Synchronicity of systolic deformation in healthy pediatric and young adult subjects: a two-dimensional strain echocardiography study

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COORDINATED CONTRACTION of the left ventricular myocardium is a mandatory prerequisite for an efficient contractile function. In heart failure patients, this contractile function is depressed due to various cellular and extracellular biochemical abnormalities that often lead to asynchronous ventricular contraction. Electromechanical dyssynchrony, in turn, causes a sequence of events that may result in pathological ventricular remodeling and contributes independently to further impairment in global systolic function (13). Cardiac resynchronization therapy (CRT) is an emerging option for treating dyssynchrony-associated heart failure in patients with pediatric or congenital heart disease. CRT has proven to be beneficial for both the acute manipulation of cardiac output after surgery of congenital heart defects and for the management of chronic systemic ventricular failure (2, 12, 14, 15, 21, 26, 29, 30, 41). An important issue in CRT that remains is the selection of patients. Current selection criteria (for adults) consist of 1) symptomatic heart failure, indicated by left ventricular ejection fraction ≤35% and New York Heart Association (NYHA) class II-IV; and 2) QRS duration ≥120 (150) ms (4, 25, 60, 65). Results from the MIRACLE trial showed that ~30% of the adult patients did not experience any significant clinical response to CRT when current selection criteria were used. In pediatric and congenital heart disease, the nonresponse rate is 20% (2, 30, 60). In fact, the rate of echocardiographic response in adults is even lower than clinical improvement (10). Previous studies (33, 45, 46, 50) have indicated that electrocardiographic indexes, such as QRS duration, are poor predictors of hemodynamic improvement achieved by CRT. These parameters have been shown to underestimate intraventricular dyssynchrony in a significant number of patients, whereas mechanical asynchrony is absent in nearly 30% of patients with prolonged QRS duration (3, 70). Besides their inaccuracy in predicting hemodynamic and clinical response to CRT, the current adult criteria cannot be easily translated to the pediatric population (31). However, given the variety of anatomic and functional substrates subjected to CRT in the pediatric age group, evaluation of mechanical dyssynchrony has become a substantial part of the decision process despite the fact that normal values are lacking.

At present, several (additional) visualization methods of assessing dyssynchrony have been proposed, varying from conventional echocardiographic techniques to more recently developed applications such as two-dimensional strain echocardiography or speckle tracking (2DSTE). This latter echocardiographic technique determines the extent and timing of myocardial deformation by means of frame-by-frame tracking and motion analysis of speckles within the B-mode images using correlation or optical flow search algorithms. Validation studies with tagged MRI and sonomicrometry in the adult population have provided the evidence that 2DSTE is a reliable method to determine ventricular myocardial function (5, 36). The fact that timing and extent of deformation using 2DSTE are less affected by passive translational motion of the heart or tethering effects of neighboring myocardial segments than velocity-motion-based techniques makes strain an attractive modality to assess regional myocardial dyssynchrony (69). Previous studies (61, 63) have indicated that speckle tracking...
provides promising echocardiographic parameters to predict beneficial effects of CRT in adult patients with heart failure. In healthy adult individuals, the timing of myocardial deformation as well as the extent of asynchronous contraction between various ventricular segments appears to be related to age (27, 53, 57). Therefore, the application of 2DSTE indexes for the assessment of ventricular dyssynchrony is dependent on establishing reference ranges across a wide range of age groups in a large group of healthy individuals. However, data regarding the normal timing of deformation and the extent of synchrony of contraction between ventricular segments in healthy children are lacking. Mapping of normal contraction times in the healthy pediatric heart may give valuable insight into normal contraction patterns and may serve as a reference for interpreting data of patients considered for CRT and patients with ischemia-induced myocardial damage. Therefore, the primary aim of this study was to establish reference values for the normal timing of left ventricular deformation in pediatric and young adult age groups as assessed with 2DSTE. In addition, we examined the relation between timing of myocardial deformation and multiple anthropometric as well as echocardiographic variables.

