA, and 24 mm by 2D. One patient was identified reporting a massive HCM by TTE (WT 32mm) without UEA but was categorized as nonmassive HCM on TTE with
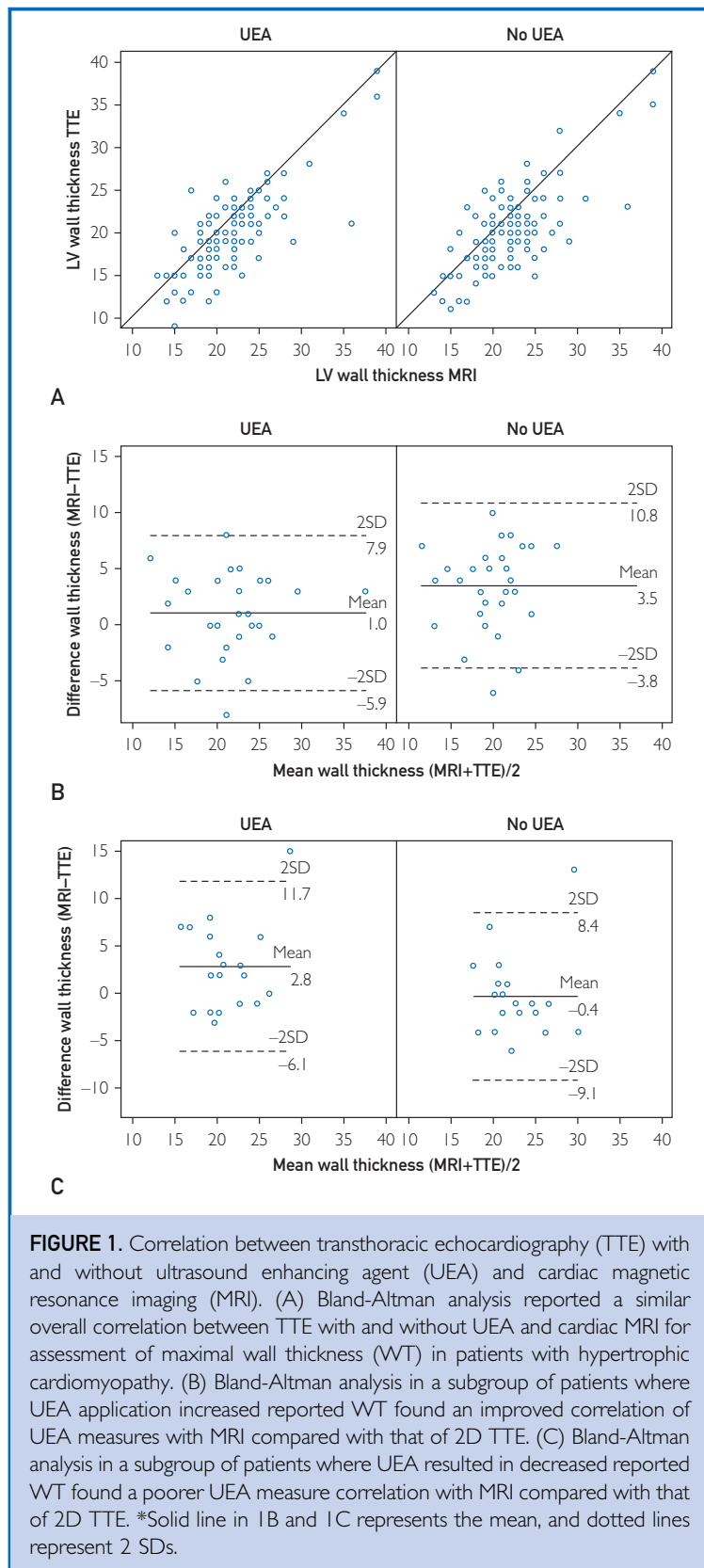
FIGURE 1. Correlation between transthoracic echocardiography (TTE) with and without ultrasound enhancing agent (UEA) and cardiac magnetic resonance imaging (MRI). (A) Bland-Altman analysis reported a similar overall correlation between TTE with and without UEA and cardiac MRI for assessment of maximal wall thickness (WT) in patients with hypertrophic cardiomyopathy. (B) Bland-Altman analysis in a subgroup of patients where UEA application increased reported WT found an improved correlation of UEA measures with MRI compared with that of 2D TTE. (C) Bland-Altman analysis in a subgroup of patients where UEA resulted in decreased reported WT found a poorer UEA measure correlation with MRI compared with that of 2D TTE. *Solid line in 1B and 1C represents the mean, and dotted lines represent 2 SDs.

