Left Ventricular Untwisting Is an Important Determinant of Early Diastolic Function

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OBJECTIVES We sought to establish the relationship between invasive measures of diastolic function and untwisting parameters measured with speckle tracking imaging.

BACKGROUND Left ventricular (LV) diastolic function is determined by early diastolic relaxation (which creates suction gradients for LV filling) and myocardial stiffness. Assessment of LV torsion has shown that untwisting begins before aortic valve closure and, in animals, might be an important component of normal diastolic filling. Studies in human subjects using indirect indexes derived from right heart catheterization have suggested a relationship between $\tau$ and measures of untwisting, but the relationship between directly measured diastolic function indexes with micromanometer catheters and untwisting parameters has not been established in human subjects.

METHODS Simultaneous Millar micromanometer LV pressure and echocardiographic assessment was performed on 18 patients (10 male, mean age 66 years) with normal systolic function and a spectrum of diastolic function. Invasive rate of the rise of LV pressure, dp/dt minimum and $\tau$ were recorded as measures of active relaxation, and the LV minimum diastolic pressure was recorded as an index of diastolic suction. The LV stiffness constant and functional chamber stiffness were estimated from hybrid pressure-volume loops. Echocardiographic speckle tracking imaging was used to quantify torsion.

RESULTS As relaxation was impaired, (prolonged $\tau$) untwisting was delayed ($r = 0.35$, $p < 0.01$). There were nonsignificant associations between reduced untwisting and longer values of $\tau$ and lower dp/dt minimum. Reduction in the extent of untwisting before mitral valve opening was associated with increased LV minimum diastolic pressure ($r = -0.30$, $p < 0.034$). No relation was observed between the LV stiffness constant ($\beta$: $r = 0.11$, $p = NS$) or the functional LV chamber stiffness ($b$: $r = 0.11$, $p = NS$) and untwisting.

CONCLUSIONS Untwisting parameters are related to invasive indexes of LV relaxation and suction but not to LV stiffness. These data suggest that untwisting is an important component of early diastolic LV filling but not later diastolic events. (J Am Coll Cardiol Img 2009;2:709–16) © 2009 by the American College of Cardiology Foundation

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Traditional measures of left ventricular (LV) diastolic function have focused on relaxation and stiffness. Early diastolic LV relaxation creates intraventricular pressure gradients or suction gradients that are important, because they allow efficient LV filling without increasing left atrial (LA) pressure (1,2), particularly during exercise (3,4).

Torsion, the rotation of the apex and the base of the LV on its longitudinal axis in opposite directions, results from the contraction of the obliquely oriented subendocardial and subepicardial helixes (5,6). The LV untwisting results begins before aortic valve closure and before longitudinal and radial expansion (7). Because it is one of the earliest events leading to LV filling, untwisting might be a critical determinant of early diastolic function. The quantification of LV untwisting might provide novel insights into diastolic function (8,9), in particular the generation of intraventricular pressure gradients (10).

Dong et al. (11) found, in a canine model, a strong correlation between recoil rate assessed with cardiac magnetic resonance and invasively measured $\tau$. More recently, Wang et al. (12) showed that untwisting rate was related to a time constant of isovolumic relaxation, both parameters being derived from echocardiographic data (13) rather than invasive measurement. Clinical studies have shown a consistent reduction in the magnitude and delay in the timing of untwisting in the context of diastolic dysfunction due to aortic stenosis (14), hypertrophic cardiomyopathy (15), and severe LV hypertrophy (16), supporting an important role for untwisting in abnormal diastolic function.

Thus, the relationship between invasively measured indexes of diastolic function and torsion parameters in human subjects is not known. We set out to establish the relationship between parameters of untwisting and invasive hemodynamic measures of early and late diastolic filling in human subjects with a range of diastolic function.

**METHODS**

**Patient selection.** Patients referred for routine coronary angiography to investigate chest pain were invited to participate. Patients with acute coronary syndrome, abnormal systolic function, regional wall motion abnormality, valvular heart disease of worse than moderate severity, atrial fibrillation, permanent pacemaker, history of coronary artery bypass graft surgery, renal impairment (estimated glomerular filtration rate <60 ml/min/1.73 m$^2$), and abnormal QRS complex morphology on electrocardiogram were excluded. This study was undertaken with the approval of the Human Research Ethics Committee of St. Vincent’s Health, and written informed consent was obtained from all subjects.

