Left Ventricular Untwisting Rate by Speckle Tracking Echocardiography

Jianwen Wang, PhD, MD; Dirar S. Khoury, PhD; Yong Yue, PhD; Guillermo Torre-Amione, PhD, MD; Sherif F. Nagueh, MD

Background—Recent studies validated the measurement of left ventricular (LV) untwisting rate (UR) by speckle tracking echocardiography. A few reports suggest that it may provide additional noninvasive insight into LV diastolic function.

Methods and Results—Simultaneous echocardiographic imaging and LV pressure measurements (7F Millar catheters) were performed in 8 adult dogs. Loading conditions were altered by caval occlusion, whereas lusitropic state was changed by dobutamine and esmolol infusions. Inferior vena cava occlusion at all experimental stages (baseline, dobutamine, esmolol) led to a significant decrease \((P<0.01)\) in LV end-systolic volume (ESV) and a significant increase in UR \((P=0.03)\). The best relation was observed between LV UR and ESV \((r=-0.8, P<0.001)\). The clinical study was conducted in 67 patients (age 57±17 years, 19 women) undergoing simultaneous right heart catheterization and echocardiographic imaging, with 20 healthy subjects as a control group. There were 34 patients with ejection fraction (EF) <50\% (25±9\%), and 33 patients with normal EF and diastolic dysfunction (64±7\%). Patients with LV systolic dysfunction had a significantly lower UR \((-55\;\text{a/s})\) in comparison with the control group \((-89\;\text{a/s})\) and patients with normal EF \((-104\;\text{a/s}, P<0.05)\), and the determinants of LV UR were twist, ESV, and \(\tau\) \((r^2=0.83, P<0.001)\). In patients with diastolic dysfunction and normal EF, twist and ESV were independent predictors \((r^2=0.71, P<0.001)\).

Conclusions—LV UR is reduced in patients with depressed EF, but not in those with diastolic dysfunction and normal EF, and is primarily determined by twist and ESV. \(\text{(Circulation. 2007;116:2580-2586.)}\)

Key Words: diastole • echocardiography • heart failure • mechanics • myocardium

Left ventricular (LV) filling results from the positive early diastolic transmitral pressure gradient. Therefore, it depends on both LV pressure drop during the isovolumetric relaxation period and left atrial (LA) driving pressure.\(^1,2\) The rapid decline in LV pressure during this phase of the cardiac cycle is caused by active myocardial relaxation and LV elastic recoil. LV elastic recoil/untwisting generates the suction force for LV filling. Accordingly, LV untwisting rate (UR) may provide an additional noninvasive insight into LV diastolic function. Previous work with cardiac magnetic resonance (MR) in an animal model, has shown that LV UR correlates closely with the time constant of LV relaxation.\(^3\) However, there are very limited data on the clinical application of UR for the assessment of LV diastolic function.\(^4\) Moreover, its hemodynamic determinants in patients with cardiovascular disease have not been examined.

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More recently, speckle tracking echocardiography was applied for the derivation of LV twist and untwisting, with validation against sonomicrometry and cardiac MR.\(^5,6\) We undertook the present study to investigate the hemodynamic determinants and the clinical application of UR measured by speckle tracking echocardiography.

Methods

Animal Preparation

The animal study was approved by the institutional Animal Protocol Review Committee, and animals were treated in compliance with the 1985 National Institutes of Health guidelines for the care and use of laboratory animals. Eight adult mongrel dogs weighing 19 to 30 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg body weight), intubated, and mechanically ventilated. A high-fidelity pressure catheter (7F Millar), calibrated relative to atmospheric pressure before introduction, was advanced into the LV (retrograde from the right femoral artery through the aortic valve) to record LV pressures continuously. A balloon catheter was advanced into the inferior vena cava (IVC) through the right femoral vein. The balloon was inflated in sequential steps to decrease LV filling. Throughout the procedure, surface ECG (lead II) and ventricular pressure signals were simultaneously acquired on a computer-based data acquisition system (Cardiodynamics BV, Leycom -CFL- 512, Argonstraat, the Netherlands).

