Prolonged left ventricular twist in cardiomyopathies: a potential link between systolic and diastolic dysfunction

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Aims
Left ventricular (LV) twist and untwist play a major role in LV mechanics. We sought to acquire new pathophysiological insights in cardiomyopathies (CM) studying LV twist dynamics by speckle tracking imaging (STI).

Methods and results
Standard echo-Doppler and STI study were performed in 67 CM patients divided in four age- and sex-matched subgroups: 18 with apical hypertrophic cardiomyopathy (Group A); 20 with asymmetrical hypertrophic cardiomyopathy (Group B); 15 with dilated cardiomyopathy (Group C); 14 with LV non-compaction (Group D). As controls, 34 age- and sex-matched normal subjects were studied. Compared with control group, all CM Groups showed significantly lower longitudinal, circumferential, and radial myocardial deformations (P<0.05). LV twist was correlated with ejection fraction (EF; r=0.62; P<0.0001). Furthermore, all CM patients had a significantly lower twist rate (P<0.05) and delayed onset of untwist (P<0.01). Of interest a significant correlation was found between isovolumic relaxation time and untwist onset (r=0.485, P=0.0001). In addition, a significant correlation was found between longitudinal deformations and the onset of untwist (strain: r=0.46, P=0.0001; strain rate: r=0.33, P=0.0056) and between longitudinal strain rate and twisting rate (r=−0.38; P=0.0015).

Conclusion
(i) All CM patients show an impairment of longitudinal, circumferential, and radial myocardial deformations; (ii) LV peak twist is impaired only in CM with reduced EF but preserved in those with normal or increased EF; (iii) LV twist is prolonged and untwisting onset is delayed in all CM, suggesting that a mechanical adaptation to subclinical systolic abnormalities might induce, by a prolonged LV twist, the early onset of diastolic dysfunction.

Keywords
Cardiomyopathy • Echocardiography • Pathophysiology

Introduction
Left ventricular (LV) twist represents the net difference in clockwise and counterclockwise rotation of the LV apex and base and plays a major role in LV mechanics.1 Twist during ejection predominantly deforms the subendocardial fibre matrix, resulting in storage of potential energy. Subsequent recoil of twist deformation (‘untwist’) is associated with the release of restoring forces, which contributes to LV diastolic relaxation and early diastolic filling. As a consequence, a delay of this recoil mechanism induces impairment of LV diastolic relaxation with a reduction of the atrioventricular diastolic gradient and the consequent onset of a diastolic dysfunction.1–4

Recently, LV twist dynamics have been accurately studied by a novel echocardiographic method to measure strain from standard 2D images (speckle tracking imaging, STI).5–7 Evidence of its accuracy is mounting by comparison with tagged magnetic resonance imaging data.8

In many diseases, the onset of LV diastolic dysfunction is often regarded as earlier when compared with systolic dysfunction; recent studies seem to doubt that an ‘isolated’ diastolic impairment really exists.9 Indeed, abnormal systolic regional contractile
properties, detected by new echocardiographic techniques, arise at an early stage even in the presence of a normal pump function.\textsuperscript{10,11} Unfortunately, data on the relationship between systolic and diastolic dysfunction are quite discordant and different models have been proposed.\textsuperscript{9}

Although in different cardiomyopathies (CM) LV twist and untwist have been extensively explored, their potential impact on LV mechanics has not been yet adequately investigated.

Thus, the aim of our study was to assess LV twist and untwist, global systolic and diastolic function, and regional myocardial deformation in patients with different CM in order to acquire new pathophysiological insights on the potential link between systolic and diastolic dysfunction.

**Methods**

**Patients**

Between September 2009 and July 2010, 105 patients with different CM were assessed at our ‘CM outpatient unit’.

