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. 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. 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. 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. In addition to these cardiac changes, arterial distensibility decreases from childhood to adulthood, a stiffening of the arterial tree that increases afterload even in normotensive individuals.

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Although heart size increases with somatic maturation, 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. 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. 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 velocity and LV torsion noninvasively, a significant advantage for the examination of children. We therefore sought to investigate the developmental...
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 TorsionX

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 LVtorw (°/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:

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

where \( V_{lat} \) and \( V_{sep} \) are velocities in the septal and lateral regions, respectively, used to measure the tangential velocity (cm/s); and \( V_{lat} \) and \( V_{sep} \) 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 \([r(t)]\), \( r_0 \) is the end-diastolic radius. LV torsional velocity (LVtor, rad/s) was calculated as

\[ V_{tor}(t) = \frac{[V_{lat}(t) - V_{sep}(t)]}{r(t)} \]

LVrot was obtained by integrating \( V_{rot}(t) \) in each slice:

\[ \int_0^1 [V_{rot}(t)] \, dt \]

LVtor and LVtorw are as defined earlier:

\[ \text{LVtor} = \text{Apical LV rotation} - \text{Basal LV rotation}, \]

and \( \text{LVtorw} = \text{LVtor} / \text{LV length} \)

Figure 1. Alterations in LV torsional deformation profile from infancy to adulthood. Averaged torsional deformation and long- and short-axis function profiles for each age group are shown. Arrows denote peak LV torsion and untwisting velocity. Upper row: LV rotation at 3 short-axis levels and LV torsion. Purple line indicates LV torsion. Blue, apical; light green, middle; and dark green, basal level rotation. Note that the increase in torsion during childhood is due to progressive development of a clockwise twist at the base, whereas the further increase in torsion during adulthood reflects an increase in apical counterclockwise twist. Lower row: Purple line indicates LV torsional velocity. Red and orange lines indicate long- and short-axis velocity, respectively. Note that in infancy, untwisting occurs almost synchronously with lengthening and expansion, whereas with age, untwisting clearly precedes lengthening and expansion and occurs largely during isovolumic relaxation. The time sequence was normalized by systolic duration (ie, \( t = 100\% \) at end systole). The error bar indicates 1 SEM and is marked at every 10% of systolic duration. Abbreviations are given for timing in a cardiac cycle as determined by the outflow and inflow Doppler profile: MC, mitral valve closure; AO, aortic valve opening; E1, peak systolic flow velocity at the LV outflow tract; AC, aortic valve closure; MO, mitral valve opening; EF, peak early filling velocity in the LV inflow tract; and E, end of early filling.
TABLE 1. Demographic Data

<table>
<thead>
<tr>
<th>Age</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>
</tr>
<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>
</tr>
<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>
</tr>
<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>66±9</td>
</tr>
</tbody>
</table>

2D echocardiographic data

- **Posterior wall thickness (W), cm**
  - Infants: 0.46±0.10
  - Children: 0.60±0.10
  - Adolescents: 0.77±0.22
  - Young Adults: 0.88±0.12
  - Middle-Age Adults: 0.97±0.17

- **End-diastolic LV length (L), cm**
  - Infants: 3.8±0.6
  - Children: 5.6±0.8
  - Adolescents: 7.6±0.5
  - Young Adults: 8.0±0.3
  - Middle-Age Adults: 8.0±0.3

- **End-diastolic LV diameter (D), cm**
  - Infants: 2.2±0.5
  - Children: 3.5±0.4
  - Adolescents: 4.7±0.4
  - Young Adults: 5.2±0.5
  - Middle-Age Adults: 4.7±0.4

- **LV wall-thickness index: W/D**
  - Infants: 0.21±0.03
  - Children: 0.17±0.03
  - Adolescents: 0.17±0.04
  - Young Adults: 0.17±0.03
  - Middle-Age Adults: 0.21±0.05

- **LV geometric index: D/L**
  - Infants: 0.29±0.05
  - Children: 0.32±0.02
  - Adolescents: 0.31±0.03
  - Young Adults: 0.32±0.03
  - Middle-Age Adults: 0.29±0.02

- **LV end-diastolic volume, mL**
  - Infants: 10.6±2.8
  - Children: 41±11
  - Adolescents: 92±33
  - Young Adults: 112±22
  - Middle-Age Adults: 84±20

