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ORIGINAL ARTICLE
Vascular and cardiac imaging

Exaggerated myocardial torsion may contribute to dynamic left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

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Aims Dynamic left ventricular (LV) outflow tract obstruction (LVOTO) is associated with symptoms and increased risk of developing heart failure in hypertrophic cardiomyopathy (HCM). The association of LVOTO and LV twist mechanics has not been well studied in HCM. The aim of the study was to compare the pattern of LV twist in patients with HCM associated with asymmetrical septal hypertrophy with and without LVOTO.

Methods and results Echocardiography (including speckle tracking) was performed in 212 patients with HCM, divided according to the absence ($n = 130$) or presence ($n = 82$) of LVOTO (defined as peak pressure gradient ≥30 mmHg either at rest and/or with Valsalva manoeuvre). Patients with LVOTO were older, had smaller LV dimensions, a higher LV ejection fraction (LVEF), a longer anterior mitral valve leaflet length, and a higher early transmitral pulsed wave to septal tissue Doppler velocity ratio (*E*/*E*′). A univariate analysis showed that peak twist was significantly higher in patients with LVOTO compared with patients without LVOTO (19.7 ± 7.3 vs. 15.7 ± 6.0, $P = 0.00015$). Peak twist was similarly enhanced in patients with LVOTO, manifesting only during Valsalva (19.2 ± 5.6, $P = 0.007$) and patients with resting LVOTO (19.9 ± 8.0, $P = 0.00004$) compared with patients without LVOTO (15.7 ± 6.0). A stepwise forward logistic regression analysis showed that LVEF, LV end-systolic dimension indexed to body surface area, anterior mitral valve leaflet length, *E*/*E*′, and peak twist were all independently associated with LVOTO.

Conclusion This study demonstrates that increased peak LV twist is independently associated with LVOTO in patients with HCM. Peak twist was similarly exaggerated in patients with only latent LVOTO, suggesting that it may play a contributory role to LVOTO in HCM.

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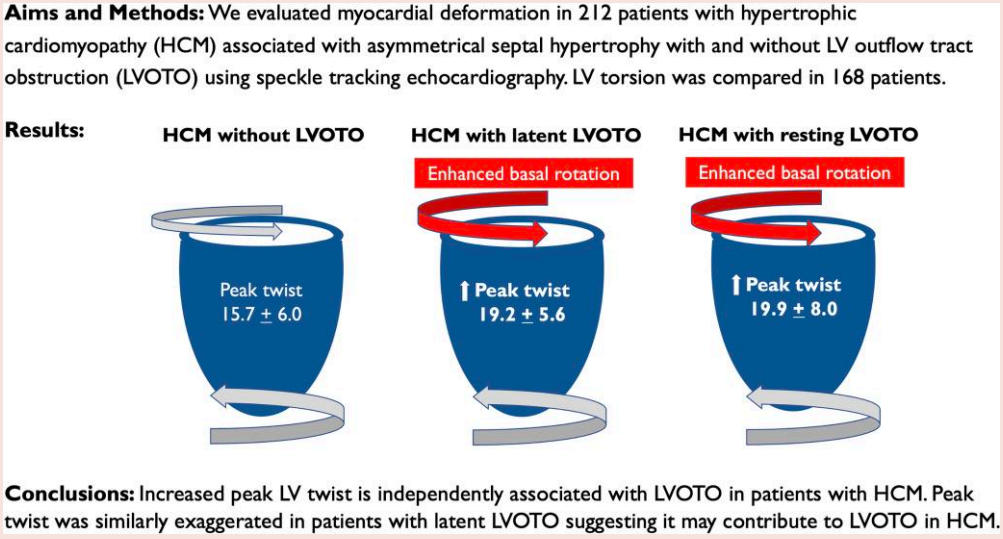
Graphical Abstract



Keywords Hypertrophic cardiomyopathy • Left ventricular outflow tract obstruction • Left ventricular twist

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease often presenting with exercise intolerance and heart failure.[1] Dynamic left ventricular (LV) outflow tract (LVOT) obstruction (LVOTO) is reported in 25–30% of patients with HCM at rest[2] and up to 70% of patients post exercise.[3] Left ventricular outflow tract obstruction is associated with increased symptoms, and resting outflow tract gradients have been shown to be independent determinants of progressive heart failure and cardiovascular mortality.[4,5]

Speckle tracking echocardiography allows the evaluation of different components of cardiac motion, including longitudinal, circumferential and radial strain, rotation, and twist,[6,7] and has been used to study myocardial deformation mechanics in HCM.[8–12] The impact of LV twist mechanics on LVOTO has not been well studied in HCM. A previous study suggested increased basal rotation in patients with HCM dependent on the pattern of hypertrophy.[9] Importantly, this study had a small sample size and did not separately evaluate patients with latent LVOTO. Comparisons between patients with resting vs. latent LVOTO vs. no LVOTO may provide incremental mechanistic insights into the genesis of dynamic obstruction. Accordingly, we sought to describe the patterns of twist in a large cohort of patients with HCM and asymmetrical septal hypertrophy (ASH) with either resting LVOTO, inducible LVOTO post-Valsalva, or no LVOTO. We hypothesized that abnormal LV twist would be associated with LVOTO at rest or post-Valsalva.

Methods

Study population

A total of 212 patients with HCM (140 males) with ASH were evaluated. The diagnosis of HCM was based on conventional echocardiographic demonstration of a non-dilated, hypertrophic left ventricle, with a septal thickness ≥15 mm and an interventricular septal/posterior wall thickness ratio >1.3 not explained by long-term hypertension or other cardiac or systemic diseases.[13–15] Patients were divided into two groups based on peak instantaneous LVOT gradients: (i) non-obstructive (<30 mmHg at rest and with Valsalva manoeuvre, $n = 130$) and (ii) obstructive [>30 mmHg either at rest ($n = 57$) or with Valsalva manoeuvre only ($n = 25$)]. The control group consisted of 46 healthy individuals with no history of cardiovascular disease, including some HCM family members who were genotype negative for the family mutation.

Figure 1 provides an outline of how the final study cohort of 212 patients with HCM was formed. Patients with poor echocardiographic images, apical or concentric increase in LV wall thickness, cardiac muscle disease secondary to known systemic conditions, significant valvular heart disease, LV ejection fraction (LVEF) <50%, atrial fibrillation, predominant ventricular pacing, prior open heart surgery, or septal reduction procedures were excluded prior to study consideration, which left 242 patients to be considered for inclusion. Four patients were subsequently excluded, because they were in atrial fibrillation at that time of the echocardiogram, and a further 26 patients were excluded because their image quality was deemed insufficient for myocardial deformation analysis. The study was approved by the Ethics Committee of the Royal Brisbane and Women's Hospital, which waived the requirement for either written or verbal informed consent for the entire study due to the retrospective nature of the evaluation without the risk of harm to study subjects.

