Maturational and Adaptive Modulation of Left Ventricular Torsional Biomechanics

Doppler Tissue Imaging Observation From Infancy to Adulthood

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Background—Left ventricular (LV) torsional deformation, based in part on the helical myocardial fiber architecture, is an important component of LV systolic and diastolic performance. However, there is no comprehensive study describing its normal development during childhood and adult life.

Methods and Results—Forty-five normal subjects (25 children and 20 adults; aged 9 days to 49 years; divided into 5 groups: infants, children, adolescents, and young and middle-age adults) underwent assessment of LV torsion and untwisting rate by Doppler tissue imaging. LV torsion increased with age, primarily owing to augmentation in basal clockwise rotation during childhood and apical counterclockwise rotation during adulthood. Although LV torsion and untwisting overall showed age-related increases, when normalized by LV length, they showed higher values in infancy and middle age. The proportion of untwisting during isovolumic relaxation was lowest in infancy, increased during childhood, and leveled off thereafter, whereas peak untwisting performance (peak untwisting velocity normalized by peak LV torsion) showed a decrease during adulthood.

Conclusions—We have shown the maturational process of LV torsion in normal subjects. Net LV torsion increases gradually from infancy to adulthood, but the determinants of this were different in the 2 age groups. The smaller LV isovolumic untwisting recoil during infancy and its decline in adulthood may suggest mechanisms for alterations in diastolic function. (Circulation. 2006;113:2534-2541.)

Key Words: aging ■ cardiac development ■ echocardiography ■ left ventricular function ■ pediatrics

For more than 100 years, myogenesis and cardiac development have been topics of investigation.1 In addition to alterations in cardiac loading conditions, contractility and myocardial function change after birth. The neonatal myocardium develops less force than that of the adult, and cardiocytes increase both myofibrillar and sarcoplasmic reticulum contents after birth.2,3 Large changes in hemodynamic load occur during cardiac development and are associated with increased contractility owing to alterations in the relative expression of sarcomeric protein isoforms.4 Similar age-related isoform changes are also seen in titin, the giant sarcomeric protein “spring” that both resists passive stretch and helps the myocyte to recoil after contraction.5 In addition to these cardiac changes, arterial distensibility decreases from childhood to adulthood,6 a stiffening of the arterial tree that increases afterload even in normotensive individuals.7

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Although heart size increases with somatic maturation,8 the helically oriented myocardial fiber architecture, which creates left ventricular (LV) torsion, has been observed in human hearts from neonates to adults, independent of sex and age.9 LV torsion has recently attracted the attention of LV mechanics researchers and is believed to be a sensitive indicator of systolic and diastolic performance and myocardial molecular properties.10 Whether torsional biomechanics changes during the complex development from infancy to adulthood is less established, but it is important for both its mechanistic import and potential diagnostic utility. Doppler tissue imaging (DTI) can assess myocardial velocity11 and LV torsion12 noninvasively, a significant advantage for the examination of children. We therefore sought to investigate the developmental

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alterations in LV torsional behavior from infancy to adulthood in normal subjects.

Methods

Study Participants
The study population consisted of 25 children (aged 9 days to 16 years; mean age, 7.5±6.8 years; 9 girls) and 20 healthy adult volunteers (aged 23 to 49 years; mean age, 34±7 years; 8 women). The reasons for echocardiographic referral of the children included the presence of a cardiac murmur, chest pain, and syncope. All subjects were (1) normotensive and clinically well from a cardiovascular standpoint; (2) in normal sinus rhythm with a normal surface ECG; (3) without structural and functional (including valvular heart disease) abnormalities on the transthoracic echocardiogram; (4) free from past or present systemic disease; and (5) between the 25th and 75th percentiles for age- and sex-based height and weight. The study protocol was approved by the institutional review board of the Cleveland Clinic Foundation. Written, informed consent was obtained before the study from all subjects.

Echocardiography
After completion of a standard, comprehensive, 2D and spectral/color flow Doppler examination, we collected color DTI data sets at the apical, middle, and basal short-axis planes and the apical long-axis plane with a Vivid 7 apparatus (GE Medical Systems, Milwaukee, Wis) with an M7S or M10S probe for children and an M3S probe for adults. The velocity range of DTI was 12 to 20 cm/s to avoid aliasing. Acquisition of specific short-axis levels was guided by internal landmarks: basal, by the presence of the mitral valve; midventricular, by the visible papillary muscles; and apical, by no papillary muscle visible.12 All pediatric examinations in the present study were performed without sedation. DTI acquisition averaged 152±18 frames per second (ie, 6.6 ms interval). Basic measurements included LV wall thickness by 2D-guided M-mode, LV length and diameter by 2D, and volume estimates by the Simpson method.

