Enhanced Ventricular Untwisting During Exercise
A Mechanistic Manifestation of Elastic Recoil Described by Doppler Tissue Imaging

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Background—The cascade of events by which early diastolic left ventricular (LV) filling increases with exercise is not fully elucidated. Doppler tissue imaging (DTI) can detect myocardial motion, including torsion, whereas color M-mode Doppler (CMM) can quantify LV intraventricular pressure gradients (IVPGs).

Methods and Results—Twenty healthy volunteers underwent echocardiographic examination with DTI at rest and during submaximal supine bicycle exercise. We assessed LV long-/short-axis function, torsion, volume, inflow dynamics, and early diastolic IVPG derived from CMM data. LV torsion and untwisting velocity increased with exercise (torsion, 11 ± 4° to 24 ± 8°; untwisting velocity, −2.0 ± 0.7 to −5.6 ± 2.3 rad/s) that was associated with an increase in IVPG (1.4 ± 0.5 to 3.7 ± 1.2 mm Hg). Untwisting in normal subjects occurred during isovolumic relaxation and early filling, significantly before long-axis lengthening or radial expansion. The clinical feasibility of this method was tested in 7 patients with hypertrophic cardiomyopathy (HCM); torsion was higher at rest but did not increase with exercise (16 ± 4° to 14 ± 6°), whereas untwisting was delayed and unenhanced (−1.6 ± 0.8 to −2.3 ± 1.2 rad/s). In concert, IVPG was similar at rest (1.2 ± 0.3 mm Hg), but the exercise response was blunted (1.6 ± 0.8 mm Hg). In normal subjects and HCM patients, there was a similar linear relation between IVPG and untwisting rate, with an overall correlation coefficient of \( r = 0.75 \) (\( P < 0.0001 \)).

Conclusions—LV untwisting appears to be linked temporally with early diastolic base-to-apex pressure gradients, enhanced by exercise, which may assist efficient LV filling, an effect that appears blunted in HCM. Thus, LV torsion and subsequent rapid untwisting appear to be manifestations of elastic recoil, critically linking systolic contraction to diastolic filling. (Circulation. 2006;113:2524-2533.)

Key Words: diastole • echocardiography • exercise • heart failure • physiology

During exercise, myocyte shortening and titin compression are greater than in the resting state because of the inotropic effects of increased sympathetic activity and circulating catecholamines, leading to a decreased end-systolic volume. Helically oriented myofibers create left ventricular (LV) torsional deformation and allow sarcomeres to shorten uniformly and store elastic energy in compressed titin and transmural shear between the myofibril sheets. As a result, titin expands with greater force from its shorter end-systolic position, causing myocytes to lengthen more rapidly during exercise, thus altering the elastic properties of the LV wall and lowering LV chamber pressure. Exercise has also been shown to increase base-to-apex intraventricular pressure gradients (IVPGs), associated with enhanced acceleration of blood across the mitral valve, allowing filling to be maintained at low left atrial pressure (LAP). A possible mechanism of IVPGs is dynamic ventricular shape change...
widely available in clinical echocardiographs, can yield myocardial velocity with better temporal resolution than magnetic resonance imaging and has recently been shown to measure LV torsion accurately.21

To better assess how LV mechanics in early diastole responds to exercise,22 we investigated the time course of LV untwisting at rest and submaximal exercise in healthy volunteers and in patients with hypertrophic cardiomyopathy (HCM), relating it to LV volume, long- and short-axis function, and LV inflow dynamics, including the IVPG,2-23 which may be considered a manifestation of diastolic suction.

Methods

Study Population

Twenty healthy adult volunteers (mean±SD age, 34±7 years; 8 women) had LV torsional deformation assessed by DTI at rest and during supine bicycle exercise. Entry criteria included (1) no evidence of structural cardiovascular disease by 2D echocardiography; (2) the absence of past or present systemic disease; (3) height and weight percentiles within the normal range of age, and weight percentiles within 25% of the height percentile; and (4) normal blood pressure. To assess the feasibility of applying this methodology in the clinical environment, we recruited 7 patients with a clinical and echocardiographic diagnosis of HCM (mean±SD age, 41±9 years; 2 women; P=0.057 [age] and P=0.43 [sex] versus normal subjects). In these patients, the mean resting pressure gradient across the LV outflow tract (LVOT) was 18±24 mm Hg, rising to 33±40 mm Hg (P=0.077) with amyl nitrite. The study protocol was approved by the institutional review board of the Cleveland Clinic Foundation, and written, informed consent was obtained from all subjects before the study.

