

Echocardiographic Wall Thickness Heterogeneity as Marker of Hypertrophic Cardiomyopathy: A Proof-of-Concept Analysis From the Prospective Multicenter IMAGE-HCM Study

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Abstract

Background

Hypertrophic cardiomyopathy (HCM) is characterized by marked phenotypic heterogeneity that may not be fully captured by conventional maximal wall thickness measurements. Wall thickness standard deviation (WTSD), a quantitative measure of regional myocardial thickness variability, may provide additional insight into disease-specific remodeling and improve phenotypic characterization.

Aims and Methods

We aimed to evaluate, for the first time, the feasibility and diagnostic performance of WTSD measured by transthoracic echocardiography (TTE) in patients with hypertrophic phenotypes, using CMR-derived WTSD as a reference. Specifically, we assessed the feasibility, reproducibility, and diagnostic agreement of TTE-derived WTSD with CMR, its diagnostic performance for identifying HCM, its ability to detect subtle or early hypertrophic remodeling in women.

Results

We retrospectively analyzed 51 patients with hypertrophic phenotype who fulfilled study inclusion criteria. Thirty-seven patients had overt HCM, while 14 had non-HCM hypertrophic phenotypes. Patients with overt HCM exhibited significantly greater myocardial wall-thickness heterogeneity than those with non-HCM hypertrophic phenotypes. WTSD was higher in HCM patients by both CMR (3.4 ± 1.3 vs. 2.6 ± 0.9 , $p = 0.020$) and TTE (3.9 ± 1.3 vs. 2.3 ± 0.9 , $p = 0.001$). Importantly, TTE-derived WTSD showed good agreement with CMR-derived WTSD ($r = 0.86$, 95% CI 0.72–0.93, $p < 0.001$), providing evidence for the reproducibility of WTSD assessment across imaging modalities. TTE-derived WTSD demonstrated comparable diagnostic performance to CMR-derived WTSD for identifying overt HCM. CMR-derived WTSD identified overt HCM with an optimal cut-off value ≥ 2.3 (AUC 0.70, 95% CI 0.54–0.85; $p = 0.028$), while echocardiographic WTSD showed comparable performance (AUC 0.69, 95% CI 0.52–0.84; $p = 0.030$).

Conclusions

WTSD represents a quantitative marker of myocardial wall-thickness heterogeneity that, to our knowledge, has not previously been systematically measured and validated using TTE. Echocardiographic WTSD demonstrated excellent agreement with CMR-derived WTSD and showed comparable ability to distinguish overt HCM from non-HCM hypertrophic phenotypes. Prospective multicenter studies are warranted to externally validate these findings and establish the clinical and prognostic implications of WTSD.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, with an estimated prevalence of approximately 1:500 in the general population.¹ It is classically defined by the presence of unexplained left ventricular (LV) hypertrophy in the absence of abnormal loading conditions or infiltrative diseases. It is mainly caused by pathogenic variants in genes encoding sarcomeric proteins, most commonly *MYH7* and *MYBPC3*. However, advances in genetic testing have progressively revealed a more complex and heterogeneous disease architecture.^{2–4}

The diagnosis of HCM still relies heavily on absolute thresholds of LV wall thickness (LVWT), typically ≥ 15 mm in the general population or ≥ 13 mm in the presence of a positive genotype or family history. While these criteria provide high specificity for overt disease, they lack sensitivity for early or subclinical stages, particularly in mutation carriers, relatives of affected individuals and women where the clinical picture generally is more subtle and diagnosis arrives usually late. To overcome these limitations, there has been growing interest in alternative imaging biomarkers that better reflect the structural complexity of HCM.

Among these, wall thickness standard deviation (WTSD) has emerged as a promising parameter. WTSD is calculated as the standard deviation of wall thickness measurements across multiple LV segments, typically obtained from cardiac Cardiac Magnetic Resonance (CMR) short-axis images. By quantifying the variability of myocardial thickness, WTSD provides a measure of hypertrophy heterogeneity rather than absolute magnitude. Initial studies have demonstrated that WTSD has excellent diagnostic accuracy for distinguishing HCM from normal hearts and from other causes of LV hypertrophy, such as hypertensive heart disease or athlete's heart. Importantly, WTSD is elevated not only in overt HCM but also in sarcomere mutation carriers without significant hypertrophy, indicating that it captures early structural remodeling. In these individuals, the myocardium often exhibits a pattern of subtle thickening in some segments and relative thinning in others, reflecting an early stage of disease expression that is not detectable using conventional criteria.⁵ The diagnostic performance of WTSD appears particularly strong in women, where it has shown higher sensitivity and specificity compared to traditional LVWT thresholds.^{5,6}

However, despite its promise, WTSD has primarily been studied using CMR, which, although highly accurate, is not universally available and may not be feasible for large-scale screening.

To address the limitations of previous studies, this retrospective study primarily aimed to validate Transthoracic Echocardiography (TTE) -derived WTSD against CMR-derived WTSD as the reference imaging modality. As a secondary objective, we evaluated the potential diagnostic role of TTE-derived WTSD in distinguishing overt HCM from non-HCM hypertrophic phenotypes.

Methods

Study design and population

This study is designed as a single-centre retrospective proof-of-concept observational analysis aimed at evaluating the feasibility and diagnostic utility of WTSD assessed by CMR and validate it with TTE in patients with hypertrophic phenotype suggestive of HCM.