LV Rotation, Torsion, and TorsionN
Terminology
In this article, we defined angular displacement of the LV in each short-axis slice as “LV rotation” (LVrot). A net difference in LVrot between the apical and basal LV slices was defined as “LV torsion” (LVtor). To account for changes in heart size and to represent the presumed potential energy stored in the myocardium by systolic torsional deformation, LVtor was also normalized by LV length (cm) and defined as LVtorN (°/cm).13 Counterclockwise rotation when viewed from the apex was expressed as a positive value.

Calculation
To measure LVrot, we calculated12 the LV rotational velocity [Vrot(t), rad/s], which was derived from velocity data sets at 4 points on the short-axis LV in each slice, as shown:

\[ V_{rot}(t) = \frac{[V_{lat}(t) - V_{sep}(t)]/2}{r(t)} \]

where Vlat and Vsep are velocities in the septal and lateral regions, respectively, used to measure the tangential velocity (cm/s); and Vant and Vpos are velocities in the anterior and posterior regions, respectively, used to measure the radial velocity (cm/s), the integral of which provides the LV radius over time [r(t)], r0 is the end-diastolic radius. LV torsional velocity (Vtor, rad/s) was calculated as

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

LVrot was obtained by integrating Vrot(t) in each slice:

\[ \int_{0}^{t} V_{rot}(t) \, dt \]

LVtor and LVtorN are as defined earlier:

\[ \text{LVtor} = \text{Apical LV rotation} - \text{Baseline LV rotation}, \]  
\[ \text{LVtor}_N = \frac{\text{LVtor}}{\text{LVlength}} \]
TABLE 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th>Children</th>
<th>Adolescents</th>
<th>Young Adults</th>
<th>Middle-Age Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (female)</td>
<td>9 (4)</td>
<td>8 (3)</td>
<td>8 (2)</td>
<td>10 (4)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>9±11 mo</td>
<td>7±3 y</td>
<td>16±2 y</td>
<td>28±3 y</td>
<td>41±4 y</td>
</tr>
<tr>
<td>Range</td>
<td>9±19 mo</td>
<td>3–9 y</td>
<td>13–18 y</td>
<td>23–33 y</td>
<td>35–49 y</td>
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<tr>
<td>Median</td>
<td>3.5 m</td>
<td>6.6 y</td>
<td>16.1 y</td>
<td>28.0 y</td>
<td>42.0 y</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>66±14</td>
<td>121±16</td>
<td>170±5</td>
<td>175±9</td>
<td>170±8</td>
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<tr>
<td>Body weight, kg</td>
<td>6.6±3.5</td>
<td>27.8±13.6</td>
<td>70.3±16.1</td>
<td>75.6±12.2</td>
<td>70.7±6.9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>146±27</td>
<td>92±12</td>
<td>63±13</td>
<td>61±12</td>
<td>67±10</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>95±16</td>
<td>99±6</td>
<td>111±13</td>
<td>105±8</td>
<td>113±14</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>57±13</td>
<td>63±4</td>
<td>69±8</td>
<td>62±10</td>
<td>69±9</td>
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2D echocardiographic data