Exercise Testing

Exercise testing was performed with a supine bicycle (Stress Echo Bed, Medical Positioning, Kansas City, Mo) at an initial workload of 25 W with a 25-W increase in resistance at 2-minute intervals. Lead II of the ECG was monitored continuously, and blood pressure was measured at rest and every minute during testing. Because the focus was on submaximal exercise, when the subject’s heart rate reached 100 bpm, echocardiographic data were collected.

Echocardiography

We collected DTI datasets in the apical, middle, and basal short-axis planes and in the apical 4-chamber plane with a Vivid 7 apparatus (GE Medical Systems, Milwaukee, Wis) with an M3S probe. The velocity range of DTI was set at 16 to 20 cm/s to avoid aliasing. We used internal landmarks to acquire proper short-axis images, as reported recently.21 We acquired standard 2D and Doppler data (including pulsed-wave Doppler at LV inflow and outflow and color M-mode Doppler [CMM] along the LV inflow tract) as well. LV end-diastolic and end-systolic volumes and ejection fraction were estimated by a modified Simpson’s rule from apical imaging planes. Stroke volume was measured from systolic velocity in the LVOT. We estimated early diastolic peak IVPG by applying the Euler equation to the transmitral CMM.16 We also estimated mean LAP by aging the velocities at the most basal, septal, and lateral regions in each short-axis DTI image: the septal and lateral regions (Vsep, respectively) for tangential velocity, and the anterior and posterior regions (Vant and Vpos, respectively) for radial velocity, to obtain the LV radius [r(t)]:

\[
V_{rot}(t) = \text{Apical}V_{rot}(t) - \text{Basal}V_{rot}(t)
\]

LV rotation was calculated by integrating the LV rotational velocity at each level:

\[
\text{LV Rotation} = \int_{0}^{t} |V_{rot}(t)| \, dt
\]

LV rotational velocity was calculated from datasets at 4 points on each short-axis DTI image: the septal and lateral regions (Vsep and Vent, respectively) for tangential velocity, and the anterior and posterior regions (Vant and Vpos, respectively) for radial velocity, to obtain the LV radius [r(t)]:

\[
V_{rot}(t) = \frac{[V_{ent}(t) - V_{sep}(t)]/2}{r(t)}, \quad r(t) = r_0 + \left[ \int_{0}^{t} \left( \left| V_{rot}(t) \right| - V_{pos}(t) \right) \, dt \right] / 2.
\]

where \( r_0 \) is the end-diastolic radius.

LV Long- and Short-Axis Motion and LV Volume

LV long- and short-axis myocardial motion was assessed by averaging the velocities at the most basal, septal, and lateral regions in the 4-chamber DTI image and the difference between anterior and posterior velocities in the midventricular short-axis DTI image. These 2 orthogonal velocity datasets were integrated to obtain both long-axis [L(t)] and short-axis [S(t)] lengths for LV volume estimation. LV volume \( V_{LV}(t) \) was calculated as a modified general ellipsoid according to the equation described by Rankin et al26:

\[
V_{LV}(t) = (\pi/6) \times L(t) \times S(t)^2.
\]

These analyses were performed with a personal computer equipped with customized software within the EchoPAC platform (GE Medical Systems, Milwaukee, Wis). Temporal plots of myocardial velocities derived from each sample region and the ECG for several cardiac cycles were transferred to a spreadsheet program (Excel 2000, Microsoft Corp, Seattle, Wash) for the aforementioned calculations. All calculations for LV rotation/torsion and long-/short-axis motion were averaged for at least 3 consecutive beats.

For temporal analysis, the time sequence was normalized to the percentage duration of systole, with onset of the ECG QRS interval defining t=0%, and aortic valve closure (from the LVOT velocity) defining end systole, where t=100%. Time intervals are provided in milliseconds as well.