The study was conducted at the Cardiovascular Imaging Unit and Hypertrophic Cardiomyopathy Outpatient Clinic of Vita-Salute San Raffaele University/IRCCS San Raffaele Hospital, Milan, Italy.

As a proof-of-concept study preceding the multicentre prospective IMAGE-HCM trial, consecutive patients previously evaluated for hypertrophic phenotype between January 2022 and January 2025 were retrospectively screened.

The study population included:

1. Patients with clinically established HCM according to current guidelines criteria.
2. Patients with unexplained hypertrophic phenotype not fulfilling definitive diagnostic criteria for HCM.
3. Genotype-positive individuals with absent or mild hypertrophy.
4. Genotype-negative patients with hypertrophic phenotype.

All patients who had performed clinical, electrocardiographic, echocardiographic, CMR, and genetic analysis in San Raffaele hospital were analyzed and included in the present study.

Particular focus was placed on subjects with subtle or heterogeneous hypertrophic remodeling, including women, early phenotypic expression, and borderline wall thickness values.

All echocardiographic examinations and CMR studies were retrospectively reviewed and analyzed by a dedicated core laboratory at IRCCS San Raffaele Hospital in Milan, Italy. WTSD measurements were independently derived from both TTE and CMR datasets in order to evaluate reproducibility and diagnostic agreement between the two imaging modalities.

Exclusion criteria included poor echocardiographic image quality precluding reliable WTSD assessment and incomplete or inadequate CMR or TTE imaging datasets. Patients with infiltrative or storage diseases were not excluded, as these conditions were included among the non-HCM hypertrophic phenotypes for comparison.

The study was approved by the local ethical committee (Protocol number: CET 35-2025). Given the retrospective nature of the proof-of-concept analysis, data were anonymized and managed according to institutional and national privacy regulations.

Echocardiography

All subjects underwent TTE following current international guidelines using Vivid E95 (GE, Wauwatosa, WI – USA) and EpiqCVx (Philips, Bothell, WA – USA) machines.⁷ Maximum LVWT was measured at end-

diastole, visually defined as the cardiac phase with the greatest LV volume. SAM of the mitral valve and LV outflow tract obstruction was explored in supine position at rest and during Valsalva manoeuvre. Presence of papillary muscles abnormalities, LV aneurysm, myocardial crypts and bridges was also evaluated. LV diastolic function and left atrial dimensions was assessed as currently recommended.⁸ In addition to conventional measurements, WTSD was calculated as the standard deviation of the maximum LVWT in 16 segments measured from a parasternal short axis view at the level of the mitral valve (six segments), papillary muscles (six segments) and apical portion of the LV (four segments) following the Cerqueira et al. (Fig. 1).⁹ The segments were measured manually tracing endocardial and epicardial contour.

Data regarding echocardiographic parameters were obtained offline using a dedicated software already used in clinical practice (TomTec Imaging Systems®, Unterschleissheim, Germany).

Cardiac Magnetic Resonance (CMR)

CMR was performed using 1.5 Testla MRI scanners (Achieva® and Achieva dStream®; Philips Medical Systems, Eindhoven, the Netherlands). Standard CMR protocols were used to carry out morphologic, functional and tissue characterization analysis with the use of gadolinium-based contrast agents (GBCAs).¹⁰ Sets of LV short axis cine images were acquired from the mitral plane valve to the LV apex using ECG triggered balanced steady-state free precession (bSSFP) pulse sequence. The end-systolic and end-diastolic cardiac phases were visually identified as the cardiac phase having, respectively, the smallest and the greatest LV volume. Then, LVWT were semi-automatically measured for all the 16 segments at end-systole and end-diastole, manually tracing endocardial and epicardial contour with the exclusion of papillary muscles. WTSD was added to recommended CMR measurements^{5,6}. Presence of secondary features of HCM was also explored.

Genetic assessment

Genetic status derived from test performed following current recommendation both in patients with diagnosed HCM, in first-degree relatives and in subjects with suspected HCM, if deemed indicated by the clinical cardiologist, were collected. Genetic tests were carried out through sampling of peripheral blood flow followed by next-generation sequencing (NGS) analysis and Sanger validation of pathogenic or likely pathogenic mutations or on variant of uncertain significance not satisfying NGS quality criteria. Blood samples were collected during the first clinical evaluation.

Endpoints

The endpoints we evaluated were threefold:

1. Evaluate the feasibility, reproducibility, and diagnostic agreement of WTSD measurements obtained by TTE compared with CMR-derived WTSD in patients with hypertrophic phenotype suggestive of HCM.
2. Assess the diagnostic performance of echocardiographic WTSD in identifying patients with HCM phenotype.
3. Analyze the ability of WTSD to detect subtle or early hypertrophic remodeling in women and genotype-positive individuals.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range) according to distribution normality assessed by the Kolmogorov–Smirnov test. Categorical variables were expressed as percentages. Comparisons between groups were performed using Student's t-test or ANOVA for normally distributed variables and Mann–Whitney U or Kruskal–Wallis tests for non-normally distributed variables, as appropriate. Categorical variables were compared using chi-squared or Fisher exact tests. Correlation and agreement between echocardiographic and CMR-derived WTSD measurements were evaluated using Pearson or Spearman correlation coefficients, intraclass correlation coefficients (ICC), and Bland–Altman analysis. Receiver operating characteristic (ROC) curve analysis were performed to assess the diagnostic performance of WTSD for identification of HCM phenotype. Area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated for predefined WTSD cut-offs, including the proposed threshold of > 2.4 . Given the exploratory and proof-of-concept nature of the study, analyses will primarily be considered hypothesis-generating and intended to inform the design and sample size estimation of the subsequent prospective IMAGE-HCM study.