- **LV end-systolic volume, mL**
  - Infants: 4±3
  - Children: 17±5
  - Adolescents: 36±17
  - Young Adults: 42±8
  - Middle-Age Adults: 31±11

- **LV ejection fraction, %**
  - Infants: 62±4
  - Children: 58±11
  - Adolescents: 56±19
  - Young Adults: 62±4
  - Middle-Age Adults: 64±8

Pulsed-wave Doppler data

- **Early diastolic peak velocity (E), m/s**
  - Infants: 0.82±0.41
  - Children: 1.04±0.15
  - Adolescents: 1.06±0.20
  - Young Adults: 0.95±0.31
  - Middle-Age Adults: 0.85±0.23

- **Late diastolic peak velocity (A), m/s**
  - Infants: 0.95±0.26
  - Children: 0.65±0.09
  - Adolescents: 0.59±0.11
  - Young Adults: 0.50±0.08
  - Middle-Age Adults: 0.58±0.11

- **E/A ratio**
  - Infants: 0.94±0.48
  - Children: 1.63±0.27
  - Adolescents: 1.89±0.59
  - Young Adults: 1.94±0.58
  - Middle-Age Adults: 1.47±0.29

- **E/E’ ratio**
  - Infants: 11.4±3.9
  - Children: 9.8±2.2
  - Adolescents: 9.2±0.8
  - Young Adults: 8.7±2.2
  - Middle-Age Adults: 9.6±3.0

- **Early diastolic propagation velocity, cm/s**
  - Infants: 48±11
  - Children: 61±10
  - Adolescents: *67±24
  - Young Adults: 57±10
  - Middle-Age Adults: 66±12

Doppler tissue imaging data

- **Long-axis function**
  - Peak systolic velocity, cm/s: 4.1±1.2
  - Peak early-diastolic velocity (E’), cm/s: -8.2±2.8
  - Peak early-diastolic velocity: 6.8±1.9
  - Peak early-diastolic velocity: 6.9±0.8
  - Peak early-diastolic velocity: 6.7±1.0

- **Short-axis function**
  - Peak systolic velocity, cm/s: 3.8±0.9
  - Peak early-diastolic velocity, cm/s: 5.3±0.9
  - Peak early-diastolic velocity: 4.9±0.8
  - Peak early-diastolic velocity: 5.9±1.0
  - Peak early-diastolic velocity: 5.3±0.8
  - Peak early-diastolic velocity: 7.0±2.5
  - Peak early-diastolic velocity: -9.5±2.3
  - Peak early-diastolic velocity: -9.8±3.8
  - Peak early-diastolic velocity: -10.2±3.0
  - Peak early-diastolic velocity: -7.2±1.8

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 workstation by anchoring them to the LV inner and midwalls at end diastole, at end systole, and after early filling to keep the correct position. 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 age term were significant at the 0.05 level. When other functions of age (such as the logarithm) were suggested by plots of the data, we chose the model with the highest R² value. For presentation, subjects were divided into 5 age groups, and the mean (and SD) of each
The upper row of Figure 1 shows LV shifting LV Rotation Pattern by dividing 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 childhood.

### Shifting LV Rotation Pattern

The upper row of Figure 1 shows LVrot at the basal, middle, and apical LV levels, along with the torsion (difference 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 counterclockwise, increasing slightly from ≈5° in infancy to ≈7° by adulthood. Basal rotation shows more significant changes, being counterclockwise 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 LVtor (Figure 3A).

### Peak LVtorN and Untwisting Recoil

Figure 3 summarizes the age-related peak LVtor (A), untwisting velocity (B), LVtorN (C), and untwisting velocity normalized to LV length (D). Peak LVtor 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, LVtorN 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 torsion, 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]/cm)/(deg/cm)</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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**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 childhood.
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 adulthood, 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 showing the adult clockwise pattern in adolescence, a finding that may indicate fundamental myoarchitectural changes in the developing heart or possibly the greater length over which the angulated epicardial fibers can act. Wulfsohn et al reported that with growth, myocardial fibers connect points at the base and apex that are farther and farther apart circumferentially. By this growth process, basal rotation becomes more prominent, conse-

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

**Figure 3.** Age-related alterations in LV torsional performance with and without normalization by ventricular size, shown with the most significant polynomial regression line. A and B, Peak LV torsion and peak untwisting velocity. Note that both parameters were best predicted by a linear function of age. C and D, Peak LV torsion and peak untwisting velocity normalized by LV length. Note that both parameters were best predicted by a quadratic function of age. By factoring the quadratic, the figure demonstrates that normalized torsion and untwisting velocity reach minima at 19.0 and 19.5 years, respectively.