Statistics

All values in Table 1, Figure 6, and the text are given as mean±SD but are shown as mean±SE in Figures 1, 2, 3, and 5. Paired and unpaired t tests were used when appropriate. Linear regression analysis was performed to determine the relation between systolic twisting and diastolic untwisting and between diastolic untwisting and IVPG. For all statistics, values of \( P<0.05 \) were considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

DTI was acquired at an average of 148±19 frames per second (ie, a 6.9±0.8-ms interval). Submaximal workload averaged 124±29 W in normal subjects and 114±28 W in patients with HCM (\( P=0.86 \) versus controls) without an increase in the LVOT pressure gradient (30±53 mm Hg, \( P=0.54 \) versus rest).
<table>
<thead>
<tr>
<th>Table 1: Response to Exercise in Normal Subjects</th>
<th>Rest</th>
<th>Exercise</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic and function response to exercise in normal subjects</strong></td>
<td></td>
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<tr>
<td>Heart rate, bpm</td>
<td>64 ± 11</td>
<td>112 ± 10</td>
<td>&lt;0.00001</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>109 ± 12</td>
<td>156 ± 13</td>
<td>&lt;0.00001</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>64 ± 9</td>
<td>75 ± 11</td>
<td>&lt;0.00001</td>
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<tr>
<td>Double product, mm Hg × min</td>
<td>7072 ± 1636</td>
<td>17 480 ± 1944</td>
<td>&lt;0.00001</td>
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<tr>
<td><strong>2DE LV volume estimated by modified Simpson’s rule</strong></td>
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<tr>
<td>LV end-diastolic volume, mL</td>
<td>98 ± 25</td>
<td>91 ± 26</td>
<td>0.24</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>36 ± 11</td>
<td>28 ± 10</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>63 ± 6</td>
<td>68 ± 7</td>
<td>&lt;0.008</td>
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<tr>
<td><strong>Pulsed-wave Doppler</strong></td>
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<tr>
<td>Systolic peak in LV outflow, m/s</td>
<td>1.0 ± 0.2</td>
<td>1.5 ± 0.3</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>80 ± 22</td>
<td>95 ± 27</td>
<td>&lt;0.001</td>
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<tr>
<td>Aortic valve closing, ie, end systole</td>
<td></td>
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<tr>
<td>Time, ms*</td>
<td>379 ± 35</td>
<td>301 ± 22</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>na</td>
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<tr>
<td>Isovolumic relaxation time</td>
<td></td>
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<tr>
<td>Time, ms</td>
<td>51 ± 19</td>
<td>22 ± 17</td>
<td>&lt;0.00003</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>14 ± 6</td>
<td>7 ± 6</td>
<td>&lt;0.0007</td>
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<tr>
<td>Mitral valve opening</td>
<td></td>
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<tr>
<td>Time, ms</td>
<td>430 ± 36</td>
<td>323 ± 27</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>115 ± 6</td>
<td>107 ± 6</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Early diastolic peak velocity, m/s</td>
<td>0.9 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>&lt;0.00001</td>
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<tr>
<td>Time to early diastolic peak velocity</td>
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<td></td>
<td></td>
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<tr>
<td>Time, ms</td>
<td>523 ± 36</td>
<td>401 ± 33</td>
<td>&lt;0.00001</td>
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<tr>
<td>%Sys-dur</td>
<td>139 ± 6</td>
<td>133 ± 6</td>
<td>&lt;0.007</td>
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<tr>
<td>Time from mitral valve opening</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Time, ms</td>
<td>93 ± 16</td>
<td>78 ± 13</td>
<td>&lt;0.0004</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>25 ± 4</td>
<td>26 ± 4</td>
<td>0.28</td>
</tr>
<tr>
<td>Velocity-time integral by the time of early diastolic peak velocity, cm</td>
<td>4.8 ± 1.5</td>
<td>6.5 ± 1.9</td>
<td>&lt;0.00002</td>
</tr>
<tr>
<td>Acceleration velocity, m/s²</td>
<td>9.9 ± 3.4</td>
<td>18.6 ± 5.9</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Whole E duration, ms (from mitral valve opening to end of early filling)</td>
<td>234 ± 34</td>
<td>168 ± 32</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Velocity-time integral by the end of early filling, cm</td>
<td>14 ± 4</td>
<td>15 ± 4</td>
<td>0.11</td>
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<tr>
<td><strong>Inflow dynamics and myomechanics response to exercise in normal subjects</strong></td>
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<td><strong>Color Doppler M-mode</strong></td>
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<tr>
<td>Early diastolic propagation velocity, cm/s</td>
<td>62 ± 11</td>
<td>102 ± 25</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>IVPG, mm Hg</td>
<td>1.4 ± 0.5</td>
<td>3.7 ± 1.2</td>
<td>&lt;0.00001</td>
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<tr>
<td>Time to peak IVPG</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Time, ms</td>
<td>465 ± 34</td>
<td>353 ± 31</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>133 ± 10</td>
<td>120 ± 11</td>
<td>&lt;0.002</td>
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<tr>
<td>Time from mitral valve opening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, ms</td>
<td>35 ± 11</td>
<td>31 ± 12</td>
<td>0.25</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>10 ± 3</td>
<td>10 ± 4</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean left atrial pressure, mm Hg</td>
<td>12 ± 2</td>
<td>12 ± 2</td>
<td>0.81</td>
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<tr>
<td><strong>DTI myocardial velocity</strong></td>
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<tr>
<td>Long-axis function</td>
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<tr>
<td>Peak systolic velocity, cm/s</td>
<td>6.8 ± 0.9</td>
<td>9.6 ± 1.7</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Time, ms</td>
<td>146 ± 33</td>
<td>114 ± 41</td>
<td>&lt;0.0004</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>39 ± 7</td>
<td>38 ± 12</td>
<td>0.71</td>
</tr>
<tr>
<td>Peak early-diastolic velocity, cm/s</td>
<td>−10.0 ± 2.3</td>
<td>−13.6 ± 2.1</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Time, ms</td>
<td>505 ± 38</td>
<td>395 ± 32</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>%Sys-dur</td>
<td>134 ± 7</td>
<td>131 ± 6</td>
<td>0.11</td>
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</tbody>
</table>
Hemodynamic and LV functional responses and LV inflow and myocardial velocity responses to exercise in normal subjects are shown in Table 1. Exercise increased LV ejection and stroke volume (10±14% increase and 20±23% increase, respectively) owing to a decrease in end-systolic volume (19±29% decrease). LV filling increased, characterized by increased early filling (velocity-time integral until peak early filling, 41±38%; E-wave acceleration, 97±65%; and color velocity propagation of early filling, 68±44% increase) owing to an increased IVPG from 1.4±0.5 to 3.7±1.2 mm Hg (190±99% increase). Exercise also decreased isovolumic relaxation time (IVRT) significantly but did not alter LAP in normal subjects.