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<th>Middle-Age Adults</th>
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<tbody>
<tr>
<td>Posterior wall thickness (W), cm</td>
<td>0.46±0.10</td>
<td>0.60±0.10</td>
<td>0.77±0.22</td>
<td>0.88±0.12</td>
<td>0.97±0.17</td>
</tr>
<tr>
<td>End-diastolic LV length (L), cm</td>
<td>3.8±0.6</td>
<td>5.6±0.8</td>
<td>7.6±0.5</td>
<td>8.0±0.3</td>
<td>8.0±0.3</td>
</tr>
<tr>
<td>End-diastolic LV diameter (D), cm</td>
<td>2.2±0.5</td>
<td>3.5±0.4</td>
<td>4.7±0.4</td>
<td>5.2±0.5</td>
<td>4.7±0.4</td>
</tr>
<tr>
<td>LV wall-thickness index: W/D</td>
<td>0.21±0.03</td>
<td>0.17±0.03</td>
<td>0.17±0.04</td>
<td>0.17±0.03</td>
<td>0.21±0.05</td>
</tr>
<tr>
<td>LV geometric index: D/L</td>
<td>0.29±0.05</td>
<td>0.32±0.02</td>
<td>0.31±0.03</td>
<td>0.32±0.03</td>
<td>0.29±0.02</td>
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<tr>
<td>LV end-diastolic volume, mL</td>
<td>10.6±6.1</td>
<td>41±11†</td>
<td>92±33†</td>
<td>112±22†</td>
<td>84±20†</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>4±3</td>
<td>17±5 §</td>
<td>36±17 †</td>
<td>42±8 †</td>
<td>31±11 †</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>62±4</td>
<td>58±11</td>
<td>56±19</td>
<td>62±4</td>
<td>64±8</td>
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Pulsed-wave Doppler data

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<th>Middle-Age Adults</th>
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</thead>
<tbody>
<tr>
<td>Early diastolic peak velocity (E), m/s</td>
<td>0.82±0.41</td>
<td>1.04±0.15</td>
<td>1.06±0.20</td>
<td>0.95±0.31</td>
<td>0.85±0.23</td>
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<tr>
<td>Late diastolic peak velocity (A), m/s</td>
<td>0.95±0.26</td>
<td>0.65±0.09</td>
<td>0.59±0.11</td>
<td>0.50±0.08</td>
<td>0.58±0.11</td>
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<tr>
<td>E/A ratio</td>
<td>0.94±0.48</td>
<td>1.63±0.27</td>
<td>1.89±0.59</td>
<td>1.94±0.58</td>
<td>1.47±0.29</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>11.4±3.9</td>
<td>9.8±2.2</td>
<td>9.2±0.8</td>
<td>8.7±2.2</td>
<td>9.6±3.0</td>
</tr>
<tr>
<td>Early diastolic propagation velocity, cm/s</td>
<td>48±11</td>
<td>61±10</td>
<td>67±24</td>
<td>57±10</td>
<td>66±12</td>
</tr>
</tbody>
</table>

Doppler tissue imaging data

<table>
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<th>Children</th>
<th>Adolescents</th>
<th>Young Adults</th>
<th>Middle-Age Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-axis function</td>
<td>Peak systolic velocity, cm/s</td>
<td>4.1±1.2</td>
<td>5.8±1.1</td>
<td>6.8±1.9</td>
<td>6.9±0.8</td>
</tr>
<tr>
<td>Short-axis function</td>
<td>Peak early-diastolic velocity (E'), cm/s</td>
<td>-8.2±2.8</td>
<td>-10.9±1.7</td>
<td>-11.5±4.9</td>
<td>-10.9±2.1</td>
</tr>
<tr>
<td>Peak systolic velocity, cm/s</td>
<td>3.8±0.9</td>
<td>5.3±0.9</td>
<td>4.9±0.8</td>
<td>5.9±1.0</td>
<td>5.3±0.8</td>
</tr>
<tr>
<td>Peak early-diastolic velocity, cm/s</td>
<td>-7.0±2.5</td>
<td>-9.5±2.3</td>
<td>-9.8±3.8</td>
<td>-10.2±3.0</td>
<td>-7.2±1.8</td>
</tr>
</tbody>
</table>

Age differences were assessed with 1-way ANOVA with post hoc comparison. LV ejection fraction was assessed using modified Simpson’s method.

*P<0.01, †P<0.05, §P<0.01, ¶P<0.005, ‡P<0.001, ¶¶P<0.0005, #P<0.0001, compared with preceding younger group.

LV Long- and Short-Axis Function

LV long-axis myocardial function was assessed by recording the velocities at the most basal septal and lateral regions in the apical 4-chamber DTI image and averaging the 2 walls at each temporal sampling point, whereas short-axis function was taken as the difference between anterior and posterior velocities in the short-axis DTI image at the midventricular level.