**Routine echocardiographic analysis.** The following echocardiographic data were acquired at end expiratory apnea: apical 4- and 2-chamber views of the LV; a parasternal long-axis view; and short-axis images at level of mitral valve, the mid-ventricle, and apex. Pulsed wave Doppler of the LV outflow tract and mitral inflow were recorded and stored in raw data format for offline analysis. Three cycles were analyzed, and the results were averaged.

To calculate ejection fraction, LV end-diastolic and end systolic volumes were measured with a Simpson’s biplane method. Mitral inflow and tissue Doppler velocities and the isovolumic relaxation time (IVRT) were recorded as previously described (17). Diastolic function was classified as abnormal on the basis of the invasive criteria (18): $\tau >48$ ms or LV end-diastolic pressure >16 mm Hg or mean LV diastolic pressure >12 mm Hg. Those with abnormal diastolic function were then classified as having impaired relaxation or pseudonormal or restrictive patterns of echocardiographic diastolic filling (19). The LV mass index was calculated with the area-length method and LV hypertrophy was defined according to standard criteria (20): LV mass index >115 g/m$^2$ for men and >95 g/m$^2$ for women.

**Speckle tracking imaging and torsion analysis.** The speckle tracking imaging (STI) algorithm and torsion analysis technique have been described in detail previously (21,22). Briefly, offline analysis of raw ultrasound data was performed with EchoPac PC software (version 4.1, GE Medical Systems, Princeton, New Jersey). Speckle tracking analysis with 2-dimensional images was performed as previously described (23). The LV mass index was calculated with the area-length method and LV hypertrophy was defined according to standard criteria (20). LV mass index >115 g/m$^2$ for men and >95 g/m$^2$ for women.

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Studies were undertaken in the catheterization laboratory with the subjects in the supine position. Echocardiography was performed with a VIVID 7 echocardiograph (GE Medical Systems). A single-use 5-F Millar micromanometer catheter (SPC-454D, Millar Instruments, Inc., Houston, Texas) was placed within the LV, and ventricular pressures were recorded with Powerlab/4sp recording unit (ADI Instruments, Mountain View, California) connected to an iMac desktop computer (Apple, Cupertino, California). The LV pressure data were acquired with Chart 3.6.3 for MacOS (ADI Instruments) during each of the 4 conditions. Data from 5 cycles at each condition were analyzed and averaged. The dp/dt minimum, \( \tau \) (25,26), and minimum LV diastolic pressure (LV minimum pressure) (27) were recorded as invasive measures of diastolic function.

Simultaneous echocardiograph and pressure recordings were obtained under 4 conditions: Pre-GTN = in the fasting state; GTN = at nadir of LV pressure after sublingual glyceryl trinitrate (GTN) administration (if the subject’s resting LV pressure was \(<110\) mm Hg [n =5], 300 \( \mu \)g of sublingual GTN was administered; for the remainder of patients, 600 \( \mu \)g was administered); Pre-fluid = stable hemodynamic state at least 15 min after GTN administration; and Fluid = after rapid infusion of 750 ml normal saline (warmed to 37°C).

**Pressure–volume relations.** With simultaneous micromanometer pressure and echocardiographic volume data, a pressure–volume relation was plotted from the coordinates under each of the hemodynamic conditions at minimum diastolic pressure and end-diastolic pressure (Fig. 2). From the micromanometer pressure versus time data, end-diastolic pressure was defined as the pressure at 10% of dp/dt maximum (28).

The LV stiffness constant, \( \beta \), was estimated from the slope of the linear regression equation relating the end-diastolic pressure to volume coordinates.

**Definition of torsion parameters.** Peak torsion (Tpeak) was defined from the torsion versus time curve and positive torsion rate as the slope of the curve from the start of systole to peak torsion (Fig. 1A). Torsion at the time of mitral valve opening (Tmvo) (Fig. 1) was used to calculate the indexes recoil (Fig. 1A) and recoil rate (recoil rate = recoil/(Tpeak - Tmvo)) (11). The real time of peak torsion and mitral valve opening was used for the calculation of recoil rate rather than normalized time. Peak positive torsion velocity and peak untwisting velocity were defined from the torsion velocity versus time curve (Fig. 1B). The time to peak untwisting velocity was measured from mitral valve opening.