LV torsion occurred mainly by counterclockwise apical rotation, augmented by somewhat less clockwise basal rotation during systole, reversing abruptly in early diastole (Figure 1). During exercise, LV rotation was augmented at both apical and basal levels (9±3° to 19±7° and −3±2° to −7±4°, respectively; P<0.0001 for both), increasing LV torsion from 11±4° to 24±8°. LV untwisting began just before end systole at rest and during exercise (13±24 and 13±14 ms, respectively; P<0.0001 for both).

**Figure 1.** LV torsional behavior at rest and during exercise in normal subjects. Averaged LV rotational and torsional velocity profiles in 20 subjects are shown, derived from an average of 3 beats each. Upper panels: LV rotational and torsional velocity profiles at rest and during exercise. Lower panels: LV rotation and torsional profiles at rest and during exercise (obtained by integrating each velocity). Blue, light green, dark green, and violet lines indicate apical, middle, and basal rotations and LV torsion, respectively. MC indicates mitral valve closure; AO, aortic valve opening; Ej, peak ejection flow velocity in the outflow tract; AC, aortic valve closure (ie, end systole); MO, mitral valve opening; Pk-IVPG, peak IVPG (the timing is inserted with arrow); Pk-E, peak early filling velocity; and En-E, end of early filling. The time sequence was normalized to systolic duration; ie, t/100 indicates the onset of the QRS interval of the ECG, and t±100, end systole (AC). Error bars are marked at every 10% of systolic duration.
21±26 ms before aortic valve closure; \(P<0.03\) and \(P<0.002\), respectively).