Echocardiographic Studies

Dogs were imaged in the standard parasternal and apical views with a GE Vivid 7 ultrasound system. Image acquisition was carried out...
at a frame rate of 80 to 100 frames/sec, and 3 cardiac cycles were stored in cineloop format, for subsequent offline analysis.

Experimental Protocols
LV filling pressures were decreased with inflation of the balloon placed in the IVC. The occlusions were performed in a sequential manner with data acquired at stepwise decrements of LV end-diastolic pressure. After achieving a stable hemodynamic state at each LV end-diastolic pressure level, LV systolic and diastolic pressures, heart rate, and 2-dimensional images were acquired.

To evaluate the influence of LV relaxation on LV UR, dobutamine was administered at a dose of 5 μg/kg per min with reacquisition of echocardiographic and pressure data. Dobutamine infusion was then terminated, and after the animals returned to their baseline state, esmolol with its negative lusitropic properties was administered (0.5 mg/kg intravenously) with subsequent reacquisition of data. To assess the interaction between LV volume and relaxation on UR, IVC occlusion was repeated during the dobutamine infusion and later with esmolol.

Data Analysis

Hemodynamic Measurements
LV systolic and diastolic pressures were measured in addition to the time constant of LV pressure decay during the isovolumetric relaxation period (τ)7

Analysis of Twist Mechanics
The analysis was performed offline by a single observer without knowledge of hemodynamic data, using an EchoPac workstation (GE Healthcare, Amersham, United Kingdom). The endocardium was traced in the frame, where its complete contour was identified by the best. The width of the region of interest was next adjusted to fit the whole myocardium. From these recordings, EchoPac selects the speckles and tracks them during the cardiac cycle. The analyst verifies the accuracy of the tracking with the option of subsequent endocardial retracing and adjustment of the size of the region of interest as needed. At the end, the analysis program displays the rotation angle against time during the cardiac cycle in the apical and parasternal short-axis tomograms at 3 distinct levels: basal (identified by the mitral valve), papillary, and apical (no papillary muscles noted). In the apical 4-chamber view, conventional Doppler and tissue Doppler velocities were obtained at end expiration as previously described.1,2 All images were stored digitally for subsequent offline analysis.

Conventional Echocardiographic Analysis
The analysis was performed offline by a single observer using EchoPac workstation without knowledge of hemodynamic data. LV volumes (end-diastolic volume, end-systolic volume (ESV), and EF), and LA volume were measured according to the recent guidelines of the American Society of Echocardiography.9 All Doppler values represent the average of 3 consecutive beats. Mitral inflow was analyzed as previously described.1,2 Ea velocity was measured and the dimensionless ratio E/Ea was computed. Similar to the canine experiments, LV twist mechanics was analyzed. Absolute time intervals were measured and also expressed in relation to systolic duration with the time at end-systole marked as 100%

Reproducibility
Interobserver reproducibility was assessed in 14 cases with the use of previously acquired images but not necessarily the same heart beats. A significant correlation was present (r=0.85, P<0.01, UR rate: 50±21%/s versus 49±22%/s) without a trend for over- or underestimation.

Hemodynamic Measurements
The pressure transducers were balanced before data acquisition with the zero level at mid-axillary line. Pulmonary artery (PA) catheters were used to measure PA pressure, mean right atrial pressure, and mean wedge pressure. The wedge position was verified by changes in waveform and O2 saturation. The τ was calculated using the previously validated expression10:

\[ \tau = \frac{1}{f_{IVRT} \left( \ln \text{LVSP} - \ln \text{PCWP} \right)} \]

where IVRT is isovolumetric relaxation time, ln is natural logarithm, LVSP is LV end-systolic pressure calculated as 0.9×systolic blood pressure,11 and PCWP is pulmonary capillary wedge pressure.