TABLE 2. Maximal Wall Thickness Measured by MRI and TTE with and without Ultrasound Enhancing Agent[a]

Group[b]	TTE Without UEA	TTE with UEA	MRI
Overall (N=107)			
WT, mean ± SD	20.0±4.7	20.1±4.6	21.8±4.6
Difference from TTE without UEA, median (IQR)	—	0 (0.0-1.0)	2.0 (0.0-4.0)
Difference from TTE with UEA, median (IQR)	0 (−1.0 to 0.0)	—	2.0 (0.0-4.0)
WT measured smaller with UEA (n=20)			
Overall WT, mean ± SD	22.6±3.9	19.5±3.6	22.2±4.3
Difference from TTE without UEA, median (IQR)	—	−3.0 (−4.0 to −1.5)	−1.0 (−4.0 to 1.0)
Difference from TTE with UEA, median (IQR)	3.0 (1.5-4.0)	—	2.0 (−1.0 to 6.0)
WT measured larger with UEA (n=32)			
Overall WT, mean ± SD	18.5±4.8	21.0±5.1	22.0±5.2
Difference from TTE without UEA, median (IQR)	—	2.0 (1.0-3.0)	4.0 (1.5-6.0)
Difference from TTE with UEA, median (IQR)	−2.0 (-3.0 to −1.0)	—	0.5 (−0.5-4.0)

[a]Abbreviations: MRI, magnetic resonance imaging; TTE, transthoracic echocardiography; UEA, ultrasound enhancing agent; WT, wall thickness.
[b]Values are expressed as number (percentage) of patients, normally distributed variables as mean ± SD and non-normally distributed variables as median (IQR).

UEA (WT 22 mm) and MRI (WT 28 mm). The use of UEA in the obese (body mass index ≥ 30 kg/m^2) did not result in closer approximation to MRI WT measures (difference in MRI—UEA WT 1.0 [0-3.0]; P=.45) compared with TTE without UEA (difference in MRI—2D WT 1.0 [0-3.0]; P=.45).

Interobserver variability for each technique was assessed with blinded remeasure, with WT measured by 2-D TTE without UAE reporting ICC of 0.84; (95% CI, 0.61-0.92), with UEA an ICC of 0.88; (95% CI, 0.82-0.92), and by MRI an ICC of 0.97; (95% CI, 0.96-0.98).
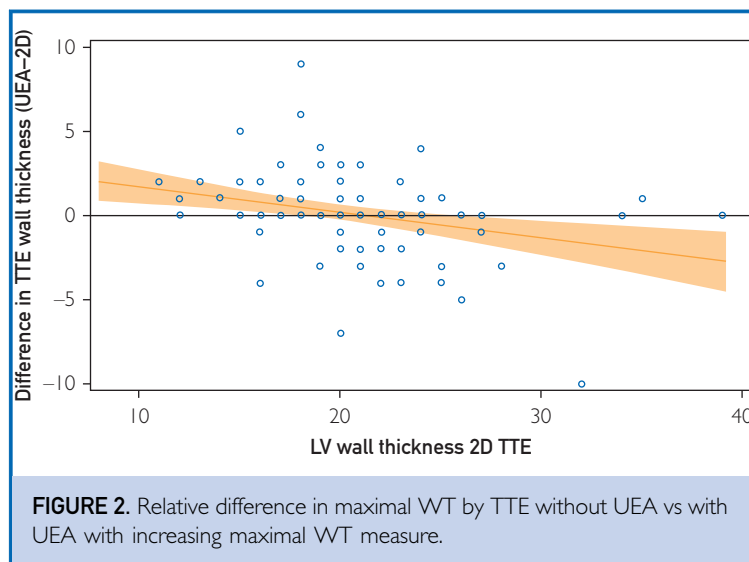
DISCUSSION