Diagnostic criteria of the different CM were: (i) Apical hypertrophic cardiomyopathy (HCM): presence of asymmetric myocardial hypertrophy of the LV apex (apex/posterior wall $> 1.5$); (ii) Asymmetrical HCM: septal thickness $> 15$ mm and a septal/posterior wall thickness ratio $> 1.3$ without any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident;\textsuperscript{12} (iii) Dilated cardiomyopathy (DCM): presence of LV ejection fraction (EF) $< 45\%$ and LV end-diastolic diameter $> 117\%$ of the predicted value corrected for age and body surface area (BSA); in the absence of epicardial coronary artery disease or other clear causes of CM (significant valvular disease, alcohol abuse, use of cardiotoxic agents such as adriamycin, or active myocarditis);\textsuperscript{13} (iv) LV non-compaction (LVNC): presence of non-compacted/compacted layer ratio at end-systole $> 2$ according to the diagnostic criteria established by Jenni et al.\textsuperscript{14}

Exclusion criteria to the study were: (i) inadequate echocardiographic resolution; (ii) obstructive HCM (LV outflow tract gradients $> 30$ mmHg under basal conditions or after the Valsalva manoeuvre); (iii) HCM and LVNC patients with EF $< 50\%$; (iv) patients with implanted cardioverter-defibrillators; (v) comorbidities (diabetes mellitus, arterial hypertension, coronary artery disease, sinus tachycardia, atrial fibrillation during the study evaluation, lung disease).

Among all the patients, 38 were excluded from the study (35 owing to the presence of exclusion criteria and 3 to inadequate echocardiographic images). The remaining 67 were enrolled and divided into four age- and sex-matched subgroups: 18 patients with apical HCM (Group A); 20 patients with asymmetrical HCM (Group B); 15 patients with DCM (Group C); 14 patients with LVNC (Group D).

In addition, we studied 34 age- and sex-matched normal subjects (CTRL group). None of the control subjects had cardiovascular structural or functional abnormalities or received any medication.

**Standard echo-Doppler study**

Standard echo-Doppler was performed using a Vivid 7 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway). Cine-loops were recorded on DVDs for offline analysis (EchoPAC PC 6.0.0, GE Medical Systems). All the measurements were analysed by two experienced readers, taking the average of three cardiac cycles.

LV diameter and wall thickness were measured according to the criteria of the American Society of Echocardiography.\textsuperscript{15} Left atrium (LA) volume was determined by the biplane-area-length method.\textsuperscript{16}

Two-dimensional measurements of LV wall thickness were assessed in four segments (anterior and posterior interventricular septum, inferior, and antero-lateral walls) at the mitral valve, papillary muscles and apical levels by parasternal short-axis views. In addition, LV EF was calculated by the Simpson biplane method.\textsuperscript{17}

As measures of global LV diastolic function peak velocities at the early (peak $E$) and late (peak $A$) diastole, their ratio, deceleration time of the $E$ wave and isovolumic relaxation time (IVRT) were assessed by pulsed-Doppler with the sample volume placed at the mitral valve leaflet tips and at the aortic outflow.\textsuperscript{18}

Finally, by pulsed tissue Doppler, peak early diastolic velocity on the septal part of the mitral annulus was measured ($E'$) and $E/E'$ ratio was calculated.

**Speckle tracking imaging study**

For the STI study, the second-harmonic B-mode images of apical (4-chamber, 2-chamber, and 3-chamber) and short-axis (at the mitral valve and apical level) views were obtained. The frame rate was $85 \pm 15$ frame/s. The LV endocardial border was manually traced at the end-systolic frame and a speckle tracking region of interest was automatically selected. The width of the region of interest was adjusted as necessary to accommodate the total thickness of the LV wall. The computer automatically tracked stable objects in each frame using the sum of absolute differences algorithm. After these steps, the workstation computed and generated strain curves.

For the analysis of longitudinal strain and strain rate, apical views were considered, while for the circumferential and radial myocardial deformations (strain and SR) as well as rotation functions (rotation, rotation rate, twist and twist rate) the short-axis views were studied.

Longitudinal and circumferential strain and SR peak values were defined as the maximum negative values of the curves from the apical and short-axis views, respectively. Radial strain and SR peak values were defined as the maximum positive values of the curves from the short-axis views.

The peak values of basal rotation (basal rotation and rotation rate) were defined as the maximum negative values of the curves from the short-axis view at the mitral valve level.

The peak values of apical rotation (apical rotation and rotation rate) were defined as the maximum positive values of the curves from the short-axis view at the apical level. Every view considered was divided into six segments, which gave six different values: the mean value of them was considered.