**Simultaneous micromanometer LV pressure and echocardiography.** Studies were undertaken in the catheterization laboratory with the subjects in the supine position. Echocardiography was performed with a VIVID 7 echocardiograph (GE Medical Systems). A single-use 5-F Millar micromanometer catheter (SPC-454D, Millar Instruments, Inc., Houston, Texas) was placed within the LV, and ventricular pressures were recorded with Powerlab/4sp recording unit (ADI Instruments, Mountain View, California) connected to an iMac desktop computer (Apple, Cupertino, California). The LV pressure data were acquired with Chart 3.6.3 for MacOS (ADI Instruments) during each of the 4 conditions. Data from 5 cycles at each condition were analyzed and averaged. The dp/dt minimum, \( \tau \) (25,26), and minimum LV diastolic pressure (LV minimum pressure) (27) were recorded as invasive measures of diastolic function.

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**Figure 1. Torsion and Torsion Velocity Versus Time Plot**

(A) Torsion versus time plot. Left ventricular torsion (black line) was calculated by subtracting basal rotation (red line) from apical rotation (orange line). Positive torsion rate (dashed line) was the slope of the torsion versus time curve from the beginning of systole to peak torsion (Tpeak). Recoil was the percentage decrement from peak torsion to torsion at mitral valve opening (Tmvo), and recoil rate was calculated as recoil divided by the time from Tpeak to Tmvo. (B) Torsion velocity versus time plot. Left ventricular torsion velocity (yellow line) was calculated by subtracting basal rotation rate from apical rotation rate. Peak positive torsion velocity and peak untwisting velocity are indicated by the arrows. AVC = aortic valve closure.
under each of the conditions (Fig. 2). The functional LV chamber stiffness, $b$, under each condition was the linear slope of the pressure-volume curve from minimum diastolic pressure to end-diastolic pressure (Fig. 2) (29,30).

**Statistics.** Normality of data was assessed with the Kolmogorov-Smirnov statistic. Where data were not normally distributed, log transformation was applied, and tests were performed on the log transformed data. Repeated-measures linear regression was performed to quantify the relationship between torsion and invasive indexes of diastolic function as previously described (11). The commercially available statistics software SPSS (SPSS Inc., Chicago, Illinois) was used. Data are presented as mean ± SD unless otherwise specified, and $p < 0.05$ was considered significant.

**RESULTS**

**Patient characteristics.** The demographic data of the 18 patients included in the study are summarized in Table 1. According to invasive criteria, 9 patients had normal diastolic function and 9 patients had abnormal diastolic function. Of the 9 patients with abnormal diastolic function by invasive criteria, 3 had an impaired relaxation pattern, 6 had a pseudonormal pattern, and none had a restrictive pattern of diastolic filling by echocardiographic criteria. Mean LV mass index was 89.2 ± 3.6 g/m$^2$ (range 58.3 to 120.8 g/m$^2$), and 3 patients had LV hypertrophy. Of the eleven hypertensive patients, 8 required 1 antihypertensive and 3 required 2 antihypertensive medications. Nine patients had angiographically smooth coronary arteries, 3 had minor diffuse disease, 4 had single-vessel stenosis of >70%, and 2 had multivessel stenoses of >70%. A pre-fluid dataset was not collected in 3 subjects, and poor image quality meant that torsion analysis could not be performed on 2 subjects in the GTN dataset.

**Effect of LV mass and preload on measures of diastolic function.** As LV mass increased, $\tau$ was prolonged ($r = 0.34, p < 0.002$), and there were reductions in peak untwisting velocity ($r = 0.57, p < 0.007$) but not recoil ($r = -0.26, p = NS$) or recoil rate ($r = 0.32, p = NS$). As preload increased (increased end-diastolic volume and pressure), $\tau$ was prolonged, but no consistent effect on untwisting parameters was observed (Table 2).

**Correlation between measures of diastolic function.** As $\tau$ was prolonged, the time to peak untwisting velocity was delayed ($r = 0.34, p < 0.01$). There were nonsignificant associations between reduced recoil and longer values of $\tau$ and lower dp/dt minimum (Fig. 3). No relationship was observed between the echocardiographic IVRT and $\tau$ or between IVRT and untwisting parameters.

The LV minimum diastolic pressure increased as $\tau$ was longer (Fig. 4A) ($r = 0.67, p < 0.001$) and recoil decreased (Fig. 4B) ($r = -0.30, p < 0.034$). No relationship was observed between LV minimum diastolic pressure and peak untwisting velocity or recoil rate.