Statistical Analyses
Analyses were performed using Sigma Stat (3.1). Continuous data are presented as mean±SD or median (25th to 75th percentiles) for normal/nonnormal data, respectively. Dichotomous data are shown as number (%). A previous study in animals noted a significant correlation coefficient of 0.92 between LV recoil rate and τ.5 Therefore, the number of animals was selected to detect a similar correlation coefficient at an α level of 0.05 and a power of 90%. The hemodynamic and echocardiographic measurements were compared in the experimental stages by use of repeated measures ANOVA with pairwise multiple comparison procedures performed using the Holm-Sidak method. For human studies, the sample size was selected to detect a minimum difference among the 3 groups (normal, patients with EF<50%, and patients with EF≥50%) in UR of 30%/s, with a SD of 30%/s, at an α=0.05 and a power of 90%. Comparisons between the 3 groups were performed using ANOVA, with subsequent pairwise comparisons carried out using the Holm-Sidak method when the data had a normal distribution. When the normality test failed, Kruskal-Wallis 1-way ANOVA on ranks was applied, with subsequent pairwise comparisons carried out by the Dunn method. The relationship between different continuous variables was analyzed using single and multiple regression analyses. Results were considered significant when P≤0.05.
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Animal Experiments
Dobutamine and esmolol infusions led to opposite changes in heart rate (beats/min) (baseline 99±10, dobutamine 119±9, esmolol 91±10; P<0.001), LV systolic pressure (mm Hg) (baseline 91±27, dobutamine 170±38, esmolol 82±26; P<0.001), \( \tau \) (ms) (baseline 39±5, dobutamine 29±5, esmolol 64±7 ms; P<0.001), ESV (baseline: 37±14; dobutamine: 26±11; esmolol: 47±15 mL; P<0.001), and untwisting rate (°/s) (baseline 75±31, dobutamine 103±45, esmolol 57±25; P=0.008). LV twist increased with dobutamine, and decreased with esmolol (P<0.001), and was significantly related to ESV and untwisting rate, with several significant correlations between twist, twisting and untwisting rates (r=0.64, P<0.01).

Impact of LV ESV on the Relation Between UR and LV Relaxation
At baseline (without drug infusion), IVC occlusion led to a significant decrease in ESV (baseline 37±14 versus 21±8 mL; P=0.01), and an increase in UR (baseline 75±31 versus 109±31°/s; P=0.03), but without a significant change in \( \tau \) (baseline 39±5 versus 35±8 ms; P=0.24). Likewise, IVC occlusion during dobutamine infusion resulted in a significant decrease in ESV (P=0.01) and an increase in UR (P=0.03) despite no significant change in \( \tau \) (P=0.4). Similar results were observed with IVC occlusion during esmolol infusion (ESV 47±15 versus 33±16 mL, P=0.01; UR 57±25 versus 73±30°/s, P=0.03; \( \tau \) 64±7 versus 60±9 ms, P=0.33). In addition, on examination of experimental stages where LV ESV was comparable (eg, baseline status versus IVC occlusion during the infusion of esmolol (baseline ESV 37±14 mL) versus IVC occlusion during esmolol infusion (ESV 33±16 mL); P=0.5), LV URs were similar (75±31 versus 73±30°/s; P=0.6), despite large and significant differences in \( \tau \) (39±5 versus 60±9 ms; P=0.01). On regression analysis, the best correlation was observed between LV UR and ESV (inverse first order where \( y = y_0 + a/x \), \( r = -0.8 \); P<0.001) (Figure 1).

Human Studies
Tables 1 and 2 present a summary of the hemodynamic and echocardiographic findings in the study sample. As expected, patients with systolic dysfunction had significantly larger LV and LA volumes and lower EF values. Likewise, they had significantly higher PA and wedge pressures (Table 1). Patients with depressed EF also had significantly higher E/A, and E/Ea ratios in comparison with patients with diastolic dysfunction and normal EF (Table 2).