Echocardiographic examination

Echocardiographic examinations were performed using a GE Vivid 7 or E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA) with an M5S probe. Comprehensive two-dimensional transthoracic echocardiography was performed in all patients. Left ventricular cavity size, wall thickness, and ejection fraction were determined according to the American Society of Echocardiography's guidelines.[16] Left ventricular ejection fraction was calculated by the modified Simpson's method. Maximum LV wall thickness was measured in parasternal short-axis view as recommended.[15] Relative wall thickness was calculated as the sum of the posterior wall thickness and interventricular septal thickness divided by LV end-diastolic dimension.[17] Left atrial volume index was measured using area-length method.[16] Anterior and posterior mitral valve leaflet lengths were measured in the apical long-axis view during diastole and with the leaflet maximally extended. The anterior mitral valve leaflet length was defined as the distance from the

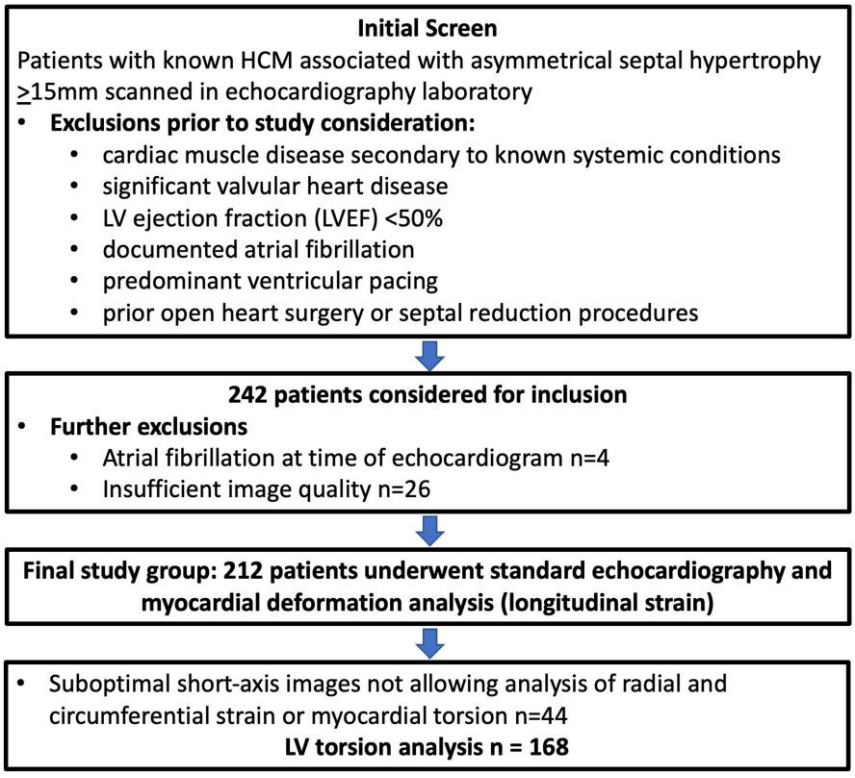


Figure 1 Flow chart describing the formation of the final study cohort.

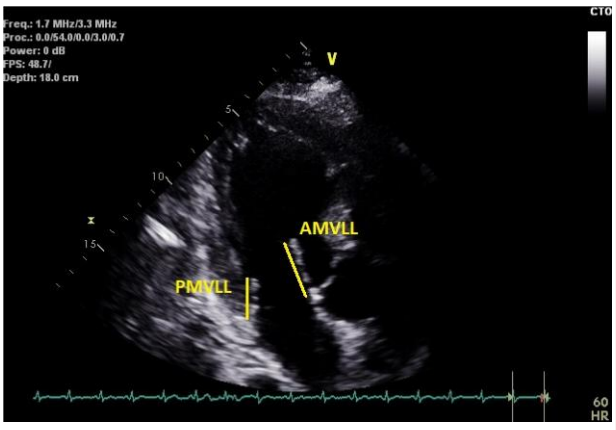


Figure 2 Measurement of anterior mitral valve leaflet length and posterior mitral valve leaflet length in apical long-axis view. The anterior mitral leaflet length (solid line) was measured as the distance from the tip of the leaflet to the insertion of the non-coronary aortic cusp and the posterior mitral leaflet length (solid line) was measured from the tip of the leaflet to its insertion at the posterior mitral annulus.

tip of the leaflet to the insertion of the non-coronary aortic cusp and the posterior mitral valve leaflet length was measured from the tip of the leaflet to its insertion at the posterior mitral annulus (*Figure 2*).[18,19]

All conventional and tissue Doppler measurements were performed at arrested shallow expiration. Mitral inflow, pulmonary venous inflow, peak tricuspid regurgitation velocity, and tissue Doppler velocities of all six walls, namely myocardial systolic (*S′*), early and late diastolic velocities (*E′* and *A′*) were obtained as previously described.[20] The combined assessment of peak early diastolic transmitral flow velocity (*E*) and *E′* was used to calculate *E*/*E′* as a surrogate of LV filling pressure. Pulmonary venous atrial reversal duration minus the mitral *A* duration was also measured as a surrogate of LV end-diastolic pressure.[21] Measurement of the LVOT gradient was performed by continuous-wave Doppler interrogation from the apical five-chamber view. Patients were classified based on peak instantaneous LVOT gradient into non-obstructive (<30 mmHg at rest and with Valsalva manoeuvre) and obstructive (≥30 mmHg at rest and/or with Valsalva manoeuvre).[3,22] Mitral regurgitation was evaluated using the semi-quantitative method and graded as follows: none or trivial (0), mild (1), moderate (2), and severe (3).[23]

Images for two-dimensional speckle tracking analysis were acquired from three apical views and three parasternal short-axis views in all patients with high frame rates (48–90 frames/s) and in arrested respiration. Great effort was made to reduce foreshortening in the apical views and for the LV cross-section to be as circular as possible in short-axis views. We defined the proper parasternal short-axis levels as follows: basal (mitral valve level), mid (papillary muscle level), and apical (LV cavity alone, distal to the papillary muscles and just proximal to the level with LV luminal obliteration at end-systole).