Enhancement of the 3 components of LV myocardial velocity (ie, long axis, short axis, and LV twisting) in normal subjects is shown in Figure 2. Although each velocity component rose with exercise, LV systolic twisting velocity \((135\pm107\%)\) increased significantly more than did long-axis shortening \((42\pm23\%)\) and short-axis contraction \((42\pm31\%)\) during systole \((P=0.0013\) and 0.0014, respectively), whereas LV untwisting velocity was similarly more augmented \((197\pm120\%)\) than early diastolic long-axis lengthening \((40\pm28\%)\) and short-axis expansion \((82\pm46\%)\) \((P=0.0001\) and 0.003, respectively). In these normal subjects, maximum ventricular untwisting occurred around the time of mitral valve opening, shortening further during exercise \((P<0.005\)). Importantly, peak IVPG, shown previously to occur between mitral valve opening and peak early filling,\(^{11}\) was significantly later than peak ventricular untwisting \((P<0.02\) at rest.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Myocardial velocity profile of 3 LV motion components during systole and early diastole in normal subjects. Averaged LV twisting and velocity profiles in 20 subjects are shown, derived from an average of 3 beats each. Long- (red line) and short- (orange line) axis myocardial velocities and the LV torsional velocity (purple line, systolic twisting and diastolic untwisting) profile at rest and during exercise are shown. After the contraction/systolic-twisting phase, the diastolic process has started. LV untwisting precedes both long-axis lengthening and short-axis expansion. During exercise, the LV untwisting velocity was markedly enhanced, keeping the temporal sequence in early diastole. Abbreviations, time sequence, and error bars are the same as in the legend to Figure 1.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** LV torsion-volume loops at rest and during exercise in normal subjects. Averaged LV torsion and volume profiles in 20 subjects are shown, derived from an average of 3 beats each. The loops start from the onset of the QRS interval (q) and end after early filling (En-E). Upper panels: Relation between LV torsion (in degrees) and LV volume (percent end-diastolic volume, %EDV). Lower panels: Relation between LV torsion (normalized to peak systolic torsion) and LV volume (percent stroke volume, %SV). Pk-UnTw indicates timing of peak LV untwisting velocity; Pk-IVPG, timing of peak IVPG. Other abbreviations are the same as in the legend to figure 1. Error bars are marked at every 10% of systolic duration. Red and blue lines denote systole and early diastole, respectively.
and \( P < 0.01 \) during exercise). Thus, peak untwisting precedes peak IVPG, which in turn precedes peak early filling (\( P < 0.0001 \) at rest and exercise). In contrast, peak long-axis lengthening and short-axis expansion tracked transmitral filling quite closely, with their peak velocities occurring virtually synchronously with peak E velocity, suggesting that these are a consequence rather than a cause of transmitral filling.

To describe the relation between LV torsion and volume (derived from the long- and short-axis dimensions), we constructed LV torsion-volume loops (Figure 3). During systole, the relation between increasing torsion and decreasing volume was nearly linear, whereas during diastole, the relation between rapid untwisting (uncoiling) and increasing volume was distinctly nonlinear. Considering absolute values, the upper panels of Figure 3 show that exercise impacted torsion much more than LV volumes; however, when the torsion-volume loops were normalized to the peak torsion and stroke volume, the exercise loop was very similar to the resting one (Figure 3, lower panels).

Approximately 40% (at rest) and 30% (during exercise) of LV untwisting occurred during IVR, reaching a maximum just after mitral valve opening, when \( \approx 20\% \) of the stroke volume had entered the LV. By the peak of the E wave, \( \approx 80\% \) to 90\% of untwisting was completed and was essentially finished by the end of the E wave, with the subsequent LV volume increase due to expansion in the short and long axes. Interestingly, the timing of peak IVPG occurred near the point of maximal curvature in the diastolic torsion-volume segment.

Figure 4A relates maximum systolic torsion to peak untwisting velocity, with a strong linear correlation both at rest and during exercise. Figure 4B extends this temporally, showing that peak untwisting is predictive of peak IVPG at rest and especially with exercise.