LV twist was defined as the difference between the mean values of the peak rotation at the apical and at the mitral valve level (twist $= \text{mean peak apical rotation} − \text{mean peak basal rotation}$).

Similarly LV twist rate was defined as the difference between the mean values of the peak rotation rate at the apical and at the mitral valve level (twist rate $= \text{mean peak apical rotation rate} − \text{mean peak basal rotation rate}$). The untwisting onset was expressed as a percentage of systolic duration (the ratio between the time to peak twist, i.e. onset of untwisting, and the duration of systole until the aortic valve closure) by the use of cardiac cycles with matched RR intervals (time to peak twist/systolic time). This normalization for systolic duration was made to overcome the heart rate dependence, as previously described.\textsuperscript{19} The studies were analysed off-line by a second blinded observer for 30 patients, corresponding to 900 segments.

Interobserver variability was calculated by the average difference between the 30 measurements realized. Interobserver variability was calculated as the absolute difference divided by the average of the two observations for all parameters.
Table I  General characteristics of the studied groups

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>Group A (ap-HCM)</th>
<th>Group B (asy-HCM)</th>
<th>Group C (DCM)</th>
<th>Group D (NC)</th>
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<tbody>
<tr>
<td>No.</td>
<td>34</td>
<td>18</td>
<td>20</td>
<td>15</td>
<td>14</td>
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<tr>
<td>Sex (M/F)</td>
<td>23/11</td>
<td>13/5</td>
<td>13/7</td>
<td>11/4</td>
<td>9/5</td>
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<td>Age (years)</td>
<td>35.5 ± 6.4</td>
<td>39.8 ± 15.6</td>
<td>35 ± 12.2</td>
<td>40.2 ± 12.1</td>
<td>34.4 ± 10.7</td>
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<td>BSA (m²)</td>
<td>1.8 ± 0.2</td>
<td>1.87 ± 0.2</td>
<td>1.71 ± 0.42</td>
<td>1.86 ± 0.2</td>
<td>1.7 ± 0.51</td>
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<td>SBP (mmHg)</td>
<td>116.8 ± 10.1</td>
<td>118 ± 14.9</td>
<td>111.9 ± 16.3</td>
<td>110.4 ± 13.7</td>
<td>113.7 ± 12.9</td>
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<td>DBP (mmHg)</td>
<td>70.7 ± 4.2</td>
<td>67.7 ± 8.9</td>
<td>67.5 ± 10.1</td>
<td>66.9 ± 10.6</td>
<td>68.2 ± 9.5</td>
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<td>HR (bpm)</td>
<td>80.2 ± 10.5</td>
<td>66.2 ± 8.3*</td>
<td>65.7 ± 7.7*</td>
<td>65.1 ± 8.9*</td>
<td>82.2 ± 12.6</td>
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<tr>
<td>Class IV</td>
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</table>

ap-HCM, apical hypertrophic cardiomyopathy; asy-HCM, asymmetrical hypertrophic cardiomyopathy; BSA, body surface area; CTRL, control group; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; NC, non-compaction; SBP, systolic blood pressure; HR, heart rate.

Ethics

The study was approved by the local research ethics committee, and informed written consent was obtained from all participants aged > 16 years or from the parents of those aged < 16 years.

Statistical analysis

Data are expressed as mean ± SD. Clinical and demographic characteristics were compared using the Mann–Whitney U test for continuous variables and the χ² test for qualitative variables, expressed as proportions (or Fisher’s exact test for subgroups containing < 5 observations).

The correlation structure set of metric parameters was inspected using Pearson’s product-moment correlation coefficient. A P-value of < 0.05 was considered statistically significant. StatView (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Characteristics of the study population

The general characteristics of the studied groups are shown in Table I.

Compared with CTRL group, all CM groups were comparable for age, sex, and BSA. In addition, all patients of Group A, B, and D were in class NYHA I, while in Group C eight patients were in NYHA II, four in NYHA III and three in NYHA IV.