Inter-Observer and Intra-Observer Reproducibility

Echocardiographic WTSD measurements were independently performed by two cardiologists, whereas cardiac magnetic resonance WTSD measurements were independently performed by cardiologists and radiologists. Each observer performed all measurements twice, first at the time of the examination and again before data analysis, blinded to the results of the previous assessment, in order to evaluate intra- and inter-observer reproducibility.

This was performed using both intraclass correlation coefficients (ICC) and Bland–Altman analysis. ICCs were calculated using a two-way absolute-agreement, single-measure model [ICC(A,1)] and are reported with 95% confidence intervals. Agreement between repeated measurements was further evaluated by Bland–Altman analysis, with calculation of the mean bias and 95% limits of agreement (LoA), defined as the mean difference $\pm$ 1.96 standard deviations of the differences. Proportional bias was assessed by linear regression of the measurement differences on their corresponding means. A p value < 0.05 was considered statistically significant.

Results

Study Population

The final study population comprised 51 patients with a hypertrophic phenotype who fulfilled all inclusion and exclusion criteria. Of these, 37 had overt HCM, whereas 14 had non-HCM hypertrophic phenotypes, including cardiac amyloidosis and hypertensive heart disease. Baseline clinical and demographic characteristics are summarized in Table 1. The cohort was predominantly male, with broadly comparable baseline characteristics between groups. Hypertension was present in 53% of patients, whereas dyslipidaemias and diabetes mellitus were each present in 25%.

Table 1
, Baseline Characteristics.

Baseline characteristics	HCM, N = 37	Hypertrophic phenotype, N = 14	p-value
Age, y.o.	57.9 ± 11.5	66.8 ± 18.6	0.125
BSA	25.1 ± 6.2	26.2 ± 10.3	0.826
BMI, kg/m2	25.7 ± 4.1	24.2 ± 2.4	0.121
Female sex, n (%)	17 (45)	5 (35)	0.54
Hypertension, n (%)	19 (51)	8 (57)	0.76
Dyslipidemia, n (%)	8 (35)	5 (21)	0.3
Diabetes mellitus, n (%)	2 (5)	1 (7)	> 0.9
Current or former smoking, n (%)	4 (10)	1 (7)	0.47
Coronary artery disease, n (%)	4 (10)	1 (7)	0.47
Atrial fibrillation, n (%)	4 (10)	4 (28)	0.19
Family history of cardiomyopathy, n (%)	9 (24)	2 (14)	0.04*
Family history of SCD, n (%)	10 (27)	2 (14)	0.04*
ICD, n (%)	3 (8)	1 (7)	0.5
NHYA class I or II, n (%)	34 (91)	13 (92)	0.5
NHYA class III or IV, n (%)	3 (8)	1 (7)	0.45

Echocardiographic Characteristics

TTE demonstrated a more asymmetric LV hypertrophic pattern in patients with overt HCM. Although maximal WT did not differ significantly between groups, IVSd was greater in HCM than in non-HCM

patients (17.9 ± 5.3 vs. 14.4 ± 3.0 mm, $P = 0.005$), resulting in a higher IVSd/PWd ratio (1.7 ± 0.6 vs. 1.1 ± 0.1 , $P < 0.001$). LV systolic function was preserved in both groups, with no significant differences in LVEF, GLS, LV dimensions, diastolic parameters, or LA size. RV morphology and function were also broadly comparable. Pericardial effusion was more frequently observed in non-HCM patients (Table 2).

Table 2
, Echocardiographic Characteristics.