These analyses were performed on a personal computer with customized software within the EchoPAC platform (GE Medical Systems, Milwaukee, Wis). Plots of myocardial velocities and of the ECG versus time derived from each sample region were transferred to a spreadsheet program (Excel 2000, Microsoft Corp, Seattle, Wash) for the aforementioned calculations. All calculations of DTI data were averaged for at least 3 consecutive beats, carefully matching beats of similar RR intervals from the various views, particularly in children, in whom heart rate variability is prominent. For analyzing DTI data, we used an elliptical sample volume for septal and lateral regions (2×4 to 4×8 mm, to fit the wall thickness) and a circular one (4×4 to 8×8 mm) for anterior and posterior regions. These sample volumes were semiautomatically tracked on the workstations by anchoring them to the LV inner and midwalls at end diastole, at end systole, and after early filling to keep the correct position.1,2 For temporal analysis, the time sequence was normalized to the duration of systole (ie, at the onset of the QRS interval, t=0%, and at end systole, t=100%). End systole was determined from the LV outflow Doppler flow profile. For clarity, the hemodynamic events through the cardiac cycle were marked with the timing of the mitral and aortic valve closure and opening, peak ejection and early filling velocity, and end of the early filling velocity in the graphs in Figure 1.

Statistics

All values are expressed as mean±SD. Age differences were assessed with a 1-way ANOVA with post hoc comparison (Tables 1 and 2). The association between age and each biomechanical parameter was assessed with a polynomial regression model, in which the parameter was the outcome and age was the predictor (Figures 2 through 4). To build this model, we began with a fourth-degree polynomial for age and removed age terms until the Type I (sequential) sums of squares for the highest-order remaining parameter was the outcome and age was the predictor.
variable was computed. A probability value <0.05 was considered statistically significant for all comparisons and correlations.

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

For a clearer display of differences with age, we divided the study population into 5 representative subgroups: infancy (<3 years), childhood (3 to 10 years), adolescents (10 to 20 years), young adults (20 to 35 years), and middle-age adults (>35 years). The age ranges and demographic data of the 5 groups are shown in Table 1. Significant somatic growth and a corresponding fall in heart rate with relatively constant blood pressure were observed with advancing age. LV wall thickness significantly increased from infancy to childhood, but cavity size increased more, so the ratio of posterior wall thickness to LV diastolic dimension decreased from infancy to adolescence. Cardiac dimensions and volumes increased with age, whereas the LV geometric index (ratio of the LV short- and long-axis diastolic dimensions) and LV ejection fraction were not different in the 5 groups. Decreasing A-wave velocity led to an increase in the E/A ratio during childhood, whereas the E/E' ratio and propagation velocity were relatively constant. This trend reversed in adulthood, with the E/A ratio falling from young to middle-age groups. Systolic and early diastolic peak velocities in long- and short-axis views increased from infancy to adulthood. As shown in Figure 3, the shifting LV rotation pattern was different between base and apical rotation. With advancing age, both peak LV torsion and untwisting velocity increased, with significant changes in the rotation pattern seen from infancy to adulthood. As shown in dark blue, apical rotation is consistently counter-clockwise, increasing slightly from ~5° in infancy to ~7° by adulthood. Basal rotation shows more significant changes, being counter-clockwise throughout most of systole in infancy but becoming more and more clockwise, so that by adolescence, 3° to 4° of clockwise rotation is seen. Thus, the heart shifts from essentially solid-body rotation with <5° torsion in infancy to a distinct wringing motion with >13° of torsion by middle age. Figure 2 summarizes these changes. Figure 2A shows the amount of rotation at 75% of systolic duration, demonstrating the age-related development of clockwise basal rotation in childhood (r=0.70, P<0.0001) with a near-constant apical rotation. On the other hand, from adolescence to middle age (Figure 2B), end-systolic basal rotation was constant, whereas apical rotation gradually increased (r=0.68, P<0.0001), leading to the overall increase in net LVtors (Figure 3A).

Peak LVtors and Untwisting Recoil

Figure 3 summarizes the age-related peak LVtors (A), untwisting velocity (B), LVtors (C), and untwisting velocity normalized to LV length (D). Peak LVtors and untwisting velocity increased with age during both childhood and adulthood. Linear regression gave a more significant fit than any higher-order polynomial. On the other hand, LVtors and the normalized untwisting velocity declined during childhood and then increased again in adulthood. As shown in Figure 3C

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**TABLE 2. LV Torsional Function Data**