Forty-six patients were under cardiac medical therapy at the time of the study: 43 patients were on beta-blockers (14 Group A, 14 Group B, and 15 Group C), and 9 were on diuretics (all Group C). 1 was on inotropics (Group C), 8 were on ace-inhibitors (all Group C), 9 were on antiarrhythmics (2 Group A, 2 Group B, and 5 Group C). Patients did not withdraw therapy before the echocardiographic evaluation, according to the rules of our institutions’ research Ethics Committees.

In addition, compared with CTRL group, all CM groups were comparable for blood pressure values, while Group A, B, and C showed significant lower heart rate (CTRL Group 80.2 ± 10.5 bpm vs. Group A 66.2 ± 8.3 bpm; Group B 65.7 ± 7.7 bpm; Group C 65.1 ± 8.9 bpm; all P-values of < 0.01), probably related to the therapy (beta-blockers).

Standard echo-Doppler analysis

All standard echocardiographic data are shown in Table 2.

Compared with CTRL group, Group A and Group D did not show significant differences in terms of LV diameter, wall thickness, and EF. On the other hand, Group B showed reduced LV end-diastolic diameter (43.7 ± 5.7 vs. 49.5 ± 2.4 mm; P < 0.01) and higher wall thickness (18.7 ± 3.5 vs. 9.1 ± 2.3 mm; P < 0.01), and Group C had increased LV end-diastolic diameters (60.8 ± 5.7 vs. 49.5 ± 2.4 mm; P < 0.01).

In addition, compared with CTRL group, all CM groups showed significantly reduced mitral peak E/A ratio (CTRL 1.7 ± 0.1, Group A 1.43 ± 0.7, Group B 1.34 ± 0.67, Group C 1.36 ± 0.52, Group D 1.29 ± 0.48; P < 0.05, P < 0.01, P < 0.01, respectively), increased deceleration time (CTRL 171.6 ± 32.1 ms, Group A 228.6 ± 64.3 ms, Group B 272.7 ± 90.8 ms, Group C 245.3 ± 59.7 ms, Group D 197 ± 46.8 ms; P < 0.01, P < 0.01, P < 0.01, respectively), increased E/E′ ratio (CTRL 5.4 ± 2.1, Group A 12.8 ± 8.4, Group B 14.9 ± 5.7, Group C 10.8 ± 4.1, Group D 8.8 ± 2.9; all P-values of < 0.01) and increased IVRT (CTRL 74.2 ± 9.4 ms, Group A 104.6 ± 21.7 ms, Group B 103.2 ± 14.1 ms, Group C 97.47 ± 20.5 ms, Group D 82.6 ± 19.4 ms; P < 0.01, P < 0.01, P < 0.01, P < 0.05, respectively), suggestive of impaired diastolic function.

Finally, LA was enlarged in Group A, B, and C (CTRL: 35.1 ± 3.2 mL/m²; Group A 35.1 ± 2.7 mL/m²; Group B 37.4 ± 4.4 mL/m²; Group C 36.3 ± 3.5 mL/m²; all P-values of < 0.001) while Group D had normal volumes (P = 0.54).

Speckle tracking imaging study

All STI analysis data are shown in Table 3.

Compared with CTRL group, all CM Groups showed significantly lower values of longitudinal, circumferential, and radial myocardial deformation (Strain and SR).

In addition, compared with CTRL Group, basal rotation, apical rotation, and twist were lower in CM patients with reduced EF.
Rotation 6.92° + 3.88° asymmetrical HCM (Group B), which was characterized by significantly global LV twist was increased in patients with Group 139.9° + 23.5°. Thus, LV twist was prolonged and onset of untwist (time to peak twist/systolic time) was delayed (CTRL Group 80.48° ± 13.69°, Group A 105.6° ± 13.68°, Group B 106.69° ± 22.68°, Group C 105.7° ± 23.51°, Group D 98.93° ± 16.91°; all P-values of <0.01; Figure 2). Of interest a significant correlation was found between IVRT and untwist onset (r = 0.485, P < 0.0001; Figure 2). Furthermore we found significant correlations between longitudinal deformations (strain and SR) and untwist onset (strain; r = 0.46, P = 0.0001; strain rate; r = 0.33, P = 0.0056; Figure 4A and B) and between longitudinal SR and twisting rate (r = −0.38; P = 0.015; Figure 5).