**Figure 4.** Age-related alterations in LV untwisting performance. A, Isovolumic untwisting recoil can be derived from the expression (LV\(\text{tor} - \text{at} - \text{AVC}) - (LV\text{tor} - \text{at} - \text{MVO}) \times 100(\%), which yields the percentage of total torsion released between aortic valve closure and mitral valve opening. This increases significantly in childhood but is relatively constant in adulthood. B, Peak untwisting performance can be derived from the expression \(\text{rad}/\text{s})^2 = 1/s, which yields the peak untwisting velocity divided by peak LV torsion: This is relatively constant throughout childhood into middle age. Note that both indices in A and B are LV length independent.
contractility is higher in children than in infants, and young adults. This result correlates with the finding that higher in infants than in older children, adolescents, and basal changes seen in childhood with relatively constant LV geometry (represented by the LV length-diameter ratio) and ejection fraction were constant from infancy to adulthood, 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 clearly demonstrated. 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. 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, 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, and alterations in connective tissue and titin, 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 N2BA to N2B. 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 transmirtal and annular E waves. Data on age-related changes in myocardial relaxation remain somewhat in conflict. Delayed and decreased apical untwisting has been reported in patients with LV hypertrophy from aortic stenosis. LV untwisting is a sensitive parameter for predicting myocardial relaxation and has previously been noted not to decline with advancing age. 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.

Enhanced LVτorN 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. LVτorN was higher in infants than in older children, adolescents, and young adults. This result correlates with the finding that contractility is higher in children <2 years of age (due to higher metabolic demand) compared with older children with uncoordinated basal rotation, as mentioned earlier. As reported by others, 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 in infancy, leading to greater normalized torsion, if the lever-arm theory is correct. Interestingly, the mouse heart has an apex-to-base angle of twist 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.

We also observed significant age-related increases in LVτor and LVτorN 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 LVτorN closely tracked changes in torsion. Histological data indicate that in normal subjects, increasing age does not result in cellular hypertrophy, although stiffening of the arterial tree may increase afterload and thereby alter diastolic function. LV torsion is afterload dependent, and a chronic increase in afterload leads to increasing apical rotation and LV torsion, 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 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. 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, 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, and alterations in connective tissue and titin, 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 N2BA to N2B. 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.
reported but was not a focus of the present study, although such future data would be very interesting. Detailed examination of LV mechanics by tissue-tagged magnetic resonance imaging showed that infant myocardial angular deformation is not homogeneous in any given short-axis LV plane, although some of this variability may reflect measurement noise. Because we calculated averaged LV rotation, our DTI method did not assess regional rotation, although our results were consistent with theirs in general, and our high-temporal resolution data sets have an inherent advantage, especially in tachycardic infants. The recently validated speckle tracking imaging technique might better reveal the inhomogeneous angle displacement and strain. Arts et al and Delhaas et al have investigated “LV torsion” as a shear strain that occurs during normal heart function, and Dong et al have also analyzed it. This shear strain was calculated as net LV torsion multiplied by the ratio of LV radius over length (i.e., a dimensionless parameter). Although we have focused on LV torsional behavior and did not measure this shear strain, the net LV torsion that we measured is proportional to shear strain because of the constant ratio between the LV long axis to the short axis from infancy to adulthood (Figure 5). In this sense, LV torsion in absolute magnitude has significance, as might LVtor, as developments in myocardial velocity mapping or tracking of relatively high-frame-rate 3D echocardiographic data sets might enable us to overcome these issues. Finally, we normalized the timing of all events, even those in early diastole, to the duration of electromechanical systole, a technique not validated for the wide range of heart rates seen here. This seems reasonable, however, as ventricular relaxation is related causally to the preceding systole, not the subsequent diastasis and atrial contraction, but it certainly may have distorted the data display somewhat.

Potential Clinical Application

Our observations about altered LV torsional behavior in infancy, including enhanced LVtor 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.

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Disclosures

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References

CLINICAL PERSPECTIVE

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, likely 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. In the present study, 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 is 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.
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