Table 1. Clinical Characteristics and Hemodynamic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Control (n=20)</th>
<th>EF&lt;50% (n=34)</th>
<th>EF≥50% (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40±12*</td>
<td>53±16†</td>
<td>61±16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>...</td>
<td>6 (18)</td>
<td>15 (45)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>...</td>
<td>6 (18)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Obesity</td>
<td>...</td>
<td>14 (41)</td>
<td>17 (52)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64±14*</td>
<td>84±16</td>
<td>83±16</td>
</tr>
<tr>
<td>SBP/DBP, mm Hg</td>
<td>124±13/70±13</td>
<td>109±18/64±16</td>
<td>128±22/65±16</td>
</tr>
<tr>
<td>PAS/PAD, mm Hg</td>
<td>50±15/26±9†</td>
<td>38±16/18±9‡</td>
<td></td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>14±7</td>
<td>11±9</td>
<td></td>
</tr>
<tr>
<td>Wedge pressure, mm Hg</td>
<td>10±2*</td>
<td>22±7‡</td>
<td>16±7</td>
</tr>
<tr>
<td>LV End-diastolic volume, mL</td>
<td>101±34</td>
<td>212±98†</td>
<td>102±45</td>
</tr>
<tr>
<td>LV End-systolic volume, mL</td>
<td>36±15</td>
<td>160±79†</td>
<td>39±22</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>65±6</td>
<td>25±9†</td>
<td>64±7</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or number (percentage). DBP indicates diastolic blood pressure; PAD, pulmonary artery diastolic pressure; PAS, pulmonary artery systolic pressure; RAP, mean right atrial pressure, and SBP, systolic blood pressure. For subjects in the control group, mean wedge pressure was derived using tissue Doppler and mitral/pulmonary venous flow A wave signals (see Quinones).

*P<0.05 vs patients with EF<50% and those with EF≥50%.
†P<0.05 vs control group and patients with EF<50%.
‡P<0.01 vs patients with EF≥50%.
LV Twist and Twisting Rate

The control group had a mean LV twist of $12 \pm 4^\circ$. This was significantly reduced in patients with SHF ($P < 0.01$ versus control group and versus patients with diastolic dysfunction) (Table 2), but not in those with diastolic dysfunction ($P > 0.2$ versus control group). Similar results were observed for LV twisting rate (Table 2), which was significantly lower in patients with SHF than the other 2 groups (Figure 2). Interestingly, patients with diastolic dysfunction who were receiving $\beta$-blockers had a significantly lower twist rate than

### Table 2. Echocardiographic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Control (n=20)</th>
<th>EF&lt;50% (n=34)</th>
<th>EF≥50% (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Volume index, mL/m²</td>
<td>22±5*</td>
<td>47±16†</td>
<td>35±18</td>
</tr>
<tr>
<td>Mitral E velocity, cm/s</td>
<td>75 (68 to 88)†</td>
<td>95 (70 to 106)</td>
<td>100 (78 to 125)</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.5 (1.2 to 1.9)</td>
<td>1.8 (1.5 to 2.8)†</td>
<td>1.1 (0.84 to 1.64)†</td>
</tr>
<tr>
<td>Mitral annulus Ea velocity (cm/s)</td>
<td>12.7 (10.5 to 13.5)*</td>
<td>4 (3 to 5.6)†</td>
<td>5 (3.9 to 6)†</td>
</tr>
<tr>
<td>E/Ea Ratio</td>
<td>6.4 (5 to 8)*</td>
<td>23 (18 to 28)†</td>
<td>17 (13 to 23)†</td>
</tr>
<tr>
<td>LV Twist, $\phi$</td>
<td>11.5 (9.8 to 15)†</td>
<td>4.9 (3.7 to 6)†</td>
<td>11.2 (7.6 to 14)†</td>
</tr>
<tr>
<td>Twisting rate, $\alpha$/s</td>
<td>94±30</td>
<td>51±20‡</td>
<td>102±33</td>
</tr>
<tr>
<td>UR, $\alpha$/s</td>
<td>−89 (−122 to −72)‡</td>
<td>−55 (−67 to −33)‡</td>
<td>−104 (−125 to −86)‡</td>
</tr>
</tbody>
</table>

Data for LA volume index and twisting rate are presented as mean±SD; all other data are presented as median (25th to 75th percentiles).