MATERIALS AND METHODS

Study population. Subjects that were routinely referred for echocardiographic evaluation of an asymptomatic, innocent heart murmur and screening purposes between May 2005 and November 2009 were retrospectively analyzed for their eligibility for inclusion in the study. All consecutive healthy subjects aged from birth to 40 yr were identified from our echocardiographic database from the outpatient clinic at both the Children’s Heart Centre and the Adult Heart Centre (Nijmegen, The Netherlands). This study was approved by the local Medical Ethical Committee. Demographic characteristics, including age and gender, were collected at the time the echocardiographic study was performed. A complete physical examination was performed, including weight, height, and blood pressure measurements (see Table 1). For each subject, a 12-lead electrocardiogram (ECG) was recorded and subsequently evaluated using age-appropriate reference values (34, 56, 64). Subjects were included only if clinical examination, transthoracic echocardiogram, and ECG showed no evidence of preexisting cardiac disease or other significant coexisting illness. On the 12-lead ECG, an abnormal cardiac rhythm, prolonged QRS duration, bundle branch block, pathological Q waves, ventricular hypertrophy, or changes consistent with myocardial ischemia resulted in exclusion as did evidence of (congenital) structural heart disease, significant valvular abnormality, impaired systolic or diastolic left ventricular function, or left ventricular hypertrophy on the transthoracic echocardiogram. Other exclusion criteria consisted of hypertension, chronic illness, recent acute illness, as well as poor echocardiographic image quality.

Conventional echocardiographic parameters. All subjects underwent a detailed transthoracic echocardiographic examination in the left lateral position according to the recommendations of the American Society of Echocardiography (39). Every examination was performed at rest, without using sedation. Images were obtained with a 3.0-MHz (S3) or a 5.0-MHz (S5) phased-array transducer using a commercially available system, the Vivid 7 echocardiographic scanner (Vingmed Ultrasound; GE Medical Systems, Horten, Norway). The choice for a S3 or a S5 transducer depended on the age and weight of the subject. Quantification of cardiac chamber size, ventricular mass, and systolic and diastolic left ventricular function was measured in accordance with the recommendations for chamber quantification by the American Society of Echocardiography’s Guidelines and Standard Committee and the Chamber Quantification Writing Group (39). Left ventricular systolic function was determined using fractional shortening, ejection fraction, left ventricular myocardial performance (Tei-) index, end-systolic wall stress, and rate corrected velocity of circumferential fiber shortening. Ejection fraction was calculated using the modified Simpson’s rule (37, 39). The pulsed wave Doppler-derived myocardial performance index was calculated by adding the isovolumetric contraction time and the isovolumetric relaxation time and dividing the sum by the ejection time (67). Left ventricular end-systolic wall stress was calculated using the modified formula of Rowland and Gutgesell (58). Velocity of circumferential fiber shortening was calculated with the formula obtained from Colan et al. (22). Left ventricular mass was calculated with the formula for estimation of left ventricular mass according to Devereux and Reichek (24) and was subsequently indexed by the body surface area.

2DSTE data acquisition. 2D multiframe B-mode (gray scale) images were obtained in the apical four-chamber (4C), parasternal midcavity short-axis view (at the level of the papillary muscle), and parasternal basal short-axis view (at the level of the mitral valve). A sector scan angle of 30–60° was chosen, and frame rates of 60–90 Hz were used since these rates are considered to be optimal for 2D speckle tracking (23, 36, 40). Data were stored at the same frame rate as the acquisition frame rate. Preferably images from five cardiac cycles triggered by the R wave of the QRS complex were digitally saved in cine-loop format. Offline speckle tracking analysis was performed using software for echocardiographic quantification (EchoPAC 6.10; GE Medical Systems). Timing of aortic valve closure and mitral valve opening with respect to peak systolic strain was manually obtained, using single gated pulsed wave Doppler or continuous wave Doppler images of the left ventricle outflow tract. For these measurements, special care was taken to keep the heart rate in the same range as during the 2D gray scale imaging used for 2D

Table 1. Demographic and anthropometric characteristics of study subjects categorized by age group