Intra- and interobserver variability were 3.6 and 5.2% for STI longitudinal, circumferential and radial values, 4.2 and 6% for LV twist, and 2.2 and 3.5% for untwisting onset.

### Table 2 Standard echocardiographic values of the studied groups

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>Group A (ap-HCM)</th>
<th>Group B (asy-HCM)</th>
<th>Group C (DCM)</th>
<th>Group D (NC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>34</td>
<td>18</td>
<td>20</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>LVd (mm)</td>
<td>49.5 ± 2.4</td>
<td>48.9 ± 6.4</td>
<td>43.7 ± 5.7*</td>
<td>60.8 ± 5.7*</td>
<td>48.9 ± 5.1</td>
</tr>
<tr>
<td>IVs (mm)</td>
<td>9.1 ± 2.3</td>
<td>8.8 ± 0.4</td>
<td>18.7 ± 3.5*</td>
<td>8.8 ± 1</td>
<td>9.1 ± 0.9</td>
</tr>
<tr>
<td>PWd (mm)</td>
<td>8.4 ± 1.2</td>
<td>8.3 ± 0.7</td>
<td>9.6 ± 1.7*</td>
<td>8.1 ± 0.2</td>
<td>8.2 ± 0.7</td>
</tr>
<tr>
<td>LA (mL/m²)</td>
<td>25.4 ± 3.2</td>
<td>351 ± 2.7*</td>
<td>37.4 ± 4.4*</td>
<td>36.3 ± 3.5*</td>
<td>26.1 ± 4.5</td>
</tr>
<tr>
<td>EF (%)</td>
<td>63.2 ± 6.4</td>
<td>65.6 ± 8.4</td>
<td>73.9 ± 6.9*</td>
<td>35.4 ± 4.3*</td>
<td>60.8 ± 4.6</td>
</tr>
<tr>
<td>E/A</td>
<td>1.7 ± 0.1</td>
<td>1.43 ± 0.7†</td>
<td>1.34 ± 0.67*</td>
<td>1.36 ± 0.52*</td>
<td>1.29 ± 0.48*</td>
</tr>
<tr>
<td>Dectime (ms)</td>
<td>171.6 ± 32.1</td>
<td>228.6 ± 6.43*</td>
<td>272.7 ± 90.8*</td>
<td>245.3 ± 59.7*</td>
<td>197 ± 46.8†</td>
</tr>
<tr>
<td>E′/E</td>
<td>5.4 ± 2.1</td>
<td>12.8 ± 8.4*</td>
<td>149 ± 5.7*</td>
<td>10.8 ± 4.1*</td>
<td>8.8 ± 2.9*</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>74.2 ± 9.4</td>
<td>104.6 ± 21.7*</td>
<td>103.2 ± 14.1*</td>
<td>97.47 ± 20.5*</td>
<td>82.6 ± 19.4†</td>
</tr>
</tbody>
</table>

DecTime, deceleration time; EF, ejection fraction; IVRT, isovolumic relaxation time; IVSd, end-diastolic interventricular septum; LA, left atrium; LVEDd, end-diastolic left ventricular diameter; PWd, end-diastolic posterior wall. For ap-HCM, asy-HCM, DCM, and NC see Table 1.