Variable	HCM, N = 37	Hypertrophic phenotype, N = 14	p-value
LVEDD, mm	43.0 ± 5.3	42.6 ± 7.8	0.865
LVESD, mm	25.1 ± 6.2	26.2 ± 10.3	0.826
IVS, mm	17.9 ± 5.3	14.4 ± 3.0	0.005
PW, mm	11.1 ± 3.1	12.6 ± 2.8	0.102
IVS/PW	1.7 ± 0.6	1.1 ± 0.1	< 0.001
RWT	0.5 ± 0.2	0.6 ± 0.2	0.540
LV mass, g	248.3 ± 89.0	215.6 ± 42.8	0.131
LV mass index, g/m ²	136.1 ± 47.9	129.5 ± 27.6	0.599
AP LA diameter, mm	38.9 ± 8.0	38.2 ± 2.9	0.744
Baseline LVOT gradient, mmHg	26.8 ± 29.6	15 ± 5	
LVOT gradient with Valsalva, mmHg	46.2 ± 39.8	19.0 ± 6	
E wave, m/s	0.8 ± 0.4	0.9 ± 0.5	0.345
A wave, m/s	0.7 ± 0.3	11.0 ± 30.4	0.343
E/A	1.2 ± 0.8	1.0 ± 0.5	0.392
Lateral e', cm/s	8.2 ± 3.1	7.3 ± 2.6	0.370
E/e'	10.3 ± 6.1	13.0 ± 4.9	0.158
LVEF, %	62.5 ± 7.7	59.1 ± 9.0	0.232
GLS, %	-16.8 ± 8.4	-15.3 ± 7.7	0.711
LVEDVi, mL/m ²	49.1 ± 14.3	48.1 ± 12.6	0.833
LVESVi, mL/m ²	18.7 ± 7.3	19.0 ± 9.0	0.936
LAV, mL	73.6 ± 32.3	60.1 ± 20.0	0.125
AP LA diameter, mm	38.3 ± 7.7	39.8 ± 4.5	0.557
LAVI, mL/m ²	39.7 ± 16.8	34.3 ± 11.6	0.269
PAPs, mmHg	28.1 ± 9.6	30.0 ± 9.6	0.645
TAPSE, mm	22.7 ± 3.8	21.0 ± 2.8	0.123
S' RV, cm/s	13.0 ± 2.0	12.0 ± 3.1	0.327
RV FAC, %	47.6 ± 4.3	46.8 ± 8.1	0.825

Variable	HCM, N = 37	Hypertrophic phenotype, N = 14	p-value
Echocardiographic WTSD	3.9 ± 1.3	2.3 ± 0.9	< 0.001

Notably, myocardial WT heterogeneity, assessed by WTSD, was significantly greater in HCM than in non-HCM patients (WTSD-TTE, 3.9 ± 1.3 vs. 2.3 ± 0.9, $P = 0.001$) (Fig. 2, **Panel A**).

CMR Findings

CMR findings are summarized in Table 3. Maximal WT was greater in HCM than in non-HCM patients (20.5 ± 6.5 vs. 17.0 ± 3.9 mm, $P = 0.024$). LVEF and RVEF were also higher in HCM (64.1 ± 9.1% vs. 56.3 ± 12.3%, $P = 0.045$, and 64.5 ± 7.3% vs. 54.9 ± 13.1%, $P = 0.019$, respectively). Conversely, RVH was more frequent in non-HCM patients (35.7% vs. 5.9%, $P = 0.017$).

LGE was highly prevalent in both groups (86.5% vs. 85.7%, $P = 0.900$), but its pattern and distribution differed significantly. HCM patients more frequently exhibited a mid-wall LGE pattern (71.4% vs. 28.6%, $P = 0.010$) and a blurred LGE pattern (45.7% vs. 7.1%, $P = 0.018$), whereas diffuse LGE was more common in non-HCM patients (57.1% vs. 17.1%, $P = 0.012$). VPI involvement predominated in non-HCM patients (57.1% vs. 2.8%, $P < 0.001$), while atrial LGE was observed exclusively in the non-HCM group (35.7% vs. 0%, $P < 0.001$).

Markers of diffuse myocardial involvement were also more pronounced in non-HCM patients. ECV was significantly higher (46.6 ± 13.4% vs. 29.5 ± 8.3%, $P = 0.001$), diffuse T1 elevation was more frequent (84.6% vs. 36.7%, $P = 0.007$), and elevated T2 values were more common (83.3% vs. 42.9%, $P = 0.035$).

Table 3
Cardiac Magnetic Resonance Parameters

Variable	HCM, N = 37	Hypertrophic phenotype, N = 14	p-value
Maximum wall thickness, mm	20.5 ± 6.5	17.0 ± 3.9	0.024
LVEF by CMR, %	64.1 ± 9.1	56.3 ± 12.3	0.045
LVEDV, mL	141.1 ± 43.2	131.1 ± 38.6	0.434
LVEDVi, mL/m ²	76.3 ± 19.9	73.1 ± 16.6	0.574
LV mass index, g/m ²	85.7 ± 53.2	77.8 ± 25.1	0.487
RVEF by CMR, %	64.5 ± 7.3	54.9 ± 13.1	0.019
RVEDVi, mL/m ²	66.4 ± 18.1	73.4 ± 21.3	0.290
LGE	32/37 (86.5%)	12/14 (85.7%)	0.9
Native T1, ms	1,110.2 ± 69.6	1,163.8 ± 102.7	0.093
T2 mapping, ms	53.5 ± 5.7	55.8 ± 5.4	0.331
WTSD	3.4 ± 1.3	2.6 ± 0.9	0.231

CMR-derived WTSD was significantly higher in HCM than in non-HCM patients (3.4 ± 1.3 vs. 2.6 ± 0.9 , $P = 0.020$)(**Figure 2, Panel B**).

WTSD and Agreement Between TTE and CMR

WTSD consistently differentiated HCM from non-HCM hypertrophic phenotypes across both imaging modalities. WTSD was significantly higher in HCM by both TTE and CMR (WTSD-TTE, 3.9 ± 1.3 vs. 2.3 ± 0.9 , $P = 0.001$; WTSD-CMR, 3.4 ± 1.3 vs. 2.6 ± 0.9 , $P = 0.020$).