Data analysis for left ventricular myocardial deformation

Off-line speckle tracking analysis was performed on all digitally stored grey-scale images with customized software (EchoPAC PC BT113: GE Healthcare). Longitudinal systolic strain was obtained from three apical views. For each of the three apical and three short-axis views, the sample

Table 1 Demographics for controls and patients with hypertrophic cardiomyopathy without and with left ventricular outflow tract obstruction

Variable	Controls ($n = 46$)	HCM without LVOTO ($n = 130$)	HCM with LVOTO ($n = 82$)	HCM without vs. with LVOTO *P*-value	*P*-value ANOVA
Age (years)	36 ± 14	44 ± 15*	52 ± 14*	0.0001	<0.001
Gender male (*n*, %)	17 (37.0%)	87 (66.9%)	53 (64.6%)		
Heart rate (b.p.m.)	65 ± 8	58 ± 8*	60 ± 8*	0.10	<0.001
Systolic BP (mmHg)	124 ± 13	130 ± 18	130 ± 18**	0.94	0.15
Diastolic BP (mmHg)	71 ± 12	73 ± 11	72 ± 9	0.37	0.57
BSA (m^2)	1.86 ± 0.20	2.00 ± 0.23*	1.95 ± 0.20**	0.11	<0.001
Weight (kg)	75.4 ± 15.5	86.2 ± 18.9*	82.5 ± 15.7*	0.13	<0.001
Height (cm)	170.3 ± 9.1	173.4 ± 12.4	171.8 ± 8.2	0.27	0.019
Hypertension (*n*, %)	1	39 (30.0%)	20 (24.4%)		
Diabetes mellitus (*n*, %)	0	6 (4.6%)	5 (6.1%)		
CKD (*n*, %)	0	3 (2.3%)	4 (4.9%)		
CAD (*n*, %)	0	16 (12.3%)	12 (14.6%)		
COPD (*n*, %)	0	2 (1.5%)	1 (1.2%)		
Stroke (*n*, %)	0	1 (0.77%)	2 (2.4%)		
Family H/O HCM	39 (84.8%)	60 (46.1%)	27 (32.9%)		
Family H/O HCM SD	16 (34.8%)	35 (26.9%)	17 (20.7%)		
NYHA class					
NYHA Class I (*n*, %)	46 (100%)	101 (77.7%)	50 (61.0%)		
NYHA Class II (*n*, %)	0	25 (19.2%)	23 (28.0%)		
NYHA Class III (*n*, %)	0	3 (3.7%)	9 (11.0%)		
NYHA Class IV (*n*, %)	0	1 (0.77%)	0		
Cardiac/unexplained syncope (*n*, %)	0	14 (10.8%)	10 (12.2%)		
NSVT (*n*, %)	0	22 (16.9%)	17 (20.7%)		
Prior cardiac arrest/sustained VT	0	6 (4.6%)	2 (2.4%)		
Past history of AF	0	10 (7.7%)	10 (12.2%)		
Digoxin (*n*, %)	0	0	0		
Loop diuretic (*n*, %)	0	3 (3.7%)	6 (7.3%)		
MRA (*n*, %)	0	1 (0.77%)	3 (3.7%)		
ACEI/ARB (*n*, %)	0	28 (21.5%)	14 (17.1%)		
Beta-blockers (*n*, %)	2 (4.3%)	53 (40.8%)	54 (65.9%)		
Ca++ blocker (*n*, %)	1 (2.2%)	22 (16.9%)	16 (19.5%)		
Amiodarone (*n*, %)	0	2 (1.5%)	0		
Disopyramide (*n*, %)	0	2 (1.5%)	0		
Other BP lowering medication (*n*, %)	0	4 (3.0%)	4 (4.9%)		
ICD (*n*, %)	0	45 (34.6%)	21 (25.6%)		

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BSA, body surface area; BP, blood pressure; CA++, calcium; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HCM, hypertrophic cardiomyopathy; H/O, history of; ICD, implantable cardioverter defibrillator; LVOTO, left ventricular outflow tract obstruction; MRA, mineralocorticoid receptor antagonist; *n*, number; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; SD, sudden death; VT, ventricular tachycardia.
*$P < 0.001$ vs. controls.
**$P < 0.05$ vs. controls.

points were placed manually along the endocardium at the end-systolic frame. The region of interest was adjusted manually (point-and-click approach) to ensure that the inner tracking line coincided with the endocardial border and the outer tracking line to the epicardial surface. A mid-wall tracking line was automatically created at the centre between the two borders. The software then automatically calculates the transmural, endocardial, and epicardial strain at each segment at each view and at each level. End systole was marked as aortic valve closure in the apical long-axis view.

Global longitudinal, circumferential, and radial strains measurements were obtained by averaging peak strain in an 18-segment model (six basal, six mid, and six apical segments).[24] Peak longitudinal, circumferential, and radial strain were reported for each individual myocardial segment, the average of apical segments, the average of mid segments, the average of basal segments, and a global average of all segments. Global longitudinal strain dispersion index (SDI) which reflects the homogeneity of LV longitudinal strain was calculated as the average of the standard deviation values of mean segmental longitudinal strain in all 18 segments.[25] Cardiac rotation,

Table 2 Two-dimensional echocardiographic measurements

Variable	Controls ($n = 46$)	HCM without LVOTO ($n = 130$)	HCM with LVOTO ($n = 82$)	HCM without vs. with LVOTO *P*-value	*P*-value ANOVA
LVEDD (mm)	46.4 ± 4.9	44.8 ± 6.2	40.5 ± 5.2*	<0.00001	<0.001
LVESD (mm)	30.9 ± 4.6	28.3 ± 6.1*	23.7 ± 4.7*	<0.00001	<0.001
LVEDDI (mm/m^2)	25.2 ± 3.1	22.6 ± 3.3*	20.9 ± 2.7*	<0.0001	<0.001
LVESDI (mm/m^2)	16.8 ± 2.6	14.3 ± 3.2*	12.0 ± 2.7*	<0.00001	<0.001
LVEDV (cm^3)	97.3 ± 24.4	94.5 ± 28.5	87.1 ± 23.2**	0.04	0.063
LVESV (cm^3)	35.7 ± 10.6	32.8 ± 12.3	27.2 ± 10.2*	0.001	<0.001
LVEDVI (cm^3/m^2)	52.1 ± 10.7	47.0 ± 12.2**	44.7 ± 10.4*	0.15	0.002
LVESVI (cm^3/m^2)	19.1 ± 4.5	16.3 ± 5.5*	13.9 ± 4.9*	0.002	<0.001
LVEF (Simpson's biplane) (%)	63.0 ± 4.5	65.1 ± 6.4**	68.9 ± 6.1*	<0.0001	<0.001
LA volume index (cm^3/m^2)	27.2 ± 6.6	37.0 ± 11.9*	44.5 ± 15.4*	0.0001	<0.001
Septal thickness (mm)	8.6 ± 1.6	20.7 ± 5.4*	22.0 ± 4.7*	0.07	<0.001
Posterior wall thickness (mm)	8.5 ± 1.7	10.8 ± 2.1*	12.2 ± 2.6*	<0.0001	<0.001
Sep/PW thickness ratio	1.02 ± 0.04	1.94 ± 0.53*	1.86 ± 0.49*	0.23	<0.001
Maximum wall thickness (mm)	9.0 ± 1.8	21.1 ± 5.5*	22.7 ± 4.9*	0.035	<0.001
Relative wall thickness (RWT)	0.38 ± 0.10	0.69 ± 0.20*	0.83 ± 0.22*	<0.00001	<0.001
LVOT diameter (mm)	22.5 ± 1.9	23.5 ± 2.3**	23.3 ± 2.9	0.63	0.07
Anterior MV leaflet length (mm)	27.3 ± 3.2	32.3 ± 5.5*	34.9 ± 5.1*	0.0010	<0.001
Posterior MV leaflet length (mm)	15.2 ± 3.4	20.2 ± 4.4*	22.2 ± 4.7*	0.0019	<0.001
MR grade					
0 (*n*, %)	46 (100%)	125 (96.2%)	41 (50.0%)		
1 (*n*, %)	0	5(3.8%)	18 (22.0%)		
2 (*n*, %)	0	0	20 (24.4%)		
3 (*n*, %)	0	0	3 (3.6%)		