The findings of this study suggest that the use of UEA in a patient with HCM may modestly improve correlation between MRI and TTE in determining WT, particularly when UEA allowed recognition of a greater WT than what was recognized without UEA. The UEA also resulted in improved interobserver variability compared with that of TTE without UEA; however, MRI reported the least interobserver variability. Although a previous smaller study suggested use of UEA resulted in a closer correlation with MRI and overall smaller WT measures,[7] this present larger study clarifies that the benefit of the use of UEA may be more apparent in certain HCM cohorts, particularly those with wall thickness greater than 21mm and those with myocardial scars. Accurate assessment of LV WT in the HCM population is critical for several reasons. First, the imaging diagnosis of HCM is predicated on the detection of an increased LV WT of ≥ 15 mm. The distribution of hypertrophy can aid in differentiating HCM from phenocopies such as athlete's heart, hypertensive heart disease, and infiltrative cardiomyopathies. Second, multiple studies have reported that the degree of LV WT is independently associated with the risk of sudden cardiac death.[3,18,19] In particular, a linear correlation between LV WT and sudden cardiac death in the population with HCM has been found.[19] Consequently, the risk of sudden cardiac death imparted by increased LV WT in a patient with HCM has affected therapeutic decision-making.[2] Although echocardiography has been the traditional means by which to determine LV WT and has served as the foundation for these initial LV WT studies, cardiac MRI has been increasingly integrated into clinical practice for assessment of the HCM and WT correlation with TTE, or lack thereof, which may affect clinical decision-making.[20] Measurement of LV mass index by TTE with or without UEA was weakly correlated with LV mass index by MRI, but it is noteworthy that the methodology for determination of LV mass index for the 2 modalities differs considerably, with TTE using an equation on the

basis of linear measurements of the septum, posterior wall, and LV dimension, and MRI using LV endocardial and epicardial contours.

Several factors, such as adjacent pulmonary tissue and myocardial trabeculations, can inhibit accurate detection of the endocardial and epicardial borders by TTE.[16] There is a growing body of literature which reports the benefits of using TTE with UEA both in general and specific patient populations.[6,7] For instance, accurate reporting of LV volumes is critical in patients with dilated or valvular cardiomyopathy. Studies performed without the benefit of UEA result in significantly smaller LV volumes when than TTE with UEA.[21] In addition, the use of UEA improved the correlation between MRI and TTE when reporting LV volumes.[21] Similarly, the use of UEA improved the agreement of LV ejection fraction between TTE and MRI compared with studies performed without UEA.[21,22] Regarding other specific cardiomyopathies, the use of UEA has proven to be beneficial in the diagnosis of noncompaction cardiomyopathy, given its ability to enhance both the endocardial border and the intracavitary trabeculations.[23] Although this study reported that the UAE resulted in a change in half of WT measurements, generally WT <21 mm resulted in a smaller measure by UEA, and WT≥21mm resulted in a higher measurement compared with measures without UEA (Figure 1D). It is likely that improved ability to exclude trabeculations from WT measurements resulted in smaller measurements in WT <21 mm with UEA; however, improved endocardial definition resulted in higher measurements in thicker walls.

The American Society of Echocardiography has recommended the utilization of UEA to assess apical HCM, but the benefits of its routine use to assess maximal myocardial WT in the entire population with HCM have been uncertain given limited clinical studies.[9] In the largest trial conducted to date, our group found that maximal reported LV WT differs between TTE without the use of UEA and MRI.[4] Additional studies have corroborated significant variation in WT measures between the modalities.[5,24] Furthermore, discrepant classification of massive LV hypertrophy occurs between the 2 modalities, which could considerably alter perceived sudden cardiac death risk.[4]

FIGURE 2. Relative difference in maximal WT by TTE without UEA vs with UEA with increasing maximal WT measure.