Among patients with paired imaging studies, WTSD obtained by TTE and CMR showed a strong positive correlation ($r = 0.86$, 95% CI 0.72–0.93, $P < 0.001$), supporting a high degree of concordance between the two modalities (Fig. 3). Within the HCM subgroup, WTSD tended to be higher in patients with sarcomeric or non-sarcomeric genetic abnormalities and in those with LGE, although these differences did not reach statistical significance.

Inter-observer and Intra-observer Variability

Intra-observer reproducibility ICC values were 0.470 (95% CI 0.113–0.718) and 0.761 (95% CI 0.542–0.883) for the first and second operator respectively. Inter-observer ICC was 1.000 at the first assessment and 0.683 (95% CI 0.411–0.842) at the second assessment. Bland–Altman analysis showed small mean biases across comparisons, with no evidence of significant proportional bias as shown in Table 4.

Diagnostic Performance

WTSD showed moderate discriminatory performance for identifying overt HCM. CMR-derived WTSD yielded an optimal cut-off of ≥ 2.3 , with an AUC of 0.70 (95% CI 0.54–0.85, $P = 0.028$). TTE-derived WTSD showed comparable performance, with the same optimal cut-off of ≥ 2.3 and an AUC of 0.69 (95% CI 0.52–0.84, $P = 0.030$) Fig. 4.

Table 4: Inter- and Intra-Observer Variability

Intra- and inter-observer reproducibility of echocardiographic WTSD measurements				
Analysis	Reliability	Agreement — Bland–Altman analysis		
	ICC (95% CI)	Mean bias	95% LoA	p for proportional bias
Intra-observer, Cardiologist 1	0.470 (0.113-0.718)	-0.12	-2.15 to 1.92	0.534
Intra-observer, Cardiologist 2	0.761 (0.542-0.883)	-0.09	-1.43 to 1.25	0.230
Inter-observer, Time 1	1.000 (1.000-1.000)	0.00	0.00 to 0.00	NA
Inter-observer, Time 2	0.683 (0.411-0.842)	0.03	-1.43 to 1.49	0.757
ICC = intraclass correlation coefficient; CI = confidence interval; LoA = limits of agreement. ICC was calculated using a two-way absolute-agreement, single-measure model [ICC(A,1)].				

Discussion

In this retrospective single-centre study of patients presenting with a hypertrophic phenotype, we evaluated myocardial wall-thickness heterogeneity using WTSD derived from both TTE and CMR. The main findings are threefold. First, WTSD can be assessed using TTE and shows excellent concordance with CMR-derived measurements, supporting its reliability across imaging modalities. Second, WTSD was significantly higher in patients with overt HCM than in those with non-HCM hypertrophic phenotypes using both techniques. Third, WTSD provided discriminatory information beyond conventional measures of hypertrophy, supporting myocardial wall-thickness heterogeneity as a distinctive feature of the HCM phenotype.

WTSD as a Feasible and Reproducible Echocardiographic Marker of Myocardial Heterogeneity

The principal finding of our study is that WTSD can be assessed using TTE and demonstrates strong agreement with CMR-derived measurements. To our knowledge, this is the first study to evaluate and validate WTSD using echocardiography. This finding is particularly relevant because it translates a quantitative marker of myocardial heterogeneity from advanced cross-sectional imaging to the most widely available first-line imaging modality.

WTSD was initially evaluated in post-mortem CMR hearts and subsequently validated in larger cohorts of patients with HCM and healthy controls, showing that patients with HCM carrying pathogenic sarcomeric variants had significantly greater wall thickness dispersion than both normal hearts and patients with non-HCM hypertrophy. However, no previous study has investigated WTSD using echocardiography.^{5,6}

Importantly, the reproducibility analysis further supports the feasibility of echocardiographic WTSD assessment. Bland–Altman analysis demonstrated low systematic bias and no evidence of proportional bias, while ICC analysis showed encouraging intra- and inter-observer reliability. These findings are encouraging for the clinical development of WTSD as a novel echocardiographic marker. Despite the exploratory nature and limited sample size of this proof-of-concept study, the low systematic bias and absence of proportional bias suggest that WTSD can be measured with acceptable reproducibility. These results provide a rationale for further validation in larger cohorts and for refinement of the measurement protocol to improve observer consistency.

CMR remains the reference technique for comprehensive morphological characterization of HCM because of its high spatial resolution, unrestricted imaging planes, and ability to identify focal hypertrophy that may be missed by echocardiography. However, TTE remains the cornerstone of the initial assessment of patients with suspected HCM. The close concordance between TTE- and CMR-derived WTSD, together with the encouraging reproducibility of echocardiographic measurements, therefore suggests that the spatial heterogeneity of myocardial hypertrophy can be captured consistently in routine clinical practice.

WTSD and the Heterogeneous Architecture of HCM

The second major finding is that patients with overt HCM showed significantly greater wall-thickness heterogeneity than patients with non-HCM hypertrophic phenotypes, both by CMR and TTE. Importantly, this difference was observed despite only a modest separation in maximal wall thickness, suggesting that WTSD is not simply a surrogate for the overall severity of hypertrophy.