### Table 3 Speckle tracking analysis of the studied groups

<table>
<thead>
<tr>
<th></th>
<th>CTRL</th>
<th>Group A (ap-HCM)</th>
<th>Group B (asy-HCM)</th>
<th>Group C (DCM)</th>
<th>Group D (NC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>34</td>
<td>18</td>
<td>20</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Long Strain (%)</td>
<td>−21.1 ± 1.3</td>
<td>−14.9 ± 2.8*</td>
<td>−16.6 ± 3.6*</td>
<td>−13.8 ± 2.9*</td>
<td>−19.7 ± 3.2†</td>
</tr>
<tr>
<td>Long SR (s⁻¹)</td>
<td>−1.4 ± 0.16</td>
<td>−0.96 ± 0.16*</td>
<td>−1.07 ± 0.23*</td>
<td>−0.85 ± 0.16*</td>
<td>−1.26 ± 0.27†</td>
</tr>
<tr>
<td>Circ Strain (%)</td>
<td>−22.2 ± 3.7</td>
<td>−18.4 ± 2.4*</td>
<td>−19.4 ± 3.1*</td>
<td>−13.2 ± 2.9*</td>
<td>−18.6 ± 2.4*</td>
</tr>
<tr>
<td>Circ SR (s⁻¹)</td>
<td>−1.82 ± 0.29</td>
<td>−1.3 ± 0.18*</td>
<td>−1.46 ± 0.25*</td>
<td>−0.91 ± 0.23*</td>
<td>−1.47 ± 0.31*</td>
</tr>
<tr>
<td>Rad Strain (%)</td>
<td>48.2 ± 11.7</td>
<td>33.2 ± 13.1*</td>
<td>35.4 ± 14.2*</td>
<td>27.5 ± 9.3*</td>
<td>23.6 ± 5.6*</td>
</tr>
<tr>
<td>Rad SR (s⁻¹)</td>
<td>2.23 ± 0.45</td>
<td>1.41 ± 0.44*</td>
<td>1.55 ± 0.41*</td>
<td>1.4 ± 0.31*</td>
<td>1.6 ± 0.74*</td>
</tr>
<tr>
<td>Bas Rotation (%)</td>
<td>−7.35 ± 1.6</td>
<td>−6.47 ± 3.18</td>
<td>−8.57 ± 3.58</td>
<td>−3.88 ± 1.33*</td>
<td>−6.68 ± 2.11</td>
</tr>
<tr>
<td>Ap Rotation (s⁻¹)</td>
<td>6.92 ± 2.56</td>
<td>6.05 ± 4.07</td>
<td>8.27 ± 2.73</td>
<td>4.63 ± 2.35*</td>
<td>6.07 ± 1.74</td>
</tr>
<tr>
<td>TWIST (s⁻¹)</td>
<td>14.22 ± 3.4</td>
<td>12.67 ± 5.88</td>
<td>16.45 ± 2.71†</td>
<td>9.09 ± 2.43*</td>
<td>12.8 ± 2.25</td>
</tr>
<tr>
<td>Bas RotRate (s⁻¹)</td>
<td>−78.01 ± 17.8</td>
<td>−61.2 ± 27.5†</td>
<td>−71.6 ± 20.9†</td>
<td>−37.8 ± 14.1†</td>
<td>−63.1 ± 17.2‡</td>
</tr>
<tr>
<td>Ap RotRate (s⁻¹)</td>
<td>609 ± 18.8</td>
<td>53.9 ± 29.3</td>
<td>53.9 ± 14.1</td>
<td>36.2 ± 11.6*</td>
<td>55.4 ± 22.3</td>
</tr>
<tr>
<td>TWIST Rate (s⁻¹)</td>
<td>139.9 ± 23.4</td>
<td>118.4 ± 46.8†</td>
<td>121.1 ± 24.6†</td>
<td>67.5 ± 18.1*</td>
<td>119.1 ± 37.3†</td>
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<tr>
<td>Untwist Onset (%)</td>
<td>80.48 ± 13.69</td>
<td>105.6 ± 13.68*</td>
<td>106.69 ± 22.68*</td>
<td>105.7 ± 23.51*</td>
<td>98.93 ± 16.91*</td>
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</tbody>
</table>

Ap, apical; Bas, basal; Circ, circumferential; Long, longitudinal; Rad, radial; RotRate, Rotation Rate; SR, Strain Rate. For ap-HCM, asy-HCM, DCM, and NC see Table 1.

*P < 0.01 vs. CTRL

†P < 0.05 vs. CTRL

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Discussion

The main finding of our study is that patients with CM, even in presence of preserved EF, show impaired regional myocardial deformation with prolonged twist and thus untwisting delay, suggesting that mechanical adaptation to subclinical systolic abnormalities might explain the onset of early diastolic dysfunction.