<table>
<thead>
<tr>
<th>Age group no.</th>
<th>0 yr</th>
<th>1–4 yr</th>
<th>5–9 yr</th>
<th>10–14 yr</th>
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<td>29</td>
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<td>13</td>
<td>13</td>
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<tr>
<td>Age, yr</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (54%)</td>
<td>19 (56%)</td>
<td>25 (69%)</td>
<td>16 (55%)</td>
<td>9 (43%)</td>
<td>16 (64%)</td>
<td>8 (62%)</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.3 ± 0.3</td>
<td>2.9 ± 1.0</td>
<td>7.2 ± 1.2</td>
<td>12.8 ± 1.6</td>
<td>17.0 ± 1.3</td>
<td>21.7 ± 1.2</td>
<td>27.3 ± 1.3</td>
<td>35.6 ± 2.6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>Height, m</td>
<td>0.62 ± 0.11</td>
<td>0.95 ± 0.10</td>
<td>1.26 ± 0.09</td>
<td>1.59 ± 0.13</td>
<td>1.76 ± 0.09</td>
<td>1.78 ± 0.10</td>
<td>1.82 ± 0.08</td>
</tr>
<tr>
<td>Age, yr</td>
<td>Weight, kg</td>
<td>6.3 ± 2.6</td>
<td>14.6 ± 3.4</td>
<td>24.7 ± 4.4</td>
<td>46.3 ± 12.0</td>
<td>66.4 ± 12.0</td>
<td>70.3 ± 11.9</td>
<td>76.5 ± 11.9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>BSA, m²</td>
<td>0.32 ± 0.10</td>
<td>0.62 ± 0.10</td>
<td>0.93 ± 0.12</td>
<td>1.43 ± 0.23</td>
<td>1.81 ± 0.20</td>
<td>1.86 ± 0.20</td>
<td>1.96 ± 0.19</td>
</tr>
<tr>
<td>Age, yr</td>
<td>BMI, kg/m²</td>
<td>15.9 ± 2.2</td>
<td>15.9 ± 1.4</td>
<td>15.4 ± 1.3</td>
<td>17.9 ± 2.1</td>
<td>21.2 ± 2.3</td>
<td>22.1 ± 2.0</td>
<td>23.1 ± 2.2</td>
</tr>
<tr>
<td>Age, yr</td>
<td>HR, beats/min</td>
<td>118 ± 12</td>
<td>101 ± 14</td>
<td>84 ± 13</td>
<td>77 ± 14</td>
<td>65 ± 9</td>
<td>63 ± 11</td>
<td>60 ± 14</td>
</tr>
<tr>
<td>Age, yr</td>
<td>SysBP, mmHg</td>
<td>82 ± 8</td>
<td>98 ± 10</td>
<td>104 ± 8</td>
<td>110 ± 10</td>
<td>116 ± 11</td>
<td>118 ± 12</td>
<td>121 ± 11</td>
</tr>
<tr>
<td>Age, yr</td>
<td>DiaBP, mmHg</td>
<td>56 ± 6</td>
<td>62 ± 10</td>
<td>70 ± 8</td>
<td>72 ± 8</td>
<td>75 ± 9</td>
<td>75 ± 8</td>
<td>77 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 195. BSA, body surface area; BMI, body mass index; HR, heart rate; SysBP, systolic blood pressure; DiaBP, diastolic blood pressure.

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strain calculations. Endomyocardial borders of the left ventricle were manually traced within the end-systolic frame. The second, epicardial tracing was automatically generated by the EchoPAC software and, when necessary, manually adjusted to cover the whole myocardial wall. The tracking algorithm then followed the myocardial speckles during the cardiac cycle. Tracking was only accepted if both visual inspection as well as the EchoPAC software indicated adequate tracking. This means that tracking of any given segment was only accepted when it was indicated with a green box. The software automatically divided the cross sectional image into six segments, which were named and identified according to the statement of the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association (16). The left ventricle segments to be analyzed were the apical, mid, and basal segments of the septal and the lateral wall of the 4CH view, as well as the anteroseptal, anterior, lateral, posterior, inferior, and septal segments of the basal and midcavity short-axis views. Speckle tracking was performed for all (three) consecutive cycles separately. Strain curves of the three consecutive cardiac cycles and values of the manual timing were imported into a custom made software package for further analysis (see APPENDIX). The Q-Q interval was estimated from the ECG signal to obtain cardiac cycle length. It is known that the duration of the systolic phase of the cardiac cycle in rest does not change with small changes in heart rate in contrast to the diastolic phase (9). Therefore, the diastolic phase of the three cardiac cycles was automatically extended and adjusted by the software package to the longest of the three cardiac cycles. This intervention prevents a shift of the peak systolic strain while averaging the individually measured three consecutive cardiac cycles. Cardiac cycles with a length \( >10\% \) different from the mean length of the three cardiac cycles were excluded from averaging and thus for further analysis. Timing of myocardial longitudinal, radial, and circumferential peak systolic strain was obtained. For a parameter \( x \), we determined \( t(x) \) as the time interval measured from the beginning of the QRS complex of the surface ECG to the peak value of the parameter \( x \) in the myocardial segment \( i \) within the analyzed heart cycle period: \( t(x_i) = \Delta t \left[ \text{peak (}x_i) - \text{QRS}_{\text{ECG}} \right] \). To determine global time to peak systolic strain, the time to peak systolic strain values of the six segments were averaged for the 4CH as well as the short-axis views. To measure the extent of synchronicity of regional deformation, a method previously described by Fonseca et al. (27) was used, which calculates the SD of the time to peak systolic strain measurements. An increased index would indicate increased regional heterogeneity with respect to time to peak systolic strain. In addition, the difference in time to peak systolic longitudinal strain between the lateral wall and septum was calculated. Correction for the influence of variation in heart rate on time to peak systolic strain values was achieved by dividing time to peak systolic strain measurements by the square root of the R-R interval in these subjects (i.e., Bazett’s formula; Refs. 7, 18, 32, 66). All offline measurements with EchoPAC were performed by a single observer (K. A. Marcus). Interobserver and intraobserver variability scores have been described previously by our research group (43). Time to peak systolic strain is expressed in milliseconds. Figure 1 shows an illustration of strain curves.