Current diagnostic frameworks are necessarily centred on maximal left ventricular wall thickness. However, this measurement represents only the thickest point of a complex three-dimensional phenotype. HCM is characterized by marked regional variation in myocardial thickness, with preferential hypertrophy of specific segments and relative preservation of adjacent myocardium. Consequently, patients with similar maximal wall thickness may have substantially different patterns of ventricular remodelling.^{11,12}

WTSD captures this additional dimension by quantifying the dispersion of wall thickness throughout the ventricle. Previous studies using CMR have suggested that patients with HCM, particularly those with sarcomeric mutations, exhibit greater wall-thickness dispersion than healthy individuals and patients with non-HCM hypertrophy. Our findings extend these observations by showing that this feature can also be identified using echocardiography.

Thus, maximal wall thickness and WTSD provide complementary information: maximal wall thickness describes *how thick the thickest segment is*, whereas WTSD describes *how heterogeneous wall thickness is throughout the ventricle*. Their combined assessment may therefore provide a more complete morphological characterization of the hypertrophic phenotype.

Diagnostic Implication and Future Directions

Differentiating HCM from other causes of left ventricular hypertrophy remains clinically challenging because substantial overlap exists in conventional measures of hypertrophy. In our cohort, WTSD showed comparable discriminatory performance using CMR and TTE, with an optimal threshold of approximately 2.3 and area-under-the-curve values of approximately 0.70.

WTSD should not be considered a stand-alone diagnostic test. Rather, its potential value lies in providing quantitative information on myocardial architecture that is not captured by maximal wall thickness alone. Echocardiographic WTSD could potentially serve as an accessible first-line marker of myocardial heterogeneity, while CMR could provide subsequent high-resolution morphological and tissue characterization in patients with an uncertain diagnosis or discordant phenotypic features.

Further prospective and multicentre studies are required to establish the incremental diagnostic and prognostic value of WTSD beyond established parameters, including maximal wall thickness, ventricular mass, hypertrophy pattern, LGE, T1 mapping, extracellular volume, and clinical variables.

Overall, our findings support a broader approach to the morphological assessment of HCM. The phenotype is defined not only by the magnitude of myocardial hypertrophy but also by its spatial distribution. WTSD provides a simple quantitative measure of this heterogeneity that can be obtained consistently using both CMR and routine TTE. The demonstration that echocardiographic WTSD is feasible, reliable, and strongly concordant with CMR measurements represents the principal finding of this study and provides an important step towards the broader clinical application of wall-thickness heterogeneity as a marker of the hypertrophic phenotype.

Limitations

Several limitations should be acknowledged.

First, this was a retrospective single-center study with a relatively small sample size, particularly in the non-HCM hypertrophic phenotype group. Consequently, statistical power was limited and subgroup analyses should be considered exploratory.

Second, the cohort included a heterogeneous group of non-HCM hypertrophic phenotypes, including cardiac amyloidosis and hypertensive heart disease. While this reflects real-world clinical practice, it may have increased variability within the comparison group.

Third, the diagnostic performance analyses were conducted within the same population used to derive WTSD thresholds. Therefore, the proposed cut-off values require external validation in independent

cohorts.

Finally, the retrospective nature of the study precludes assessment of the prognostic significance of WTSD. Whether increased wall-thickness heterogeneity is associated with clinical outcomes, disease progression, arrhythmic risk, or heart failure development remains unknown and warrants prospective investigation.

Conclusions

This study provides the first validation of WTSD by TTE, demonstrating excellent concordance with CMR-derived measurements. TTE-derived WTSD was significantly greater in overt HCM than in non-HCM hypertrophic phenotypes, indicating that myocardial wall-thickness heterogeneity is a distinctive feature of the HCM phenotype. These findings establish WTSD as a feasible echocardiographic marker of myocardial heterogeneity and support its further validation as an accessible tool for phenotypic differentiation in patients with left ventricular hypertrophy.

Declarations

Fundings

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Data availability

Due to the strict ethical approvals provided in our study, the data used is available from the corresponding author upon request and after establishment of data sharing agreement between institutions.

Ethics approval and consent to participate

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the local ethical committee (Protocol number: CET 35-2025). Informed consent was provided by all participants, or their substitution decision maker, prior to enrollment. Given the retrospective nature of the proof-of-concept analysis, data were anonymized and managed according to institutional and national privacy regulations.

Consent to publish declaration

Not applicable.

Competing interests

The authors declare no competing interests.

Author Contribution

Monica Barki, Eustachio Agricola, Alessandro Aresu and Federico Biondi contributed to the conception and design of the study, data analysis and interpretation, and manuscript drafting. Alessandro Aresu and Diego Fanti contributed to data analysis and interpretation and manuscript drafting. Giorgio Escalar contributed to figure preparation and data visualization. All other authors contributed to the acquisition, analysis, and/or interpretation of data and to the preparation of tables and figures. All authors critically reviewed the manuscript, revised it for important intellectual content, and approved the final version.