Table 2 shows the correlations between peak untwisting and other parameters of diastolic function, including E-wave velocity, acceleration, timing, and long- and short-axis expansion. Note that a number of correlations did not reach statistical significance for rest and/or exercise alone, likely due to the relatively homogeneous sample of normal volunteers, but these became highly significant when rest and exercise were pooled.

**HCM Patients**

Acquisition of all echocardiographic data for this protocol was feasible in all 7 HCM patients both at rest and during exercise.

In contrast to Figure 3, the HCM patients showed delayed untwisting that was not significantly augmented with exercise (Figure 5). Indeed, the timing of peak untwisting was almost coincident with peak early filling (peak untwisting versus peak early filling, 136±17% of systolic duration versus 140±8% at rest, \( P = 0.646 \); 140±17% versus 137±6% during exercise, \( P = 0.667 \)).

Overall, peak systolic torsion was greater than that in normal subjects at rest, but it was less efficient at generating untwisting and was not augmented by exercise (Figure 6A). At rest, peak untwisting velocity was slightly lower in HCM than in normal subjects (1.6±0.8 versus \( -2.0±0.7 \) rad/s, \( P = 0.200 \)), as was the peak IVPG (1.2±0.3 versus 1.4±0.5 mm Hg, \( P = 0.288 \)). These differences became more dramatic with exercise, however, with the HCM patients...
showing much lower untwisting velocities ($-2.3 \pm 1.2$ versus $-5.6 \pm 2.3$ rad/s, $P<0.0001$) and IVPGs ($1.6 \pm 0.8$ versus $3.7 \pm 1.2$ mm Hg, $P<0.0001$; Figure 6B). Interestingly, at both rest and during exercise, the data points relating untwisting velocity and IVPG lay along a regression line not significantly different from that for normal subjects.

Discussion
The present study has described, at rest and during exercise, the quantitative and temporal relation of LV torsion to the dynamic events of early diastole, in particular IVPG. LV systolic torsion and rapid untwisting increased significantly with exercise, storing additional potential energy, which was released as increased diastolic suction. LV untwisting started near end systole until just after mitral valve opening, a critical interval for pressure decay in the LV and effective ventricular filling, particularly during exercise. By making the link between systolic torsion and untwisting velocity and subsequently IVPG and diastolic filling, we believe we have shown a potential mechanistic connection between systolic events and diastolic dysfunction.

Courtois et al measured IVPG, assuming that IVPGs reflected released energy from elastic recoil. However, no study to date has directly related IVPG to elastic recoil from ventricular untwisting. Importantly, all measurements were made with commercially available echocardiography systems. Indeed, the approach worked well in the complex geometry of HCM, wherein we showed that both untwisting and IVPG were severely reduced with exercise but that the quantitative relation between untwisting and IVPG was indistinguishable from that of normal subjects, lending confidence that this is a true mechanistic relation.