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th>Children</th>
<th>Adolescents</th>
<th>Young Adults</th>
<th>Middle-Age Adults</th>
<th>P</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak LV torsion, degree</td>
<td>5.8±1.3</td>
<td>6.8±2.3</td>
<td>8.8±2.6</td>
<td>8.7±2.7</td>
<td>13.8±3.3</td>
<td>&lt;0.001</td>
<td>0.53</td>
</tr>
<tr>
<td>Peak LV torsionN, degrees/cm</td>
<td>1.6±0.4</td>
<td>1.2±0.4</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
<td>1.7±0.4</td>
<td>&lt;0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>Peak untwisting velocity, rad/s</td>
<td>-1.1±0.7</td>
<td>-1.4±0.4</td>
<td>-1.6±0.5</td>
<td>-1.8±0.6</td>
<td>-2.2±0.7</td>
<td>&lt;0.001</td>
<td>0.43</td>
</tr>
<tr>
<td>Peak untwisting velocity normalized by LV length, (rad/s)/cm</td>
<td>-0.28±0.09</td>
<td>-0.24±0.09</td>
<td>-0.21±0.07</td>
<td>-0.23±0.07</td>
<td>-0.31±0.08</td>
<td>0.045</td>
<td>0.14</td>
</tr>
<tr>
<td>Timing of peak untwisting velocity, % systolic duration</td>
<td>139±11</td>
<td>125±12</td>
<td>120±10</td>
<td>117±11</td>
<td>118±8</td>
<td>&lt;0.001</td>
<td>0.38</td>
</tr>
<tr>
<td>% Isovolumic untwisting recoil, %</td>
<td>2±14</td>
<td>21±11</td>
<td>27±17</td>
<td>31±13</td>
<td>41±29</td>
<td>&lt;0.001</td>
<td>0.36</td>
</tr>
<tr>
<td>Peak untwisting velocity normalized by LV torsionN, (rad/s)/(degree/cm)=1/s</td>
<td>-10.9±2.9</td>
<td>-11.5±2.9</td>
<td>-10.9±2.9</td>
<td>-12.6±3.4</td>
<td>-9.7±3.4</td>
<td>0.98</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P was assessed by overall model F-test of the regression model. R² indicates R-squared value.

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**Figure 2. Different patterns of apical and basal LV rotation change with advancing age in childhood (A) and in adulthood (B).** In childhood, basal rotation is progressively clockwise, with a relatively constant apical rotation, whereas in adulthood, apical rotation increases, with a relatively constant basal rotation.

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**Figure 3.** Summary of age-related peak LV torsion (A), untwisting velocity (B), LV torsion (C), and untwisting velocity normalized to LV length (D).
and 3D, these were best fit by a quadratic equation, with a minimum value for these parameters occurring at ages 19.0 and 19.5 years, respectively. Table 2 shows the same trend in each age group by intergroup comparison.

Another significant change occurs in the timing of untwisting behavior and short- and long-axis lengthening (Figure 1, lower row). In infancy, untwisting (purple line) occurs simultaneously with long- (red) and short- (orange) axis lengthening. By childhood, an earlier onset of untwisting in isovolumic relaxation is evident, a trend that continues to middle age, when untwisting is largely completed before mitral valve opening (Table 2 and Figure 4A). This isovolumic untwisting may serve to rapidly reduce systolic pressure and establish the intraventricular pressure gradient that helps the ventricle to fill at low mean atrial pressure. In contrast, long- and short-axis relengthening consistently occurs after mitral valve opening, plateauing in childhood, and then becoming less vigorous from young adulthood to middle age. Furthermore, if we define “peak untwisting performance” as the ratio of peak untwisting velocity divided by peak LV torsion (1/s), this index shows relatively steady values throughout at ~11/s, although there is a suggestion that it may be starting to decline in the older age groups (Figure 4B; note that the 7 oldest subjects had values on or below the regression line).

Discussion

The present study used DTI data sets with high temporal resolution to describe the developmental and adaptive alterations of LV torsional deformation from infancy to middle age. Modulation of LV torsion appears to reflect both myocardial mechanical maturation in childhood and further adaptive changes in adulthood, influenced by contractility, loading conditions, and possibly myogenetic changes through life.