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Figures

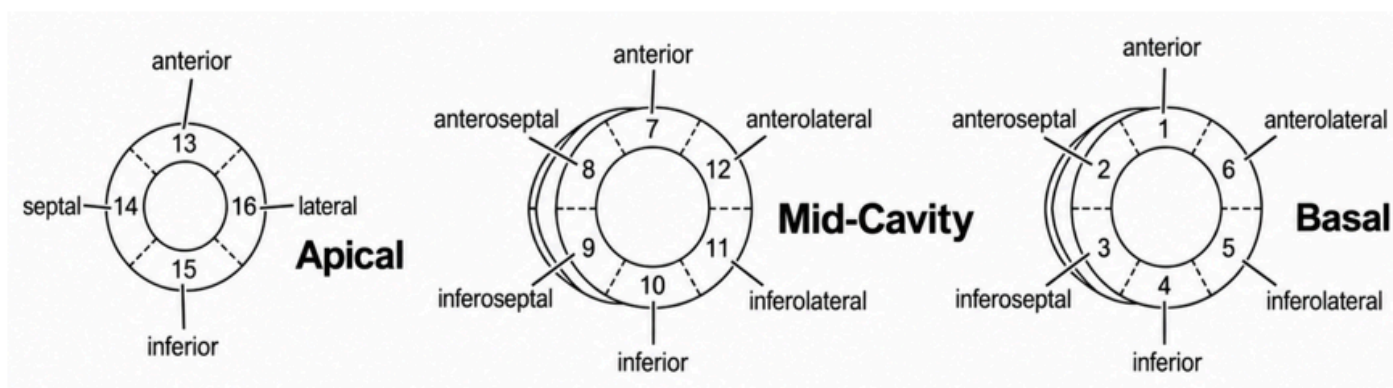


Figure 1

LV segmentation model from Cerqueira et al.

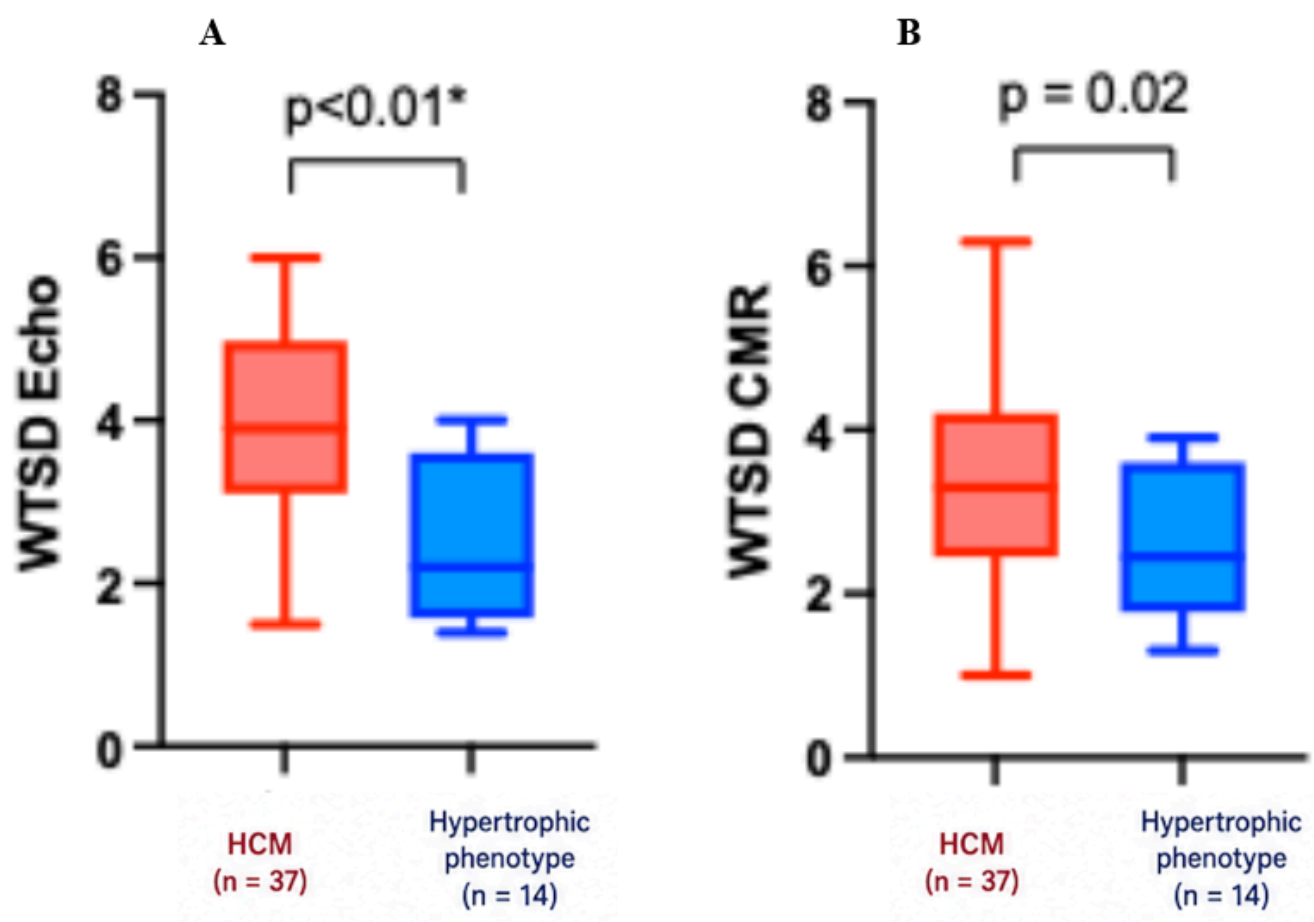


Figure 2

Box-and-whisker plots showing the distribution of wall thickness standard deviation (WTSD) measured by echocardiography (WTSD-ECHO – Panel A) and cardiac magnetic resonance (WTSD-CMR – Panel B) in patients with overt hypertrophic cardiomyopathy (HCM) compared with non-HCM hypertrophic phenotypes. WTSD was significantly higher in patients with overt HCM than in those with non-HCM hypertrophic phenotypes for both echocardiography and CMR ($p=0.001$ and $p=0.020$, respectively). Boxes represent the interquartile range, the horizontal line indicates the median, and whiskers indicate the range of the data.