* $P < 0.05$ vs patients with EF<50% and those with EF≥50%.
† $P < 0.05$ vs patients with EF≥50%.
‡ $P < 0.05$ vs control group and patients with EF≥50%.

**Figure 2.** Examples of LV twist and its time derivative from 3 cases. Top left, the twist curve from a subject in the control group (twist=17°). Top middle, from a patient with diastolic dysfunction and normal EF (16°); top right, the reduced twist from a patient with depressed EF (5°). Lower left, the time derivative of LV twist from a normal subject (UR=90°/s). Lower middle, from a patient with diastolic dysfunction and normal EF (UR=90°/s); and lower right, from a patient with systolic dysfunction (UR=−50°/s).
those who were not on this medication (7.6° versus 13.6°; P<0.01).

**Left Ventricular UR**

Patients with LV systolic dysfunction had a significantly lower UR (Table 2) in comparison with the control group and patients with diastolic dysfunction. This was caused by differences at the basal (SHF 32, versus control 59, and diastolic dysfunction 57°/s; P<0.05) and apical (SHF −37, versus control −69, and diastolic dysfunction −70°/s; P<0.05) levels. However, no significant differences existed between patients with diastolic dysfunction and the control group. These results were unchanged (P=0.4) when comparison was limited to the control group and patients with heart failure and normal EF (ie, when the 9 patients with impaired LV relaxation and normal mean wedge pressure were excluded). Interestingly, patients with diastolic dysfunction who were receiving β-blockers had a significantly lower UR than those who were not on this medication (90°/s versus 117°/s, P=0.02).

LV untwisting began an average of 15±15 ms before aortic valve closure in the control group. Similar findings were noted in the group with diastolic dysfunction (5±48 ms, P>0.1). However, there were 12 patients with diastolic dysfunction where LV untwisting occurred after aortic valve closure by 26±18 ms. In comparison, LV untwisting was significantly delayed in SHF patients and began 37±63 ms after aortic valve closure (P<0.05 versus the other 2 groups). In relation to mitral inflow, peak LV untwisting (116±10% of systolic duration) occurred before mitral E velocity in all subjects in the control group, whereas it was delayed in patients with SHF (165±23% of systolic duration; P<0.01). In the diastolic dysfunction group, peak untwisting occurred at a time (118±33% of systolic duration) that was not significantly different from that in the control group (P>0.1). However, the 12 patients with delayed onset of untwisting also showed delayed peak untwisting that occurred almost simultaneously with mitral E velocity (133±6% of systolic duration). In the other 21 patients with diastolic dysfunction, peak untwisting preceded mitral E velocity. Interestingly, the 12 patients with delayed untwisting showed a trend of having a larger LA volume (40±13 versus 33±16 mL/m²; P=0.08) and a higher PA systolic pressure (43±11 versus 35±16 mm Hg; P=0.06).

**Hemodynamic Determinants of LV UR in Patients With Depressed EF**

LV UR was significantly related to systolic twist (r=0.6, P=0.001) (Figure 3), τ (r=−0.78, P<0.001) (Figure 4), LV end-diastolic volume (r=−0.50, P=0.05), LVESV (r=−0.64, P<0.001) (Figure 5), and LVEF (r=0.55, P=0.03), but not heart rate (P>0.1). A nonsignificant association was present with mean wedge pressure (r=−0.4, P=0.06). On multiple regression analysis, τ, ESV, and twist were the independent predictors of LV UR (r²=0.83, P<0.001).