**RESULTS**

A total of 226 subjects were evaluated for inclusion in the study. Of those subjects, 31 (13.7\%) were subsequently excluded in light of incomplete echocardiographic data or suboptimal imaging quality. In total, 195 healthy subjects (139 children and 56 young adults) were enrolled in the study. Subject characteristics and anthropometric parameters are described in Table 1. None of the subjects used medication for cardiovascular illness. Conventional echocardiographic parameters of the study subjects are presented in Table 2. All standard echocardiographic findings were within previously described normal values for age.

Tracking was feasible in 91\% of all segments of the 4CH view, in 96\% of all segments in the short-axis view at the level of the papillary muscle, and in 91\% of all segments in the short-axis view at the level of the mitral valve. Left ventricular time to peak systolic strain parameters corrected for heart rate using Bazett’s formula are presented in Tables 3, 4, and 5.

Even after correction for heart rate, statistically significant

![Fig. 1. Radial and circumferential strain curves of the septal wall at the level of the papillary muscle. ECG, electrocardiogram; ES, end-systolic; SAX-PM, short-axis view at the level of the papillary muscle.](http://aphp.heart.physiology.org/)
TIMING OF MYOCARDIAL DEFORMATION WITH SPECKLE TRACKING

Table 2. Conventional echocardiographic parameters of study subjects categorized by age group

<table>
<thead>
<tr>
<th>Age group no.</th>
<th>0 yr</th>
<th>1–4 yr</th>
<th>5–9 yr</th>
<th>10–14 yr</th>
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<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>34</td>
<td>36</td>
<td>29</td>
<td>21</td>
<td>25</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Bas. Sept.</td>
<td>362 ± 20</td>
<td>394 ± 22</td>
<td>424 ± 25</td>
<td>425 ± 28</td>
<td>433 ± 26</td>
<td>422 ± 29</td>
<td>443 ± 25</td>
<td>453 ± 33</td>
</tr>
<tr>
<td>Mid. Sept.</td>
<td>334 ± 18</td>
<td>360 ± 21</td>
<td>390 ± 24</td>
<td>392 ± 26</td>
<td>400 ± 25</td>
<td>388 ± 24</td>
<td>397 ± 26</td>
<td>422 ± 28</td>
</tr>
<tr>
<td>Apic. Sept.</td>
<td>313 ± 16</td>
<td>342 ± 17</td>
<td>368 ± 18</td>
<td>368 ± 20</td>
<td>370 ± 19</td>
<td>362 ± 21</td>
<td>380 ± 24</td>
<td>362 ± 27</td>
</tr>
<tr>
<td>Apic. Lat.</td>
<td>329 ± 16</td>
<td>358 ± 17</td>
<td>382 ± 17</td>
<td>380 ± 20</td>
<td>392 ± 20</td>
<td>374 ± 23</td>
<td>392 ± 26</td>
<td>385 ± 30</td>
</tr>
<tr>
<td>Mid. Lat.</td>
<td>352 ± 17</td>
<td>384 ± 19</td>
<td>400 ± 21</td>
<td>413 ± 22</td>
<td>417 ± 24</td>
<td>395 ± 25</td>
<td>422 ± 28</td>
<td>440 ± 30</td>
</tr>
<tr>
<td>Bas. Lat.</td>
<td>372 ± 19</td>
<td>401 ± 21</td>
<td>435 ± 23</td>
<td>439 ± 24</td>
<td>445 ± 25</td>
<td>448 ± 29</td>
<td>454 ± 23</td>
<td>468 ± 32</td>
</tr>
<tr>
<td>Global T2P SL</td>
<td>341 ± 10g,4,5,6,7,8</td>
<td>373 ± 10g</td>
<td>400 ± 20s</td>
<td>402 ± 23s</td>
<td>410 ± 22s</td>
<td>398 ± 24s</td>
<td>415 ± 25s</td>
<td>422 ± 31s,2</td>
</tr>
<tr>
<td>P5 Global T2P SL</td>
<td>305</td>
<td>335</td>
<td>361</td>
<td>356</td>
<td>350</td>
<td>365</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>P95 Global T2P SL</td>
<td>377</td>
<td>411</td>
<td>439</td>
<td>448</td>
<td>446</td>
<td>465</td>
<td>484</td>
<td></td>
</tr>
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Values are means ± SD; n = 195. LVET, left ventricular ejection time; LVETc, LVET corrected for heart rate; QTc, QT duration corrected for heart rate using Bazett’s method; Syst. BP, systolic blood pressure; Tei index, left ventricular myocardial performance index; VCFc, heart-rate corrected velocity of circumferential fiber shortening; FS, fractional shortening; EF biplane, ejection fraction measured by modified Simpson’s method; ESWS, end-systolic wall stress; LV mass/BSA, left ventricular mass corrected for body surface area.