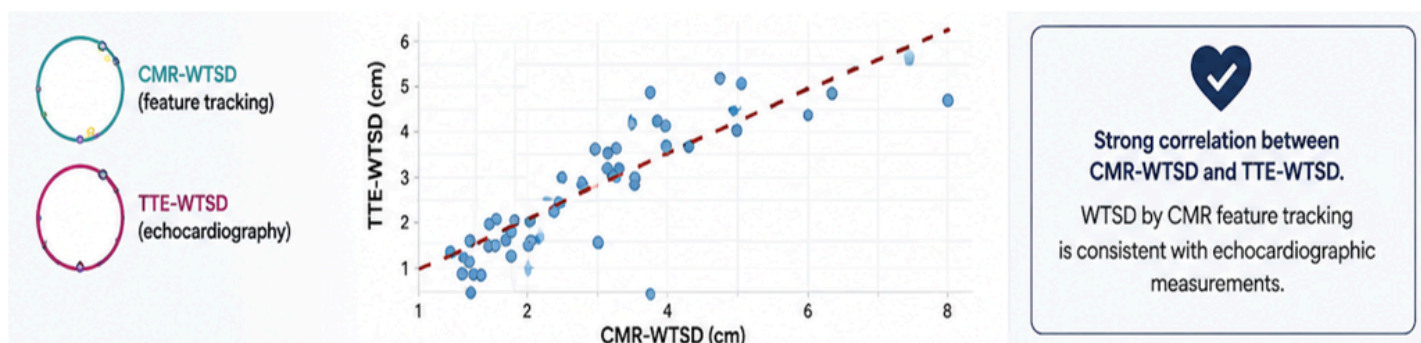


Figure 3

Scatter plot showing the correlation between WTSD measured by echocardiography (WTSD-TTE) and cardiac magnetic resonance (WTSD-CMR). A strong positive correlation was observed between the two measurements (**Pearson's $r = 0.86$, $p < 0.01$**), indicating excellent agreement between echocardiographic and CMR-derived WTSD values. Each point represents an individual patient; the solid line represents the linear regression line and the dashed lines indicate the corresponding 95% confidence interval.

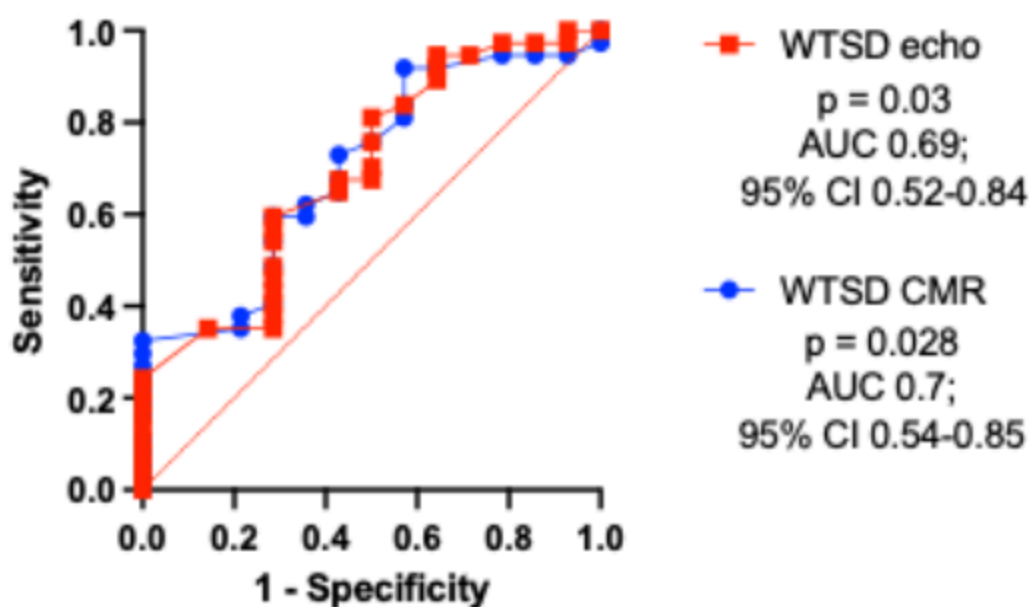


Figure 4

Diagnostic performance of tissue-specific dispersion (TSD) for identifying overt hypertrophic cardiomyopathy (HCM). Receiver operating characteristic (ROC) analysis demonstrated moderate discriminatory performance of WTSD for the identification of overt HCM. CMR-derived wall-thickness-specific dispersion (WTSD) showed an optimal cut-off of ≥ 2.3 , with an area under the curve (AUC) of

0.70 (95% CI, 0.54–0.85; $P = 0.028$). Echo-derived WTSD showed comparable discriminatory performance, with the same optimal cut-off of ≥ 2.3 and an AUC of 0.69 (95% CI, 0.52–0.84; $P = 0.030$).