**Hemodynamic Determinants of LV UR in Patients With Diastolic Dysfunction**

LV UR was significantly related to systolic twist (r=0.61, P=0.001) (Figure 3), pulmonary capillary wedge pressure (r=−0.5, P=0.05), LV end-diastolic volume (r=−0.50, P=0.05), LVESV (r=−0.8, P<0.001) (Figure 5), and LVEF (r=0.6, P=0.02). No significant relationships were noted between the UR and heart rate (P>0.05) and τ (r=−0.29, P=0.15) (Figure 4). On multiple regression analysis, ESV and twist were the independent predictors of LV UR (r²=0.71, P<0.001).
Discussion
This study shows that LV twist, twisting rate, and UR are reduced in patients with LV systolic dysfunction and depressed EF, but not in those with diastolic dysfunction and normal EF. In both patient groups, LV twist and ESV had strong and significant relations with the UR.

Hemodynamic Determinants of LV UR
In normal subjects, LV filling occurs as a result of the rapid decline in LV pressure caused by LV relaxation and elastic recoil. The latter term refers to the energy stored during systole that is released in early diastole. In that regard, previous studies with cardiac MR in animals have shown that 40% of systolic twist is released during the isovolumetric relaxation period. Similar results were noted in human studies with tissue Doppler–based measurements of LV twist. Although the previous animal study with MR supports the premise that LV UR can be used as a noninvasive index of LV relaxation, there are other factors that affect it and limit its clinical application for that purpose.

These variables include LV contractility/ESV (along with the relation of ESV to the equilibrium volume) and LV twist. Therefore, the significant correlations of LV UR to LV twist and to ESV (Figures 3 and 5) are not surprising. Importantly, the animal experiments show that, at a comparable ESV, LV UR was similar despite large and significant differences in τ. The results from the animal experiments help explain the lack of a correlation between LV UR and τ in patients with heart failure and normal EF. However, the results of our animal model, wherein short-term changes were induced in LV relaxation and preload, cannot be extrapolated to patients with chronic systolic heart failure. Therefore, additional insights may be gained by examination of the hemodynamic determinants of the twist mechanics in an animal model of chronic systolic heart failure.

LV UR is also affected by LV preload, in that we observed significant inverse correlations between UR and 2 measurements of preload: end-diastolic volume and mean wedge pressure. In that regard, our observations are similar to previous work in humans in which a different method was used to calculate LV UR. In that previous study, simultaneous pressure and biplane cinefluoroscopic marker images were used to examine the effect of loading conditions and inotropic stimulation on LV twist mechanics. The authors noted that volume loading with saline infusion decreases early diastolic untwisting. It is possible to explain this observation when one considers that volume loading can lead to higher ESV and therefore to reduced recoil forces.

LV UR in Patients With Depressed EF
In the presence of systolic heart failure, reduced LV filling exists, in part caused by an impaired ability to utilize suction. This has been shown in animal models as well as in patients. As a result of reduced contractility, ESV may not be lower than the equilibrium volume, even though the latter is increased. These changes result in a reduction in the restoring force. In turn, interstitial remodeling and changes in the relative expression of titin isoforms may provide a plausible hypothesis that can explain the reduction in restoring forces. The deformation of titin during systole below slack length generates a restoring force. Titin exists in 2 isoforms, a stiffer N2B isoform and a larger, more compliant N2BA isoform. The N2BA isoform results in a lower passive stiffness as well as a reduced restoring force in comparison with the N2B isoform. In that regard, we have recently shown that the ratio of N2BA to N2B titin isoforms is increased in patients with idiopathic dilated cardiomyopathy, and this ratio was significantly correlated with LV ESV, such that patients with the highest ratio had the largest ESV.