Systolic Torsion for Diastolic Untwisting
During exercise, stroke volume increased by $\approx 20\%$, with a concomitant reduction in end-systolic volume. Nikolic et al and Yellin et al have demonstrated that the restoring force magnitude is inversely related to end-systolic volume. The actual location of this elastic storage remains controversial, but it likely involves both the myocyte and the myocardial interstitium. Helmes et al cite titin-based restoring forces at the sarcomere level, showing that the relengthening velocity of the sarcomere is inversely related to end-systolic length, a microscopic analogy of ventricular contraction below equilibrium volume. Conversely, Ashikaga et al have shown significant deformation within the myocardium as the counterwound helixes contract against each other, storing significant energy in the interstitium as a global LV “spring”. Extending our previous observations that IVPG increases with improvement in systolic function after revasculariza-
We have previously shown\(^{30}\) that peak diastolic annular movement precedes peak early filling in normal subjects. The present study shows that peak untwisting occurs \(\sim 60\) ms earlier than long-axis lengthening or short-axis expansion at rest and exercise, indicating the importance of this mechanical sequence for relaxation and suction. The occurrence of untwisting before filling\(^{19}\) and radial expansion\(^{41}\) has been reported in dogs and in studies with implanted markers\(^{31–33}\) and magnetic resonance imaging tissue tagging\(^{19,20,34,35}\). Our results are consistent, providing data in normal humans and those with HCM. Although a full study of HCM pathophysiology awaits a larger dedicated study, our feasibility data are intriguing, with torsion higher than in normal subjects at rest (as Young et al\(^{36}\) reported) but with delayed and depressed untwisting, reflecting ineffective uncoiling of the myocardium.\(^{37}\) Moreover, during exercise, the HCM ventricle failed to increase torsion, untwisting, and IVPG, consistent with the report of Ciampi et al\(^{38}\) on exercise-induced systolic dysfunction in HCM, thus providing an explanation for the diastolic dysfunction commonly seen in this disorder. Delayed LV untwisting was also reported to cause abnormal relaxation in aortic stenosis,\(^{39}\) confirming the importance of this temporal sequence to normal diastolic function. Using these methods to explore exercise tolerance in patients with heart disease\(^{22,40}\) is an important future study. The high-frame-rate nature of this methodology is also suitable to exploration of ventricular activation and isovolumic contraction. For example, the initial small negative torsion shown in Figures 1 through 3 may be explained by electrical activation beginning in the endocardium.\(^2\)

**Diastolic Untwisting for LV Suction**

“Suction” is a term often used variously in diastolic function, sometimes referring to the relaxation of small, nonfilling ventricles to subatmospheric pressure, as shown well by Yellin et al,\(^{27}\) and sometimes referring to the “negative compliance” of the ventricle in early diastole, when pressure continues to drop despite an increase in volume. Here we refer to the way IVPG promotes the movement of blood to the apex, allowing efficient filling at low mean LAP. The present study shows that \(\sim 40\%\) of LV untwisting occurs by the time of mitral valve opening both at rest and during exercise in normal subjects. IVRT is determined by the rate of LV pressure decay and LAP. During exercise, the shortened IVRT caused by the increased rate of LV pressure decay without an elevated LAP helps to prolong the suction phase, which we consider to include IVRT and the acceleration phase of early filling (acknowledging that the influence of IVPG is not so precisely delimited in time). Furthermore, in normal subjects, the torsion-volume loop (Figure 3) shows that rapid untwisting continues after mitral valve opening, so that an additional 40% of the untwisting occurs by the time of peak early filling, reflecting the time during which IVPGs are present within the ventricle. In other words, the potential energy stored during systole is converted to kinetic energy during early diastole, thus effectively bridging the 2 periods.

Lele et al\(^{41}\) reported that the inability to increase filling without a significant rise in LAP was a major limitation of peak exercise capacity. One way to quantify this suction is to recognize the “hysteresis” between systole and diastole in the torsion-volume loop (in essence, looking at the area enclosed by the loop and viewing LV torsional deformation as a process of intrinsic loading/unloading [storing/restoring force] producing LV “suction work” [or filling work]; Figure 3, upper panels) Interestingly, HCM patients showed delayed and depressed untwisting and a loop with a much less enclosed area (Figure 4). Further assessment of LV torsional mechanics by this loop quantification in various disease states is a promising area for future study.

Because the rate of LV filling increased with exercise, it is possible that the more rapid decline in LV pressure with exercise would not continue after mitral valve opening unless aided by other factors. As shown in Figure 3, the rapid untwisting (against volume change) occurs in normal subjects during IVRT and the subsequent suction phase until peak IVPG, where the torsion-volume loop shows an inflection point. The temporal sequence of peak untwisting velocity, peak IVPG, and peak early filling velocity argue for mechanohemodynamic causality (like a cascade effect) in early diastole.

It is unknown whether early diastolic ventricular untwisting would also be observed in a preparation of nonfilling diastole.\(^{27}\) Nikolic et al\(^{12}\) observed that the equilibrium volume–end-systolic volume difference was 45% of stroke volume. This volume corresponds to \(\sim 50\%\) to 60% of untwisting, where IVPG nears a maximum (Figure 3).