LV filling evaluation

All CM groups, also those with normal EF (A, B, and D groups), show an abnormal mitral flow pattern (reduced E/A ratio, increased deceleration time and IVRT) suggestive of 'apparently isolated' diastolic dysfunction. These data are in agreement with

Figure 1 Left ventricular twist and ejection fraction. There is a significant linear correlation between left ventricular twist and ejection fraction. A specific symbol identifies patients according to their cardiomyopathy. AP, apical; ASY, asymmetrical; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NC, non-compaction; EF, ejection fraction.

Figure 2 Peak twist and untwist curves. Controls (upper left), cardiomyopathies with preserved ejection fraction (upper right) and cardiomyopathies with impaired systolic function (lower left). AVC, aortic valve closure; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NC, non-compaction.

Figure 3 IVRT and untwisting onset. The untwist rate and thus the degree of untwisting delay significantly correlates with IVRT. IVRT, isovolumic relaxation time.
previous studies showing an early onset of markers of diastolic dysfunction in patients with CM. Indeed, as potential causes of this functional impairment, several mechanisms have been invoked: microvascular myocardial ischaemia, abnormal calcium handling, and mechanical dyssynchrony may explain abnormalities of active relaxation, while fibrosis and myocardial hypertrophy may increase passive LV stiffness.

Impairment of LV filling is also supported by our STI data, showing a delayed untwisting, with an untwist onset after aortic valve closure. Indeed, the potential energy stored during the systolic twisting phase is released in the subsequent diastolic recoil (untwisting) which, in normal hearts, begins in late systole and is completed during the isovolumic relaxation and the early period of diastole, before the mitral valve inflow. Accordingly, we found a significant correlation between untwisting delay and IVRT. Similarly, Burns et al. showed that the untwisting delay significantly correlated to the invasive indexes of LV relaxation (prolonged $\tau$) but not to LV stiffness.

Wang et al. reported normal untwisting rate in patients with diastolic dysfunction and normal EF, suggesting that it could be related to a normal or reduced LV end-systolic volume and higher ratio of N2B to N2BA titin isoforms. However, as Dwivedi et al. noted, this reasoning is too simplistic and divergent from a number of other studies, which have shown that patients with diastolic dysfunction have prolonged untwisting and delayed peak untwisting, both at rest and during exercise.

**Left ventricular twist dynamics**

LV twist is reduced only in patients with CM and impaired pump function (DCM group). Our data, suggesting a significant correlation between peak systolic twist and EF, are consistent with those of Kanzaki et al. which, by studying patients with DCM
by use of magnetic resonance tagging method, showed an impairment in peak LV systolic twist proportional to the degree of global LV dysfunction. This impairment was related to a reduced amplitude of the rotation both at the base and apex. On the other hand, LV systolic twist is normal or increased in patients with preserved EF (NC and HCM groups). Of interest, in our asymmetrical HCM group LV twist is increased, according to Young et al.\textsuperscript{10} that studied HCM patients by magnetic resonance tagging showing an increased degree of LV rotation. Owing to the afterload-dependency of LV twist (i.e. twist decreases at higher end-systolic

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**Figure 5** Longitudinal deformations and twisting rate. The twisting rate and thus the degree of twist prolongation significantly correlates with longitudinal strain rate. LONG, longitudinal.

**Figure 6** Pathophysiological cascade of heart failure in cardiomyopathies. DCM, dilated cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LV, left ventricular; NC, non-compaction.
volumes when end-diastolic volumes are held constant), this increase may be related also to the increased mass/volume ratio and thus reduced afterload usually characterizing many asymmetrical HCM patients. Accordingly, in our apical HCM patients, consistent with a quite normal mass/volume ratio and thus LV afterload, systolic twist is not increased.

Finally, unlike Bellavia et al.13—who showed impaired LV twisting in patients with LVNC, in our LVNC group systolic twist is comparable to the control subjects. Probably this reflects the extension of myocardial abnormalities (trabeculations, ischaemia) that are usually confined to the endocardial layer in this disease while LV twist is governed by epicardial fibres.