No significant sex-related differences in time to peak systolic strain were found. Figures 2, 3, 4, and 5 show the degree of asynchronous deformation among left ventricular myocardial segment in longitudinal, circumferential, and radial direction according to age. Even after correction for heart rate, the degree of synchrony decreased significantly with age (Table 6 and Figures 2–5). Our data indicate that the degree of synchrony decreases with age and body growth (indexes; Table 7). There were no statistically significant correlations between synchronicity parameters and fractional shortening or LV ejection fraction. QRS duration, QT duration corrected for heart rate using Bazett’s method, and blood pressure did not correlate with the strain parameters under investigation (Table 7).

DISCUSSION

Electromechanical dys synchrony, with early and late contracting ventricular myocardial segments, results in inefficient ventricular performance. Late contracting segments are stretched by the early contracting regions and perform a higher local myocardial workload. This workload is to some part wasted because late contraction appears after semilunar valve closure and at the end of the ventricular ejection phase (30, 55). The uneven distribution of work load leads to changes in both regional blood flow and metabolism in addition to pathologic remodeling (54). Van Oosterhout et al. (52) showed development of asymmetric myocardial hypertrophy due to electromechanical dys synchrony with decrease in regional wall thickness and volume at the early contracting sites and increase in the areas of late contraction. Together, these series of events lead to reduced overall cardiac efficiency and increases myocardial energy demands, which eventually result in (progression of) heart failure (49). Furthermore, dysynnergistic ventricular contraction and relaxation have been associated with a proarrhythmicogenic effect (59).

Table 3. Time to peak systolic longitudinal strain corrected for heart rate of study subjects categorized by age group

<table>
<thead>
<tr>
<th>Age group no.</th>
<th>0 yr</th>
<th>1–4 yr</th>
<th>5–9 yr</th>
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<td>484</td>
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</tbody>
</table>

Values are means ± SD; n = 195. Time values are presented in milliseconds. Bas., basal; Sept., septum; Apic., apical; Lat., lateral; SL, longitudinal peak systolic strain; T2P, time to peak systolic strain. Correction for heart rate was calculated by dividing the time to peak systolic strain by Y-R interval for each individual. *P < 0.05, when compared with age groups denoted by superscript numerals, determined by means of one-way ANOVA with Bonferroni correction for multiple comparisons.
Several visualization methods of assessing the extent of ventricular dysynchrony have been proposed to overcome the above mentioned limitations, varying from conventional echocardiographic techniques to more novel applications such as Tissue Doppler imaging (TDI) and 2D strain echocardiography. TDI initially showed promising results for the assessment of dysynchrony in small clinical trials. However, TDI is limited by several characteristics of Doppler-based techniques. Firstly, TDI measures only the vector of motion that is parallel to the direction of the ultrasound beam and is thus inherently angle dependent. Secondly, TDI measures absolute tissue velocity and is unable to discriminate passive motion (related to translation or tethering) from active motion (fiber shortening or lengthening). Recently, large, prospective randomized clinical trials have shown that TDI is inadequate to predict response from CRT in patients with heart failure and is associated with considerable intra- and interobserver variability (17, 20, 61).