As with previous trials noting the benefits of UEA in TTE,[21-23,25] most of the echocardiographers in our study found the addition of UEA to be beneficial, with nearly one-half adjusting their reported maximal WT on the basis of UEA images. Although the overall discrepancy of reported maximal WT between TTE and MRI remained unchanged with the use of UEA, it helped in certain scenarios. In particular, when UEA resulted in an increase in the reported LV maximal WT, the agreement with MRI significantly improved in nearly 80 percent of cases (P<.001) with the discrepancy between the 2 modalities being 300 percent closer (0.5 mm) when compared with the entire study population (2.0 mm). This finding was consistent with the previous study of LV volumes, where TTE without UEA underestimated LV volumes and led to worse correlation with MRI when compared with studies using TTE with UEA.[21] Furthermore, in this study, the use of UEA proved beneficial in improving agreement between MRI and TTE in patients with HCM with myocardial scars (delayed enhancement on MRI). The exact mechanism behind this finding is unclear, but perhaps changes in myocardial configuration because of scars were more easily assessed with the use of UEA.

The findings of this study suggest that UEA may be useful in determining maximal WT in a patient with HCM. This measurement is of

TABLE 3. Correlation of MRI Maximal Wall Thickness with TTE both with and without the use of Ultrasound Enhancing Agents[a]

Variable[b]	TTE Without UEA Closer to MRI (n=18)	TTE With UEA Closer to MRI (n=33)	No Change (56)	P
TTE UEA measurement larger	6 (33)	26 (79)	0 (0)	0.001[c]
TTE UEA measurement smaller	12 (67)	7 (21)	1 (2)	0.001[c]
Age (y), mean ± SD	54.7±13.0	56.1±13.8	56.3±14.9	0.92
Male	12 (67)	18 (55)	31 (55)	0.66
Body mass index (kg/m^2), mean ± SD	34.3±7.1	31.3±7.2	31.0±5.9	0.16
Family history				
HCM	4 (22)	10 (30)	8 (14)	0.19
SCD	3 (17)	7 (21)	11 (20)	0.93
Symptoms				
NYHA III/IV	12 (67)	21 (64)	33 (59)	0.81
Presyncope	8 (44)	17 (53)	17 (30)	0.10
Syncope	1 (6)	4 (12)	8 (14)	0.61
Comorbidity				
AF (paroxysmal or chronic)	1 (6)	4 (12)	10 (18)	0.40
VT/VF	0 (0)	4 (12)	5 (9)	0.32
Hypertension	10 (56)	11 (33)	28 (50)	0.21
COPD	0 (0)	0 (0)	4 (7)	0.15
LV mass by TTE (g), mean ± SD	209.5±89.1	248.2±108.7	242.0±152.8	0.63
Obstruction (resting ≥30 mm Hg or provoked ≥50 mm Hg)	11 (61)	20 (61)	41 (73)	0.63
≥Moderate mitral regurgitation	4 (22)	6 (18)	17 (30)	0.42
Delayed MRI enhancement	7 (39)	26 (79)	40 (71)	0.011
Morphologic subtype				
Sigmoidal	9 (50)	21 (64)	35 (63)	0.23
Reverse curve	1 (6)	5 (15)	9 (16)	—
Apical	3 (17)	5 (15)	8 (14)	—
Neutral	2 (11)	1 (3)	2 (4)	—

[a]Abbreviations: AF, atrial fibrillation; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricular; MRI, magnetic resonance imaging; NYHA, New York Heart Association; SCD, sudden cardiac death; TTE, transthoracic echocardiography; VT, ventricular tachycardia; VF, ventricular fibrillation.