Maturing LV Twist During Childhood

Distinct patterns of apicobasal twisting were seen with maturation; counterclockwise apical rotation was almost constant during childhood, whereas the age-related increase in LV torsion during childhood resulted from a striking change in basal rotation, initially counterclockwise in infancy to neutral in early childhood and then becoming less vigorous from young adulthood to middle age. Furthermore, if we define “peak untwisting performance” as the ratio of peak untwisting velocity divided by peak LV torsion (1/s), this index shows relatively steady values throughout at ~11/s, although there is a suggestion that it may be starting to decline in the older age groups (Figure 4B; note that the 7 oldest subjects had values on or below the regression line).
quentiy increasing net LV torsion. Although the small basal rotation has not been emphasized in prior studies, it should not be neglected for its influence on effective twisting and untwisting in childhood, and it should be taken into account for comparison with pathological states. Nagel et al\textsuperscript{14} reported reduced basal rotation (and increased apical rotation) in severe aortic stenosis patients, and Donofrio et al\textsuperscript{15} reported reduced basal (and apical) rotation in pediatric heart transplant patients. It is well known that the right ventricles of newborn infants are hypertrophied compared with those of older children and adults owing to the systemic pressure and resistance of the right ventricle faces in utero. This hypertrophy recedes over a matter of months, with a concomitant change in fiber architecture. In the present study, infants showed relative LV hypertrophy, as previously reported.\textsuperscript{16} Whether the hypertrophy compensates for the low torsion or whether the 2 are manifestations of another phenomenon is unclear and should be a fruitful area for investigation. Interestingly, exaggerated counterclockwise midelevel LV rotation was observed in patients with secundum atrial septal defect (without right-sided pressure overload) but was not seen in combined right ventricular pressure and volume overload or in other disease states.\textsuperscript{17}

Enhanced LV $\text{tor}_N$ in Infancy and Middle-Age Adults

When torque is applied to a cylinder, the angle of twist it produces and the associated shear stress are proportional to the magnitude of the torque and shaft length.\textsuperscript{18} LV $\text{tor}_N$ was higher in infants than in older children, adolescents, and young adults. This result correlates with the finding that contractility is higher in children $\leq 2$ years of age (due to higher metabolic demand)\textsuperscript{2} compared with older children\textsuperscript{19} with uncoordinated basal rotation, as mentioned earlier. As reported by others,\textsuperscript{8,19} the present study confirmed that LV geometry (represented by the LV length-diameter ratio) and ejection fraction were constant from infancy to adulthood, with relative anatomic hypertrophy\textsuperscript{16} in infancy, leading to greater normalized torsion, if the lever-arm theory is correct.\textsuperscript{20} Interestingly, the mouse heart has an apex-to-base angular deformation that is but a fraction of the adult human heart; however, when torsion is calculated as deformation per unit length, torsion in the 2 species is equal.\textsuperscript{21}

We also observed significant age-related increases in LV $\text{tor}$ and LV $\text{tor}_N$ during adulthood, but this increase was due to a gradual increment in apical rotation rather than the basal changes seen in childhood with relatively constant LV length, so LV $\text{tor}_N$ closely tracked changes in torsion. Histological data indicate that in normal subjects, increasing age does not result in cellular hypertrophy,\textsuperscript{22} although stiffening of the arterial tree may increase afterload and thereby alter diastolic function.\textsuperscript{7} LV torsion is afterload dependent,\textsuperscript{23} and a chronic increase in afterload leads to increasing apical rotation and LV torsion,\textsuperscript{13} consistent with our data. Higher fiber stress is associated with enhanced torsion, and in general, fiber stress rises with age in adults, predicting that there should be an age-related rise in torsion. Oxenham et al\textsuperscript{24} reported that peak apical rotation and LV torsion were increased in older subjects (69 years) more so than in younger ones (22 years). Our results suggest that LV torsion increases even earlier, as shown in our middle-aged adults (averaging 42 years).

Decreased Isovolumic Untwisting Recoil in Infancy and Declined Peak Untwisting Performance During Adulthood