This untwisting progression is comparable to the pressure decay seen in the apical LV.\(^{11}\) That is, the first 40% of LV untwisting contributes to the large rapid pressure fall of IVRT, and the next 40% of untwisting produces an additional pressure fall, as well as the LV suction to pull blood efficiently into the apex. In this way, LV untwisting can be correlated with both the relaxation time constant (during IVR)\(^{20}\) and IVPG (after mitral valve opening to peak early filling), as we have shown here.

Apical rotation is the main creator of global LV systolic twist, and apical backrotation also plays the dominant role in the subsequent diastole. The rapid apical backrotation reduces wall stress and causes a faster decline in LV pressure while creating the IVPG, pulling blood into the apex without an increase in LAP, even during exercise. Although a similar peak early filling velocity was observed in HCM subjects during exercise, these appeared to result from an elevated LAP and not an increased IVPG. Davis et al\(^{42}\) and Steine et al\(^{15}\) have previously speculated on the importance of apical relaxation for LV suction. Thus, it is now reasonable to conceptualize enhanced ventricular untwisting as a mechanistic manifestation of elastic recoil.

**Limitations**

There are inherent limitations to 2D echocardiography in attempting to define 3D deformation. We took care to orient our scan accurately, but some misalignment is inevitable, particularly during exercise.
LV torsion was derived from multiple DTI images, which because of the Doppler effect only capture the component of velocity parallel to the ultrasound beam. However, our method isolates both the rotational velocity and radial motion to be aligned with the beam. Future work in non-Doppler velocimetry (eg, B-mode speckle tracking) might resolve this issue further, whereas use of 3D datasets would allow determination of torsion from a single dataset. The effect of maximal exercise was beyond the scope of the present study, but DTI has sufficient temporal resolution to study this, although excessive respiratory movement may degrade the images somewhat. LV torsion and volume assessment during maximal dobutamine infusion might overcome this obstacle. The relevance to invasively measured tau is also interesting, but we did not invasively measure that parameter in this study.

Conclusions
LV untwisting (1) occurs from end systole until just after mitral valve opening; (2) precedes the peak IVPG, which itself precedes peak early filling and LV dilation and lengthening; (3) increases with submaximal exercise more significantly than does LV lengthening or expansion; (4) provides a mechanistic link between systolic torsion and IVPG at rest and during exercise in normal subjects; and (5) plays a similar role in HCM, even though it is delayed and unenhanced in this disorder.

Thus, we believe that LV untwisting during IVRT facilitates LV suction by generating IVPG, with enhancement during exercise. LV untwisting appears to be a measurable manifestation of elastic recoil.

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References
How does the heart convert the increased contractility of exercise into this enhanced filling? In this study, we used exercise echocardiography and tissue Doppler imaging to define the mechanical events linking systole to diastole. During systole, the normal heart twists gradually, storing energy in torsion and compression of the sarcomeric molecular spring titin, the interstitium, or both. With aortic valve closure, however, the ventricle abruptly untwists, with more than half of the torsion released during isovolumic relaxation. This recoil leads to a 1- to 2-mm Hg intraventricular pressure gradient between the base and the apex of the heart, which helps pull blood across the mitral valve. With exercise, the untwisting rate and intraventricular pressure gradient rise in concert almost 3-fold, significantly augmenting transmitral flow. In patients with hypertrophic cardiomyopathy, however, both untwisting and intraventricular pressure gradient are dramatically blunted with exercise, but the relation between them is similar to that in normal hearts. Therefore, we believe that torsion during systole stores energy, which is released during isovolumic relaxation. This recoil leads to a 1- to 2-mm Hg intraventricular pressure gradient between the base and the apex of the heart, which helps pull blood across the mitral valve. With exercise, the untwisting rate and intraventricular pressure gradient rise in concert almost 3-fold, significantly augmenting transmitral flow. In patients with hypertrophic cardiomyopathy, however, both untwisting and intraventricular pressure gradient are dramatically blunted with exercise, but the relation between them is similar to that in normal hearts. Therefore, we believe that torsion during systole stores energy, which is released during isovolumic relaxation to generate the diastolic suction that allows the ventricle to fill efficiently, even with the demands of exercise.
Enhanced Ventricular Untwisting During Exercise: A Mechanistic Manifestation of Elastic Recoil Described by Doppler Tissue Imaging

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