[b]Values are expressed as number (percentage) of patients, normally distributed variables as mean ± SD and non-normally distributed variables as median (IQR).
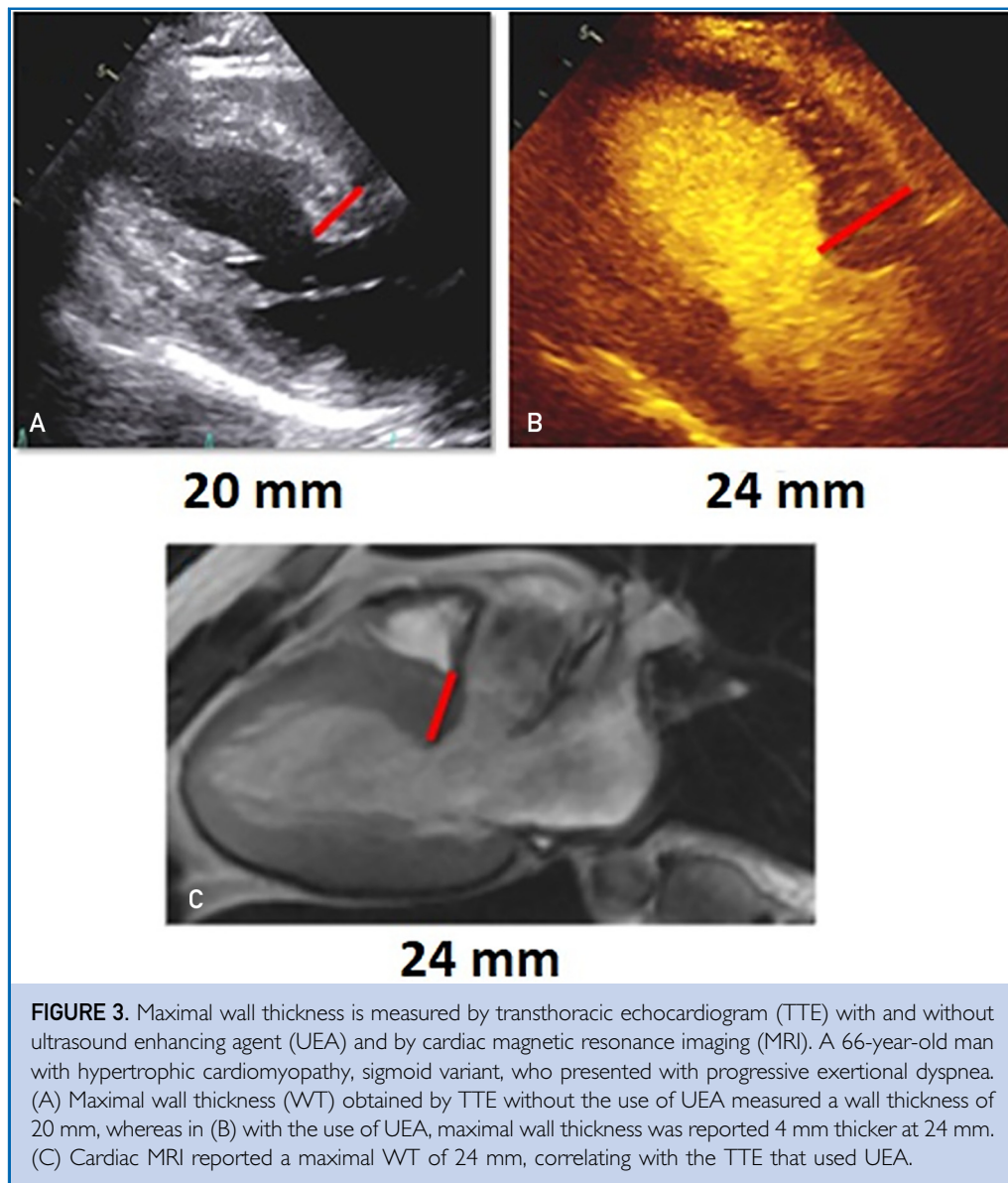
[c]Comparison does not include no change group.

critical importance as it has potential diagnostic,[2] prognostic,[2,3] and therapeutic[2,3] implications for the patient. Data from this trial indicates that the most of the echocardiographers will find the implementation of UEA useful and that it may result in a change in their reported maximal LV WT. If the reported thickness is greater than that anticipated without the use of UEA our study would suggest that this would likely lead to a greater correlation with MRI (Figure 2). If it results in a reduction in reported maximal WT, this could potentially worsen agreement with MRI. Therefore, additional clinical caution should be used in this scenario, with this study suggesting

favoring the reporting of the greatest WT obtained (with or without UEA).