HCM, hypertrophic cardiomyopathy; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEDDI, left ventricular end-diastolic diameter indexed to body surface area; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDI, left ventricular end-systolic diameter indexed to body surface area; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume indexed to body surface area; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; MV, mitral valve; *n*, number; PW, posterior wall; Sep, septum.
*$P < 0.001$ vs. controls.
**$P < 0.05$ vs. controls.

twist, and untwist were computed by speckle tracking.[26,27] Left ventricle rotation is the myocardial rotation around the long axis of the LV. It is the rotational displacement and is expressed in degrees. Counterclockwise rotation, as viewed from the LV apex, was expressed as a positive value, whereas clockwise rotation was expressed as a negative value. Peak basal rotation and peak basal rotation rate were the maximum negative values of the rotation curves from the parasternal short-axis view at the level of the mitral valve. Peak apical rotation and peak apical rotation rate were the maximum positive values of the rotation curves from the parasternal short-axis view at the apical level. Left ventricular twist was the absolute difference in rotation between the apex and the base of the left ventricle as viewed from the LV apex.

Reproducibility of myocardial mechanical analysis

The intra-observer variability was assessed for global longitudinal strain, basal and apical rotation, and twist in 15 randomly selected cases. The same sonographer re-measured the selected cases a month apart. The inter-observer variability was determined by a second sonographer (who was blinded to the clinical details of all patients) performing the measurements on the same 15 cases. Intra- and inter-observer variabilities were calculated as the absolute difference divided by the average of the two observations for all these measurements.

Statistical analysis

All continuous data were normally distributed and therefore expressed as mean ± standard deviation. Comparisons between two different groups were performed using Student's *t*-test. Comparisons among more than two different groups were performed using one-way analysis of variance (ANOVA). A *P*-value <0.05 was considered statistically significant. To identify significant independent correlates of dynamic LVOTO, the variables that were statistically significant in univariate analysis (including age) were introduced in a logistic regression model. Stepwise forward, multiple linear regression analyses were performed to find the independent correlates of dynamic LVOTO. Intra- and inter-observer agreement was assessed using Bland–Altman analysis. The absolute difference divided by the mean of the repeated observations and expressed as a per cent was also calculated for each measurement. All statistical analyses were performed using SPSS version 23 (SPSS, IBM, Chicago, USA).

Results

Patient demographics

Clinical characteristics of study patients are summarized in *Table 1*. A total of 82 patients with HCM associated with LVOTO [mean age

Table 3 Conventional and tissue Doppler measurements

Conventional and tissue Doppler	Controls ($n = 46$)	HCM without LVOTO ($n = 130$)	HCM with LVOTO ($n = 82$)	HCM without vs. with LVOTO *P*-value	*P*-value ANOVA
Mitral *E* velocity (m/s)	0.73 ± 0.15	0.67 ± 0.15*	0.79 ± 0.23	<0.0001	<0.001
Mitral *A* velocity (m/s)	0.45 ± 0.13	0.51 ± 0.18*	0.65 ± 0.22**	<0.00001	<0.001
Mitral DT (ms)	200 ± 30	222 ± 64**	246 ± 78**	0.018	<0.001
Mitral *E*/*A*	1.72 ± 0.59	1.48 ± 0.67*	1.35 ± 0.59**	0.13	0.006
Pulmonary venous *S* velocity (m/s)	0.52 ± 0.14	0.53 ± 0.14	0.53 ± 0.12	0.79	0.86
Pulmonary venous *D* velocity (m/s)	0.53 ± 0.13	0.44 ± 0.12**	0.41 ± 0.12**	0.075	<0.001
Pulmonary venous AR velocity (m/s)	0.23 ± 0.07	0.32 ± 0.12**	0.34 ± 0.12**	0.20	<0.001
Pulmonary venous AR duration (ms)	113 ± 30	154 ± 32**	166 ± 37**	0.012	<0.001
PVAR duration-mitral *A* duration (ms)	−16 ± 36	26 ± 39**	36 ± 35**	0.06	<0.001
LVOTO peak gradient (mmHg)	6 ± 2	10 ± 6**	73 ± 26**	<0.00001	<0.001
PASP (mmHg)	22 ± 6	28 ± 7**	31 ± 8**	0.02	<0.001
E′sep (cm/s)	11.8 ± 3.5	6.3 ± 2.7**	5.1 ± 2.1**	0.001	<0.001
A′sep (cm/s)	8.2 ± 2.1	7.5 ± 2.6	6.8 ± 1.9**	0.023	0.003
S′sep (cm/s)	8.2 ± 1.1	6.9 ± 1.8**	6.1 ± 1.4**	0.003	<0.001
E′lat (cm/s)	15.7 ± 4.5	9.7 ± 4.1**	7.8 ± 3.0**	0.0002	<0.001
A′lat (cm/s)	8.3 ± 2.9	7.5 ± 3.0	7.2 ± 2.4*	0.46	0.09
S′lat (cm/s)	9.6 ± 2.2	7.1 ± 3.0**	6.3 ± 2.0**	0.02	<0.001
E/*E*′sep	6.6 ± 2.0	12.6 ± 6.2**	17.5 ± 7.8**	<0.00001	<0.001
E/*E*′lat	5.0 ± 1.9	8.2 ± 4.3**	11.7 ± 5.7**	<0.00001	<0.001

A, late diastolic; *A*′, late diastolic myocardial velocity; AR, atrial reversal; D, diastolic; DT, deceleration time; *E*, early diastolic; *E*′, early diastolic myocardial velocity; HCM, hypertrophic cardiomyopathy; Hg, mercury; lat, lateral; LVOTO, left ventricular outflow tract obstruction; PVAR, pulmonary venous atrial reversal; PASP, pulmonary artery systolic pressure; *S*, systolic; sep, septal; *S*′, systolic myocardial velocity.
*$P < 0.05$ vs. controls.
**$P < 0.001$ vs. controls.