LV untwisting also changed significantly in both timing and magnitude with maturation. In adolescents and adults, untwisting occurred mainly during isovolumic relaxation, as reported previously, playing an important role in the LV restoring force and relaxation.\textsuperscript{25,26} In infants, however, untwisting occurs later and at a lower velocity than in older subjects, with little isovolumic untwisting indicating more clearly that uncoiling in the infant heart occurs too late to contribute to the intraventricular pressure gradient at mitral valve opening, a situation that we term “ineffective untwisting.” Because the ability to augment the intraventricular pressure gradient with exercise was recently shown to be a good predictor of maximal oxygen consumption,\textsuperscript{27} this ineffective untwisting may have important clinical implications. The altered untwisting may be related to immature LV torsion creation (Figures 1 and 2), immature active transport of calcium into the sarcoplasmic reticulum,\textsuperscript{28} and alterations in connective tissue\textsuperscript{29} and titin,\textsuperscript{5,10,30} which is responsible for elastic recoil within the sarcomere. Titin in particular is interesting, as it exists in 2 isoforms, N2B and N2BA, the latter of which has less restorative force. From fetal life to adulthood, the proportion of titin switches gradually from predominant N2B to N2BA.\textsuperscript{5} Thus, titin-based ventricular recoil should increase throughout postnatal development as expression shifts toward N2B titin, consistent with the increase in LV untwisting observed in the present study.

The amplitude of early diastolic LV filling (E wave) is dependent on active myocardial relaxation and ventricular recoil, so it is likely that faster relaxation and enhanced recoil may contribute to understanding of the developmental increase in peak velocities of the transmitral and annular E waves.\textsuperscript{31} Data on age-related changes in myocardial relaxation remain somewhat in conflict.\textsuperscript{32,33} Delayed and decreased apical untwisting has been reported in patients with LV hypertrophy from aortic stenosis.\textsuperscript{13} LV untwisting is a sensitive parameter for predicting myocardial relaxation\textsuperscript{25,26} and has previously been noted not to decline with advancing age.\textsuperscript{34} Our results show that untwisting velocity and isovolumic untwisting recoil are preserved at least until middle age, whereas peak untwisting performance may start to decline during middle age, although we would need additional older patients to demonstrate this with certainty. These findings suggest that maturational and adaptational modulation of ventricular relaxation is closely related to changes in LV torsional biomechanics, although which (if either) of these is the causal factor remains to be demonstrated.

Limitations

We should address several limitations with regard to the present study. The sample size of each group was relatively small (8 to 10 subjects), although the characteristics of LV torsional deformation were clearly demonstrated. LV torsional deformation in elderly people has previously been...
untwisting recoil of systolic torsion might allow preclinical identification of cardiac disease as a mechanistic manifestation of the diastolic property during childhood and adult life.

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References

Potential Clinical Application
Our observations about altered LV torsional behavior in infancy, including enhanced LV\(\text{torN}\), but reduced total torsion and ineffective untwisting, may have impact on the medical and surgical treatment of these infants. Having normal reference values for LV torsion could be helpful in assessing various disease states. LV systolic torsion is a sensitive index of cardiac performance, and assessment of LV torsional performance may provide beneficial mechanical information for patients of all ages with cardiomyopathy, hypertension, or diabetes or those receiving chemotherapy. Studies of the untwisting recoil of systolic torsion might allow preclinical identification of cardiac disease as a mechanistic manifestation of the diastolic property during childhood and adult life.

Figure 5. Age-related increases in LV (L) and diameter (D), with a constant ratio between them (D/L).
The concept of systole and diastole as isolated events is simplistic, as we now understand them to be only parts of a single, integrated pumping and filling cycle. One of the factors connecting systole to diastole appears to be torsion, the base-to-apex torque of the ventricle that forms as the counterwound myofibrillar helixes contract against each other. This stores considerable elastic energy during systole. Largely in both the myocardial extracellular matrix and titin, the giant molecular “spring” within the sarcomere that resists overcontraction and overextension of the myocyte. Although torsion develops gradually during systole, untwisting occurs abruptly, with >50% of torsion released during isovolumic relaxation.

We have recently shown that this untwisting rate predicts the magnitude of diastolic suction (base-to-apex intraventricular pressure difference) and that it is particularly important during the shortened diastole of exercise. We have demonstrated that torsion is relatively undeveloped in infants, with the heart rotating essentially as a solid body but assuming the adult pattern by adolescence. Toward middle age, torsion increases again, but untwisting is delayed, perhaps contributing to less efficient diastolic filling in the elderly. The cause of these maturational changes are unknown, but intriguingly, they parallel known changes in titin isoforms from the N2BA fetal form (which has relatively little restorative force) to the stiffer N2B adult form. This work provides normative data for age-related changes in LV torsion as well as suggests future research into the role of torsion in mediating ventricular function in congenital heart disease.
Maturational and Adaptive Modulation of Left Ventricular Torsional Biomechanics: Doppler Tissue Imaging Observation From Infancy to Adulthood
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