LV UR in Patients With Diastolic Dysfunction and Normal EF
Patients with diastolic dysfunction and normal EF have a LV UR that is similar to that observed in the control group, but significantly higher than that in patients with depressed EF. With respect to this finding, our observations with speckle tracking echocardiography are similar to those reported with other techniques. Specifically, Hees et al used cardiac MR to show that diastolic changes with aging occur in the presence of a normal UR. Likewise, Notomi et al used tissue Doppler to show that patients with hypertrophic cardiomyopathy (and diastolic dysfunction) have a UR similar to normal subjects. Collectively, these observations indicate that LV relaxation is not the main determinant of untwisting in this population.

The relation between LV UR and ESV can help explain the above findings. In particular, patients in this group have a normal or reduced ESV and increased restoring forces. A recent study is suggestive of a higher ratio of N2B to N2BA titin isoforms in patients with diastolic heart failure. When compressed, the N2B isoform results in higher restoring forces and can account for the normal LV UR seen in this group. Finally, the normal UR in patients with diastolic heart failure may be viewed as a compensatory mechanism that helps LV filling, given the presence of abnormalities in diastolic function that can adversely affect LV filling. The presence of a trend toward larger LA volumes and higher PA pressures in patients with delayed untwisting favor this hypothesis, but additional studies with more patients are needed for definitive proof.

Aside from the implications of the present study for LV diastolic function in this population, the presence of normal twist mechanics is indicative that this aspect of systolic function is preserved, and does not contribute to heart failure symptoms.

Limitations
The accurate measurement of LV twist/untwist by speckle tracking is contingent on high-quality recordings, high tracking quality, and the correct recognition of anatomic structures that identify the basal and apical short-axis levels. Our results were obtained using the highest frame rate that allows for accurate tracking and we also verified the tracking accuracy visually, retracting and repositioning the region of interest as needed. Nevertheless, 9 patients (12%) were excluded for technical reasons. The control group was younger than the other 2 groups, and patients with depressed EF were also younger than those with diastolic dysfunction. However, most recently, Kim et al have shown no significant change with age in basal and apical URs in healthy normal volunteers between <31 to >60 years old. Similar results were also reported by cardiac MR where
the recoil rate had no significant relation with age ($r=0.19$, $P=0.11$) in 122 normal subjects between 21 and 92 years old. Furthermore, in consideration of only age-matched patients (depressed and normal EF) and controls (ie, excluding 6 controls, 8 patients with depressed EF, and 6 patients with diastolic dysfunction), the results in Table 2 were still present at a significant level ($P<0.05$). Finally, it would have been ideal to measure $\tau$ in patients with high-fidelity pressure catheters. However, the method used has been well validated previously. In addition, LV catheterization was not indicated at the time of the study, and it was difficult to subject the patients to the additional risks of such catheterization for the sole purpose of this investigation. Exercise stress testing can show differences between healthy subjects and patients with heart failure and normal EF. However, stress was not included in the study design, given the fact that these were heart failure patients undergoing invasive hemodynamic measurements and were unable to exercise.

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**Disclosures**

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**CLINICAL PERSPECTIVE**

Left ventricular (LV) twist and untwist can provide unique insight into myocardial systolic and diastolic function. Speckle tracking echocardiography was recently validated as an accurate method that can assess twist mechanics, which extends the potential application of this measurement to settings where cardiac magnetic resonance imaging is not appropriate. This study was performed to investigate the hemodynamic determinants and the clinical application of LV untwisting rate. In an animal model, LV end-systolic volume was the primary determinant of the untwisting rate, such that LV untwisting best tracked changes in end-systolic volume rather than the time constant of LV relaxation. In 34 patients with ejection fraction $<50\%$, twist and untwisting rate were significantly lower than normal controls, whereas in cardiac patients with ejection fraction $>50\%$, they were similar to the control group. In both groups, the primary determinants of untwisting rate were LV twist and end-systolic volume. These findings indicate that in heart failure patients with normal ejection fraction, LV twist and untwisting rate are preserved, and appear not to contribute to their symptoms.
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