Relationships were observed between the magnitude of peak untwisting velocity and that of the systolic torsion parameters peak torsion ($r = -0.75, p < 0.001$), positive torsion rate ($r = -0.60, p < 0.001$), and peak positive torsion velocity ($r = -0.42, p < 0.002$).

**Relation between LV stiffness and untwisting indexes.** No relation was observed between measures of stiffness, the LV stiffness constant, $\beta$, and the functional LV chamber stiffness, $b$, and the untwisting indexes recoil, recoil rate, and peak untwisting velocity (Table 3).
DISCUSSION

We have shown in human subjects with invasive measures of LV pressure that indexes of untwisting are related to parameters of early diastolic filling but not events happening later in diastole. Reductions in the rate and magnitude of untwisting were associated with worsening of diastolic relaxation and reduced early diastolic suction. These findings lend further weight to the hypothesis that untwisting is important in generating early diastolic LV suction, an important component of early diastolic filling. There was a close relationship observed between systolic and diastolic torsion parameters, suggesting that torsion might be an important mechanistic link between the phases of the cardiac cycle.

Our data are in keeping with earlier findings in a canine model where, with cardiac magnetic resonance, Dong et al. (11) described a close relation between recoil rate and invasively measured τ. Wang et al. (12) found that the untwisting rate correlated with a time constant of isovolumic relaxation in patients with systolic LV dysfunction, but this correlation was not maintained in patients with preserved LV ejection fraction. This inconsistency might be due to a failure to interpolate temporally normalized STI data or an artefact of the method used to derive τ from echocardiographic and right heart catheterization data (13) rather than direct invasive measurement, as we have used in this patient group with normal ejection fraction.

The correlations between invasive and untwisting parameters in our study were weaker than those reported with published animal data (11) but are still consistent with an important role for untwisting in early diastolic function. In our study, the method of Weiss (25) was used, which assumes that the LV pressure decays to a zero asymptote, whereas in the study by Dong et al. (11), a zero pressure asymptote was not assumed. There is some controversy about the use of a zero pressure asymptote (31); however, it has been the most commonly used method in human studies and has established reference values (26). In addition, Dong et al. (11) calculated recoil with torsion at 64 ms after mitral valve opening as a proportion of maximal torsion. This differs slightly from the definition of recoil used in contemporary studies employing STI (24,32). The arbitrary time point of 64 ms does not completely account for isovolumic relaxation, the load independent period of negative torsion. To reflect the changes in torsion during the isovolumic period, an argument could be made that the torsion at end systole should be used rather than the peak torsion. However, in some patients, maximal tor-

![Figure 3. Recoil Versus τ and Recoil Versus dp/dt Minimum](image)

Eighteen subjects underwent simultaneous Millar catheter micromanometry and echocardiography under 4 conditions: at rest (Pre-GTN) (brown squares); after 600-μg sublingual GTN (GTN) (red triangles); after a period of re-equilibration (Pre-fluid) (orange circles), and after 750-ml intravenous saline bolus (Fluid) (yellow diamonds). Torsion parameters were measured with speckle tracking imaging, and repeated measures linear regression was used to quantify relations between invasive and torsion indexes. We observed nonsignificant associations between reduced untwisting and longer values of the time constant of isovolumic relaxation, τ (A), and a lower rate of the rise of left ventricular pressure (dp/dt) minimum (B) in keeping with previous work in animal models. This supports an important role for untwisting in early diastolic function.

| Table 2. Correlation Coefficients Between Measures of Preload and Diastolic Parameters |
|-----------------|-----------------|-----------------|-----------------|
|                  | τ               | Recoil          | Recoil Rate     | Peak Untwisting Velocity |
| End-diastolic    | r = 0.36        | r = 0.11        | r = 0.09        | r = 0.05 |
| volume p         | p < 0.01        | p = NS          | p = NS          | p = NS  |
| End-diastolic    | r = 0.41        | r = 0.17        | r = 0.08        | r = 0.15 |
| pressure p       | p < 0.003       | p = NS          | p = NS          | p = NS  |
sion occurs after end systole, and this would lead to an inconsistency in the measurement (16). Therefore, we calculated recoil and recoil rate as the decrement in torsion from peak to mitral valve opening (Fig. 1).