Massive LV hypertrophy, which serves as a class IIA indication for implantable cardioverter-defibrillator implantation in HCM,[26] was most frequently identified by MRI, followed by TTE with UEA, and was least likely to be recognized by TTE without UEA. These findings further support the use of UEA with TTE in the population with HCM; however, MRI imaging remains invaluable both for WT assessment and evaluation of scar burden. Regarding safety, UEA TTE has been studied in 250,000 patients with no associated deaths or reported increase in

FIGURE 3. Maximal wall thickness is measured by transthoracic echocardiogram (TTE) with and without ultrasound enhancing agent (UEA) and by cardiac magnetic resonance imaging (MRI). A 66-year-old man with hypertrophic cardiomyopathy, sigmoid variant, who presented with progressive exertional dyspnea. (A) Maximal wall thickness (WT) obtained by TTE without the use of UEA measured a wall thickness of 20 mm, whereas in (B) with the use of UEA, maximal wall thickness was reported 4 mm thicker at 24 mm. (C) Cardiac MRI reported a maximal WT of 24 mm, correlating with the TTE that used UEA.

myocardial infarction or mortality when compared with a control population.[16] Furthermore, the Food and Drug Administration removed the contraindication label from UEAs in 2016. No safety data are available for pediatric patients under 5 years of age or pregnant patients.[16] Although this study used Optison as the UEA, national guidelines do not distinguish between specific agents for the assessment of myocardial walls[16] and although possible, we believe it would be unlikely that the use of a different UEA would have considerably changed results.

Three-dimensional echocardiography is a potential alternative means by which to enhance the capability of TTE to evaluate WT. This technique has previously been employed in the population with HCM to further refine assessment of HCM, including LV mass distribution[27] and geometry.[28] However, there are no current data regarding the influence of 3-D TTE on improving the correlation of maximal WT with MRI in a patient with HCM. Furthermore, its use with UEA is limited. Finally, the use of automated LV wall thickness software to potentially improve

WT reproducibility deserves further assessment.[29]

Limitations

The current investigation was performed at a single, tertiary referral center, which could result in a potential referral and selection bias. The reported age and sex distribution of this study population are consistent with the general population with HCM. The administration of UEA increases cost and requires additional time. This study was not designed to assess the downstream effects of the utilization of UEA on clinical decision-making for the patient population with HCM. However, the use of UEA has previously been found to result in considerable patient management adjustments while simultaneously reporting financial savings, albeit not in a study with a dedicated population of patients with HCM.[30]

As with our previous study,[4] the imaging studies were conducted by multiple operators (cardiologists and cardiac radiologists) and a variance in techniques for assessment of LV WT could influence results. The presence of right ventricular trabeculations can make WT measures more challenging and introduce variability by TTE, both at the apical and basal septum. Biplane mode was not routinely applied as it is associated with lower frame rates. However, all operators adhered to standard guidelines for the basic approach to analyzing LV maximal WT,[16] and blinded second read by a single experienced cardiac imager was performed for each modality to assess for interobserver variability. Moreover, evaluating the results of multiple operators—rather than a selected few—is more representative of current clinical practice. Because the data were not blinded to operators and technicians during the study, they could have reviewed the reports of the other imaging techniques when they were available before performing their study. Most of the patients in this study were White, which may limit generalizability.

CONCLUSION

Although the use of UEA did not eliminate differences in WT discrepancy between the modalities, the addition of UEA to TTE aided in WT determination and improved correlation with MRI in patients with HCM and a higher degree of WT or the presence of myocardial scar.

POTENTIAL COMPETING INTERESTS

The authors have no conflicts of interest to disclose.

ACKNOWLEDGMENTS

The study was funded in part by a grant from GE Healthcare.

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