52 ± 14 years, 53 males (64.6%)], 130 patients with HCM without LVOTO [mean age 44 ± 15 years, 87 males (66.9%)] and 46 control individuals [mean age 36 ± 14 years, 17 males (37.0%)] were enrolled. Patients with HCM were older compared with control subjects, and patients with LVOTO were older compared with patients without LVOTO.

Two-dimensional echocardiographic measurements

Echocardiographic data are summarized in *Table 2*. Left ventricular end-diastolic and end-systolic diameters and volumes were smallest in patients with HCM associated with LVOTO while the LVEF was highest. The maximum LV wall and relative wall thickness and LA volume index were highest in the LVOTO group. There were no differences in LVOT diameter; however, patients with HCM had longer anterior and posterior mitral valve leaflet lengths compared with the control subjects and patients with HCM with LVOTO had significantly longer mitral valve leaflet lengths than patients without LVOTO. There was no mitral regurgitation or trivial mitral regurgitation in all control subjects and in 96.2% of the HCM subjects without LVOTO, whereas only 50% of patients with LVOTO had either no or trivial mitral regurgitation. In the remaining subjects with LVOTO, 22% had mild, 24.4% had moderate, and 3.6% had severe mitral regurgitation.

Conventional and tissue Doppler measurements

As shown in *Table 3*, patients with HCM with LVOTO had higher mitral *E* and *A* velocities and longer mitral deceleration time compared with patients without LVOTO. Myocardial systolic (*S*′sep, *S*′lat), early diastolic (*E*′sep, *E*′lat) and late diastolic (*A*′sep) tissue velocities were lower, and the *E*/*E*′ ratio was significantly higher in patients with LVOTO.

Myocardial deformation measurements

Forty-four of the 212 patients with HCM had suboptimal short-axis images, so measurements of circumferential and radial strain, and myocardial torsion (including rotation and twist) were not possible (*Figure 1*). Global longitudinal strain, global circumferential strain, and global radial strain were highest in the control group and similar between the two HCM groups (see *Table 4*). There was an increasing gradient of longitudinal strain from base to apex in all three groups. The longitudinal SDI which reflects the homogeneity of LV longitudinal strain was lowest in the control group, and it was significantly different comparing patients with and without LVOTO ($P = 0.0005$) indicating significantly greater variation in segmental longitudinal strain in the obstructive group (see *Table 4* and Supplementary material online, *Table S1*).

Patients with HCM had higher peak basal rotation, peak apical rotation, and peak twist compared with the control group (see *Table 4*). Peak basal rotation, peak twist, peak basal rotation rate, and peak twist rate were further exaggerated in patients with HCM with LVOTO when compared with patients without LVOTO (*Figure 3*). Time to peak twist (indexed to R–R interval) was significantly more prolonged in the patients with HCM with LVOTO. Peak basal rotation and peak twist were similarly enhanced in patients with LVOTO whether manifest only during Valsalva (peak basal rotation −8.9 ± 4.5 and peak twist 19.2 ± 5.6) or present at rest (peak basal rotation −8.2 ± 4.4 and peak

Table 4 Myocardial strain and deformation measurements

Parameter	Controls ($n = 46$)	HCM without LVOTO ($n = 130$) ($n = 105$)*	HCM with LVOTO ($n = 82$) ($n = 63$)*	HCM without vs. with LVOTO *P*-value	*P*-value ANOVA
Global longitudinal strain (GLS) (%)	−21.2 ± 2.3	−16.9 ± 3.9**	−16.1 ± 3.4**	0.15	<0.001
GLS basal LV (%)	−19.5 ± 2.5	−15.7 ± 3.4**	−13.2 ± 3.4**	<0.00001	<0.001
GLS mid LV (%)	−20.3 ± 2.1	−15.8 ± 3.8**	−14.9 ± 4.1**	0.08	<0.001
GLS apical LV (%)	−24.0 ± 3.8	−19.0 ± 5.6**	−20.3 ± 5.0**	0.09	<0.001
Long strain dispersion index (SDI)	4.3 ± 1.6	5.2 ± 1.5**	6.2 ± 2.8**	0.0005	<0.001
Global circumferential strain (%)*	−20.3 ± 2.8	−18.0 ± 3.3**	−18.0 ± 3.7**	0.996	0.019
Global radial strain (%)*	49.7 ± 13.3	39.8 ± 13.0**	39.6 ± 11.6**	0.89	<0.001
Peak apical rotation (degrees)*	8.7 ± 5.9	11.0 ± 6.4*	12.6 ± 7.3**	0.12	0.011
Peak mid rotation (degrees)*	3.0 ± 9.2	1.3 ± 6.2	1.2 ± 6.6	0.97	0.36
Peak basal rotation (degrees)	−4.2 ± 4.6	−5.7 ± 4.6	−8.4 ± 4.4**	0.00018	<0.001
Peak twist (degrees)*	13.3 ± 6.3	15.7 ± 6.0*	19.7 ± 7.3**	0.00015	<0.001
Time to peak torsion (ms)*	330 ± 50	347 ± 48	370 ± 42**	0.002	<0.001
Time to peak torsion (% R–R)*	36.0 ± 6.4	34.8 ± 7.9	38.3 ± 5.6	0.0012	0.009
Peak apical rotation rate (degree/s)*	66.0 ± 38.5	66.7 ± 33.2	67.4 ± 32.6	0.89	0.98
Peak basal rotation rate (degree/s)*	−48.6 ± 46.4	−44.3 ± 48.1	−67.6 ± 29.2*	0.0001	0.003
Peak twist rate (degree/s)*	87.4 ± 46.5	88.2 ± 38.5	108.2 ± 33.8*	0.0008	0.003
Peak apical untwist rate*	−61.3 ± 38.0	−56.2 ± 29.3	−58.9 ± 41.4	0.66	0.70
Peak basal untwist rate*	48.4 ± 46.3	49.4 ± 48.2	68.9 ± 35.0*	0.003	0.013
Peak untwist rate (degree/s)*	−94.0 ± 61.1	−84.6 ± 62.9	−87.8 ± 83.3	0.79	0.75

GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; Long, longitudinal; LV, left ventricle; LVOTO, left ventricular outflow tract obstruction; *n*, number; R–R, R–R interval.
*$P < 0.05$ vs. controls.
**$P < 0.001$ vs. controls.