We have shown that suction was reduced in subjects with decreased recoil. Although LV minimum diastolic pressure is an accepted index of suction in clinical studies (27), the gold standard assessment involves the measurement of intraventricular pressure gradients with a triple sensor micromanometer catheter placed across the mitral valve to record LA, basal LV, and apical LV pressures. This technique is limited to animal models (1) and the clinical open heart surgery setting (2). More recently, the mitral inflow propagation velocity derived from color M-mode Doppler has been validated as a noninvasive index of intraventricular pressure gradient (4,33). With this technique and tissue Doppler-derived measurement of torsion, Notomi et al. (10) suggested that untwisting velocity is an important determinant of early diastolic LV suction. Our study provides invasive data to support this hypothesis.

The observed effect of increased LV mass on untwisting velocity is consistent with the findings of clinical studies involving patients with LV hypertrophy (14–16). No relation was observed between untwisting parameters and the LV stiffness constant or the functional LV chamber stiffness. Untwisting begins before aortic valve closure (7,10), and a lack of correlation with late diastolic parameters of stiffness is not unexpected. Although invasive pressure-volume loop analysis with conductance catheters is the gold standard to measure stiffness, pressure-volume loops derived from simultaneous micromanometer pressure and echocardiographic volume are well-validated (26). The end-diastolic pressure-volume relation is generally modeled from conductance catheter data with nonlinear equations (34); however, the ranges of diastolic pressure and volume coordinates produced by the hemodynamic manipulations in the current study could be accurately modeled with linear regression as previously described (30,35).

The observation of close relations between systolic and diastolic torsion indexes lends weight to the hypothesis that torsional motion results from the buildup and release of elastic energy (10,36), possibly in the molecule of the large elastic cardiomyocyte protein titin, which acts as a bidirectional spring (37). Titin itself has been shown to be a major determinant of early diastolic function (38,39), and changes in titin isoforms have been documented in the context of ventricular dysfunction (40). In an animal heart failure model, rapid ventricular pacing induced a change to stiffer titin isoforms, resulting in reduced systolic twist and diastolic untwisting associated with reduced suction gradients (41). Further work is required to elucidate

| Table 3. Correlation Coefficients Between Invasive Measures of Stiffness and Diastolic Torsion Parameters |
|-------------------------------------------------|---------------------|---------------------|
|                                                | Recoil   | Recoil Rate | Untwisting Velocity |
| LV stiffness constant                           | 0.11     | -0.023      | -0.015              |
| Functional LV stiffness                         | 0.11     | -0.10       | -0.049              |
| LV = left ventricular.                           |          |             |                     |

Figure 4. - Versus LV Minimum Diastolic Pressure and Recoil Versus LV Minimum Diastolic Pressure

Left ventricular (LV) suction is an important component of early diastolic function that allows LV filling without excessive increases in left atrial pressure. Lower LV minimum diastolic pressure increases suction. We found that impaired suction was associated with slower isovolumic relaxation (A). As untwisting decreased, suction was also impaired (B), further evidence for an important role for untwisting in early diastolic function.
the role of titin in untwisting and diastolic suction in humans.

**Study limitations.** Eighteen patients with normal systolic function were assessed in this study, of whom one-half had diastolic dysfunction on invasive criteria. The failure to reproduce the strong correlations between invasive and torsion indexes of diastolic function might relate to the small sample size in our cohort and the relatively narrow dynamic range through which the invasive parameters were manipulated in our experiment relative to what can be achieved in the animal model with varying pacing modes, dobutamine, and esmolol. Although GTN and fluid administration have some effect on afterload, their predominant effect is on preload. Maneuvers to specifically manipulate afterload, such as vasopressor administration, would be of great interest but were felt to be unwarranted in this experiment. To elucidate the clinical utility of measuring torsion parameters to characterize diastolic function, a larger group of systolic and diastolic heart failure patients with more severe diastolic dysfunction would need to be studied.

The advent of echocardiographic STI has enabled reproducible noninvasive quantification of twisting motion (22,42,43). Cubic spline interpolation and normalization are mandatory to allow accurate subtraction of apical and basal data at the same time points (44), which makes the technique for torsion analysis in the present study labor intensive. Automated analysis of torsion has recently been described (45) that will facilitate the translation of these parameters to clinical practice.

**CONCLUSIONS**

Untwisting is an important component of early diastolic function. Reduced untwisting in patients with abnormal diastolic function might attenuate suction gradients necessary for normal LV diastolic filling. Measurement of untwisting might provide a useful means to identify and quantify abnormal diastolic function in patients with normal ejection fraction.

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