Of interest, regardless the state of LV pump function (decreased, normal or increased), STI analysis shows in all our studied CM patients a reduced myocardial deformation on the longitudinal, radial and circumferential planes. Accordingly Jin et al.28 studying children with DCM by STI, found a decreased circumferential and radial function with a reduced systolic twist. Likewise, Wang et al.29 performed an STI study in patients with HCM showing an impaired LV longitudinal, circumferential and radial functions with a preserved systolic twist. More recently, Abozguia et al.30 by studying STI 56 HCM patients, confirmed a reduced longitudinal, radial and circumferential strain and SR despite normal LV EF. These concordant data in literature probably reflect the evidence that in CM, unlike coronary heart diseases, early myocardial damage is not confined to subendocardial layers and thus to longitudinal LV mechanics, but involve also midwall and subepicardial fibres, with significant impact on radial and circumferential function.

New pathophysiological insights

Our CM patients showed, even in presence of a normal peak LV rotation, a decreased twist rate (i.e. an increased duration of systolic twist) associated to concomitant alterations of the regional myocardial deformation (decreased longitudinal, radial and circumferential strain, and SR). According to our significant inverse correlation between longitudinal SR and twist rate, we speculated that the increased duration of systolic twist might be a compensatory mechanism to preserve the degree of LV systolic rotation and thus ensure a normal EF. Indeed LV twist, allowing a uniform distribution of LV fibre stress and fibre shortening across the wall, is mandatory to warrant a preserved systolic function.31–33

However, the increased duration of systolic twist, due to subclinical systolic dysfunction, induces a untwisting delay, with elevated LV early diastolic pressures, reduced transmural pressure gradient and impaired LV early diastolic filling.29 The significant correlation in our patients between longitudinal deformation (strain and SR) and untwisting delay supports our hypothesis strengthening the relationship between systolic and diastolic dysfunction. Thereafter, with the myocardial damage progression this compensatory mechanism gradually results inadequate so that, besides a diastolic dysfunction, a global systolic impairment may become clinically evident (Figure 6).

Accordingly, Tan et al.34 demonstrated that heart failure with normal EF is not an isolated disorder of diastole as it is characterized by widespread systolic and diastolic abnormalities that include reduced myocardial systolic strain, rotation and delayed untwisting. At an early stage of LV dysfunction, as in our CM patients in NYHA class I, peak systolic twist is still preserved but prolonged with untwisting delay and impaired LV early diastolic filling.

Indeed, De Keulenaer et al.9 proposed a time-dependent progression model of the heart failure in which systolic function is preserved by a compensatory mechanism characterized by the capacity of the heart to delay the onset of ventricular relaxation up to an overt diastolic dysfunction. Initially, even in the presence of abnormal relaxation and ‘mild systolic dysfunction’, global pump function is quite preserved. Subsequently, these adaptive mechanisms become insufficient and the ventricle irreversibly evolve into so-called adverse remodelling with evident global pump dysfunction.

To confirm the earlier onset of subtle regional systolic impairment, Matsumura et al.35 studying by Tissue Doppler Imaging asymptomatic relatives of patients with familial DCM, found impaired systolic but not diastolic function, in the presence of LV enlargement and normal EF.

Study limitations

According to other STI studies on CM,25,30 some of our patients were taking medications (i.e. beta-blockers) at the time of the study. As a consequence, the heart rate is lower in some groups (HCM and DCM) and such therapy might have affected the findings in these patients.

Nevertheless, the pertinent physiologic parameter (untwist onset) was corrected for heart rate by converting systolic interval to 100% as previously described.3,29 Furthermore, all the systolic parameters (longitudinal, radial and circumferential strain, twist) were heart-rate-independent because we did not measure timing but peak values.

Conclusions

All CM patients have an impairment of the longitudinal, circumferential, and radial myocardial deformations. Peak LV twist is reduced only in CM patients with lower EF (DCM) but preserved in those with normal or increased EF. However, LV twist is prolonged and untwisting is delayed in all CM patients (even with normal EF and peak systolic twist), suggesting that a mechanical adaptation to subclinical systolic abnormalities might induce, by a prolonged LV twist, the onset of an early diastolic dysfunction.

Although further studies are needed to define the implications of these new pathophysiological insights, our data, showing that in CM patients a subclinical systolic dysfunction is always associated to (or precedes) diastolic impairment, could modify our approach in the daily clinical practice.

Conflict of interest: none declared.

References

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