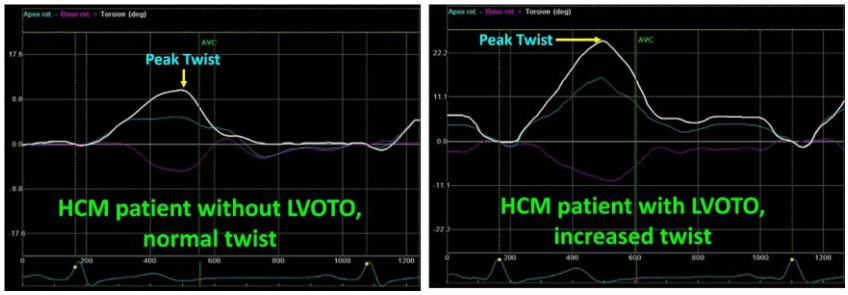


Figure 3 Increased twist in a patient with HCM with LVOTO compared with normal twist in a patient with HCM without LVOTO. Left panel: twist in a patient with HCM without LVOTO. Right panel: twist in a patient with HCM with LVOTO. HCM, hypertrophic cardiomyopathy; LVOTO, left ventricular outflow tract obstruction. Middle line represents apical rotation. Bottom line represents basal rotation. Top line represents twist.

twist 19.9 ± 8.0) compared with patients without LVOTO (peak basal rotation −5.7 ± 4.6 and peak twist 15.7 ± 6.0; see *Table 5*).

Independent correlates of left ventricular outflow tract obstruction

Stepwise forward logistic regression models to identify independent correlates of LVOTO contained the following variables significant on univariate analysis: relative wall thickness, biplane LVEF, *E*′sep, *E*/*E*′ sep, peak twist, LVESD, LVESD indexed to body surface area (LVESDI), and anterior mitral valve leaflet length. In the final model, LVESDI, anterior mitral valve leaflet length, LVEF, *E*/*E*′sep, and peak twist were independently associated with LVOTO (see *Table 6*). The LVESDI and LVESD were not included in the same model due to collinearity. However, alternative models containing either variable showed peak twist as an independent predictor.

Reproducibility

Bland–Altman graphs for intra- and inter-observer variabilities for global longitudinal strain, peak basal and peak apical rotations, and peak

Table 5 Rotation and twist measurements in the three hypertrophic cardiomyopathy groups divided according to the absence or presence of resting/latent left ventricular outflow tract obstruction

Variable	HCM without LVOTO ($n = 105$)	HCM with resting LVOTO ($n = 43$)	HCM with latent LVOTO ($n = 20$)	HCM with resting vs. latent LVOTO *P*-value
Peak apical rotation (degree)	11.0 ± 6.4	13.3 ± 8.1	11.2 ± 5.0	0.22
Peak mid LV rotation (degree)	1.3 ± 6.2	1.5 ± 6.7	0.6 ± 6.4	0.63
Peak basal LV rotation (degree)	−5.7 ± 4.6	−8.2 ± 4.4*	−8.9 ± 4.5*	0.58
Peak twist (degree)	15.7 ± 6.0	19.9 ± 8.0*	19.2 ± 5.6*	0.70
Peak apical rotation rate (degree/s)	66.7 ± 33.2	68.8 ± 35.3	64.4 ± 26.6	0.63
Peak basal rotation rate (degree/s)	−44.3 ± 48.1	−65.0 ± 32.2*	−73.3 ± 20.6**	0.22
Peak twist rate (degree/s)	88.2 ± 38.5	106.7 ± 36.8*	111.4 ± 26.8*	0.61

HCM, hypertrophic cardiomyopathy; LVOTO, left ventricular outflow tract obstruction; *n*, number.
*$P < 0.05$ vs. HCM without LVOTO.
**$P < 0.001$ vs. HCM without LVOTO.

Table 6 Independent correlates of dynamic left ventricular outflow tract obstruction on multivariate analysis

Variable	Odds ratio	95% CI	*P*-value
LVESDI	0.808	0.682–0.958	0.014
LVEF	1.102	1.025–1.185	0.009
E/*E*′sep	1.230	1.135–1.333	<0.001
Peak twist	1.083	1.015–1.155	0.016
AMVL length	1.179	1.079–1.287	<0.001

Variables entered into the equation: heart rate, relative wall thickness, *E*′sep, LVESDI, LVEF, *E*/*E*′sep, peak twist, and AMVL length.
AMVL, anterior mitral valve leaflet; CI, confidence interval; *E*, early diastolic mitral *E* velocity; *E*′, early diastolic myocardial velocity; LVEF, left ventricular ejection fraction; LVESDI, left ventricular end-systolic diameter indexed to body surface area; RWT, relative wall thickness; sep, septum.

twist are shown in *Figures 4* and *5*, respectively, and demonstrated satisfactory reproducibility for all four measurements.

Discussion

In this study, for evaluating deformation mechanics in patients with HCM associated with ASH, we demonstrated that despite patients with LVOTO having similar maximal septal wall thickness and global measures of myocardial strain, they had increased dispersion of segmental longitudinal strain and increased peak twist largely due to increased basal rotation and increased time-to-peak twist when compared with patients without LVOTO.

Left ventricular outflow tract obstruction in HCM is associated with increased symptoms and risk of developing heart failure. The narrowing of the LVOT, thickened basal septum, and anterior wall together with anterior displacement of the mitral valve and longer mitral valve leaflet length facilitate mitral-septal apposition during systole leading to dynamic LVOTO.[28–33] Earlier studies have reported smaller LVOT area and longer mitral valve leaflet lengths in patients with HCM associated with LVOTO.[29,33] In our study, septal thickness, septal/posterior wall thickness ratio, and LVOT diameter were similar in patients with and without LVOTO. However, LV diastolic dimension was smaller (such that the relative wall thickness was higher) coupled with smaller LV systolic dimension and volume (such that the LVEF was higher) in patients with LVOTO. Similar to previous studies, mitral valve leaflet length was longer in patients with LVOTO. All these factors may contribute to LVOT overcrowding placing the mitral valve leaflets closer to the septum during systole.[34] As expected, while most patients without LVOTO had trivial mitral regurgitation, half of the patients with LVOTO had mild-to-severe mitral regurgitation.

Despite the LVEF being higher in patients with HCM compared with control subjects, the absolute values of global longitudinal, circumferential, and radial strain were all lower. Global measures of strain were similar in patients with and without LVOTO, although basal longitudinal strain was lower in the obstructive HCM group. Other studies comparing obstructive and non-obstructive HCM have reported conflicting results: either reduced global longitudinal strain and increased global circumferential strain (using velocity vector imaging)[35] or increased longitudinal strain (using two-dimensional speckle tracking)[25] in obstructive HCM. The discrepancy may be due to the use of different imaging modalities, number of LV segments analysed, small patient cohorts, age, and different septal morphology.

Prior studies have reported conflicting findings regarding the changes in LV rotation and twist in obstructive HCM: either similar[11,35,36] or increased,[9] although these findings were based on smaller cohorts. In our study, patients with LVOTO had significantly increased basal rotation and twist when compared with patients without LVOTO. Indeed, peak twist was independently associated with LVOTO. It is possible that increased LV twist itself may contribute to the slightly higher LVEF observed in patients with LVOTO despite similar global measures of myocardial strain when compared with patients without LVOTO; however, geometrical factors such as the smaller LV dimensions may also contribute to this.[37]

Previous investigators have suggested that LVOTO itself could lead to abnormal myocardial deformation.[11] To explore this further, we compared patients with resting LVOTO to patients with latent LVOTO that only developed during the Valsalva manoeuvre. We observed that peak twist (evaluated in the resting state) was similar in patients with HCM with either resting or latent LVOTO, and both groups had significantly higher peak twist compared with patients without LVOTO. This suggests that exaggerated twist itself may contribute to dynamic LVOTO rather than being a secondary phenomenon. While the mechanism responsible for increased twist remains unclear, we postulate that regional variation in myocardial strain may contribute

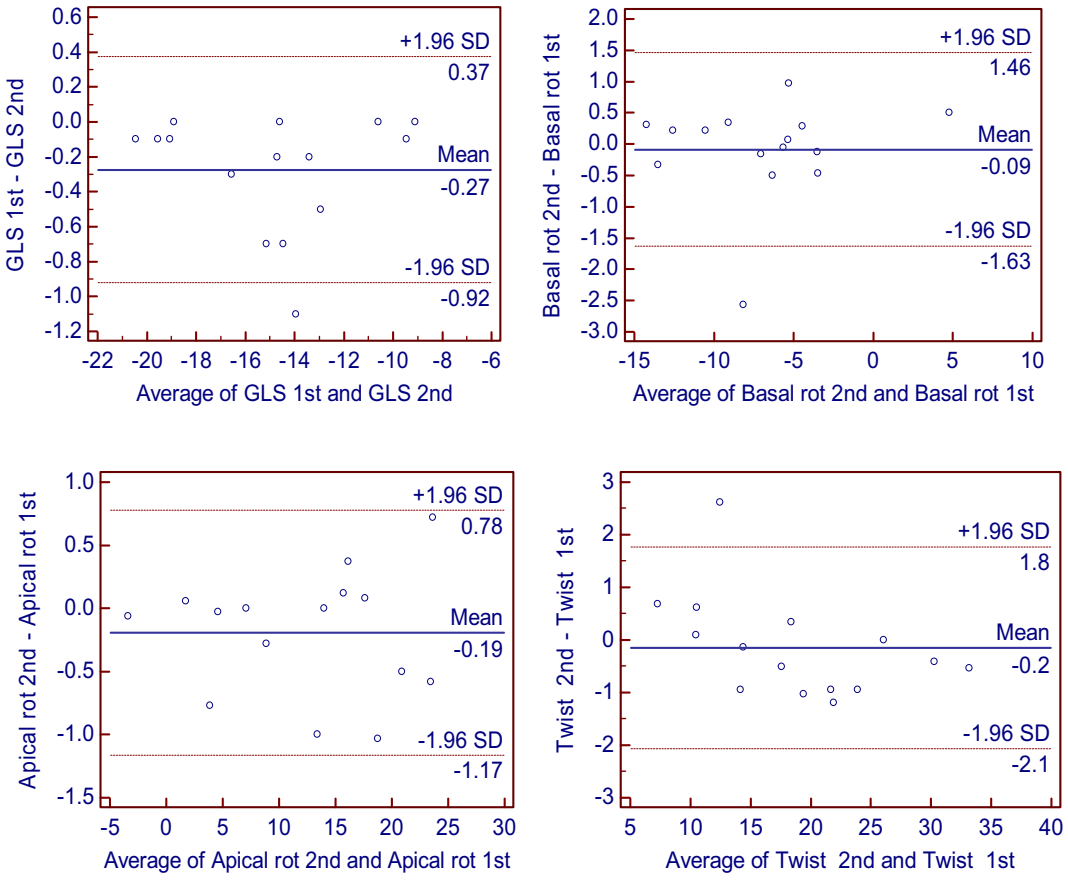


Figure 4 Bland–Altman graphs for intra-observer variabilities for global longitudinal strain, peak basal and peak apical rotation, and peak twist. Top left panel: global longitudinal strain; top right panel: peak basal rotation; bottom left panel: peak apical rotation; bottom right panel: peak twist.

given that patients with LVOTO had significantly greater dispersion of segmental strain compared with patients without LVOTO.

Clinical implications

While these findings are largely mechanistic, they provide intriguing insights into the underlying pathophysiology of dynamic obstruction in HCM and could provide clinicians with a more reproducible biomarker to identify patients with latent LVOTO. It is well recognized that LVOTO in HCM is a dynamic process affected by volume status, heart rate, and afterload, limiting its use to monitor treatment response in patients with symptomatic LVOTO. While this has been less of an issue in the absence of disease-specific therapies, the recent favourable results reported with mavacamten in the EXPLORER-HCM[38] and VALOR-HCM[39] studies suggest we may require more reliable approaches to firstly identify patients with symptomatic LVOTO and secondly monitor their response to treatment. Future studies are required to evaluate the effect of selective cardiac myosin inhibition on myocardial torsion, including whether exaggerated twist is abrogated by this approach.

Limitations

This study was performed in a tertiary centre; thus, our study population may not reflect the broader population of patients with HCM. While most patients with HCM are either diagnosed or referred to such centres, we cannot exclude a selection bias towards sicker patients. Our final cohort was somewhat selected given that we only included patients with good echocardiographic image quality and excluded patients with predominant apical and concentric increases in LV wall thickness, atrial fibrillation, predominant ventricular pacing, prior open heart surgery or septal reduction procedures, cardiac muscle disease secondary to known systemic conditions, or significant valvular heart disease. This was to avoid confounding factors that might contribute to abnormal myocardial deformation given that our focus was on addressing the mechanisms responsible for LVOTO in patients with HCM associated with ASH. Our findings may therefore not apply to patients with HCM associated with concentric or apical hypertrophy. A total of 21% of patients had suboptimal short-axis images; hence, we were only able to evaluate myocardial torsion in the remaining 168 patients. Nonetheless, the size of the remaining cohort was sufficient to allow a comparison of myocardial torsion in patients with and without LVOTO.

Some subjects may have coexisting undiagnosed coronary artery disease, which may have affected the strain measurements. Furthermore, we evaluated patients on their usual medical therapy. Patients with obstructive HCM were slightly older; however, increased peak twist remained independently associated with LVOTO in multivariable models that included age and sex. Furthermore, some patients without LVOTO on their resting echocardiogram may develop LVOTO with

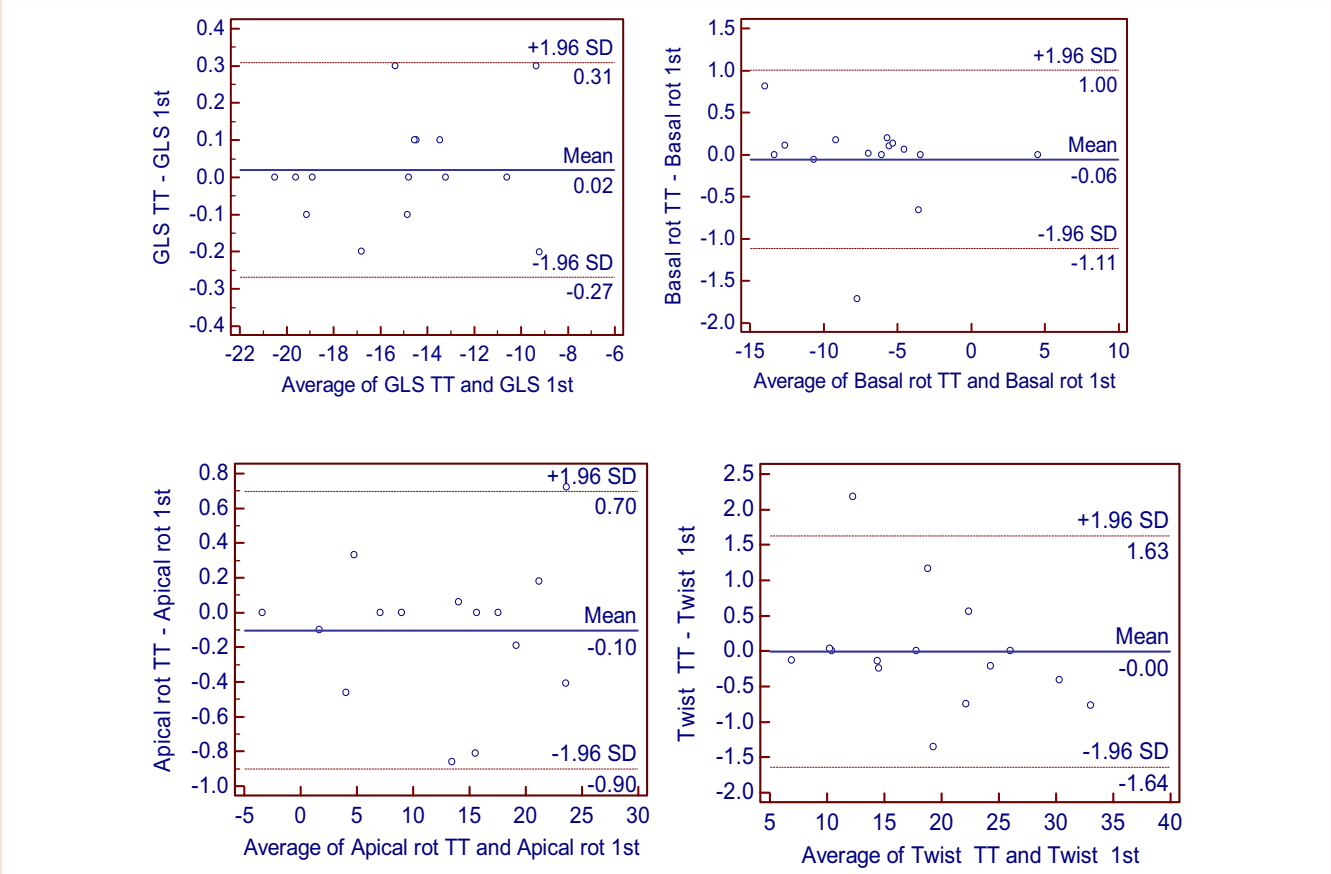


Figure 5 Bland–Altman graphs for inter-observer variabilities for global longitudinal strain, peak basal and peak apical rotation, and peak twist. Top left panel: global longitudinal strain; top right panel: peak basal rotation; bottom left panel: peak apical rotation; bottom right panel: peak twist.

exercise. These patients would have been included in the group without LVOTO in our study; however, this would have biased the results towards the null hypothesis. We were unable to provide further insights regarding the mechanism underlying exaggerated myocardial twist in obstructive HCM. Future studies could include CMR evaluation to determine whether heterogeneous myocardial fibrosis could play a role. While the relationship between peak twist and other speckle tracking measures was not explored in detail in this study, we note that other studies have suggested that mechanical dispersion may be a useful prognostic marker for arrhythmia risk in HCM.[40]

Conclusions

The mechanisms underlying LVOTO in patients with HCM associated with ASH are multifactorial. We demonstrated that a smaller LVESDI, longer anterior mitral valve leaflet length, higher *E*/*E*′, and exaggerated peak twist were independently associated with LVOTO. While we were unable to infer a mechanistic association, peak twist was similarly exaggerated in patients with latent LVOTO, suggesting that abnormal myocardial deformation may contribute to dynamic LVOTO. Future studies will be required to address the mechanisms underlying exaggerated myocardial twist in obstructive HCM and the effect of therapeutic interventions such as pharmacological agents and septal reduction therapy on myocardial deformation in HCM.

Lead author biography

Ms Ada K.C. Lo is the Echosonographer-in-charge of the Echocardiography Laboratory in the Cardiology Department, Royal Brisbane and Women's Hospital in Brisbane, Australia. She has more than 28 years of experience in echocardiography. She is deeply involved in research, education, and training of cardiac scientists and cardiology advanced trainees. She obtained her master's degree in Applied Science (Medical Ultrasound) in 2007. Currently, she is undertaking a PhD through the University of Queensland evaluating the clinical utility of advanced echocardiography in patients with hypertrophic cardiomyopathy.

Data availability

Institutional data policy does not allow release of patient-specific data, however aggregate and summary data may be available by emailing the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Ethics approval

This study was approved by the Royal Brisbane and Women's Hospital Human Research Ethics Committee: Reference No. HREC/16/QRBW/225.

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Conflict of interest: A.K.C.L. has received consultancy payment from Bristol Myers Squibb (BMS). J.J.A. chaired the BMS Australia Hypertrophic Cardiomyopathy Mavacamten Advisory Board, but receives no personal payments, with consultancy fee paid to his employer, Metro North Hospital and Health Service.

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