Strain imaging derived from 2DSTE enables quantification of regional myocardial function without tethering effect and Doppler angle dependence. It measures the extent and timing of regional myocardial deformation with high temporal and spatial resolution. Although 2DSTE is sensitive to signal noise,
it may facilitate the detection of ventricular dyssynchrony and the prediction of outcome after CRT (61). A prospectively designed study, performed by Suffoletto et al. (63) showed that 2DSTE is able to quantify dyssynchrony and predict immediate and long-term response to CRT with good results. In addition, they demonstrated the feasibility of 2DSTE to detect the site of latest mechanical activation. Identification of the most delayed segment is of importance, since previous reports (6, 63) have indicated that left ventricular lead placement at the most delayed segment resulted in the greatest immediate improvements from CRT. Previous speckle tracking studies, in pediatric patients, have revealed abnormal timing of systolic deformation in various congenital and acquired cardiac conditions. These studies (1, 28, 44, 47, 48) indicated that various pathological conditions are associated with a prolonged required amount of time to reach maximum peak systolic strain in addition to a greater extent of inter- and intraventricular dysynchronous deformation. If validated by additional prospective studies, 2DSTE may prove particularly helpful in selecting appropriate candidates with congenital heart disease for CRT in whom conventional criteria are not applicable. However, the application of 2DSTE indexes in the assessment of ventricular dyssynchrony is dependent on establishing reference values across a wide range of age groups, since both timing of myocardial deformation and the extent of dyssynchrony between various ventricular segments appear to be related to age (27, 53, 57).

While mapping of normal contraction times in the normal (pediatric) heart may give valuable insight into normal contraction patterns, data regarding the normal timing of deformation and the extent of synchrony of contraction between ventricular segments in healthy children and young adults were lacking. Therefore, in the present study reference values for the normal timing of left ventricular deformation in the pediatric and young adult age groups were assessed using 2DSTE. Our results demonstrated a significant correlation between time to peak systolic strain and age as well as heart rate. The influence of heart rate on strain measurements was previously described by others in a TDI study (11). Since heart rate decreases with age, we subsequently assessed the relationship between age and time to peak systolic strain after correction for heart rate.

![Fig. 2](image-url)  
Age in years; difference in time to peak systolic longitudinal strain between lateral wall and septum in milliseconds corrected for heart rate by Bazett’s formula; lines indicate: regression line (mean) in the middle and 95% individual prediction interval.

![Fig. 3](image-url)  
Age is in years. Deviation T2PS_L: SD of time to peak systolic longitudinal strain in milliseconds is corrected for heart rate by Bazett’s formula. Lines indicate regression line (mean) in the middle and 95% individual prediction interval.

![Fig. 4](image-url)  
Age is in years. Deviation T2PS_CP: SD of time to peak systolic circumferential strain at the level of the papillary muscle in milliseconds is corrected for heart rate by Bazett’s formula. Lines indicate regression line (mean) in the middle and 95% individual prediction interval.

![Fig. 5](image-url)  
Age is in years. Deviation T2PS_RP: SD of time to peak systolic radial strain at the level of the papillary muscle in milliseconds is corrected for heart rate by Bazett’s formula. Lines indicate regression line (mean) in the middle and 95% individual prediction interval.
As expected, the present study identified strong relationships between timing of myocardial deformation and age as well as multiple anthropometric variables and echocardiographic indexes. No significant sex-related differences in time to peak systolic strain were found. Surprisingly, we did not find a significant relation between timing of left ventricular deformation and conventional echocardiographic functional indexes such as left ventricular ejection fraction, fractional shortening, and end-systolic wall stress, neither after correction of timing of deformation for heart rate. These findings are in contrast to those of Rosen et al. (57). A possible explanation for these contradictory findings could be that our study included only subjects free from risk factors for cardiac disease in contrast to the study by Rosen et al. where the majority of subjects had cardiovascular risk factors (such as smoking, diabetes mellitus, hypertension, smoking, and obesity). Conventional echocardiographic functional indexes in our study showed little variation, which could offer an explanation for the absence of a relation between these conventional parameters and 2DSTE timing indexes. In all age groups, time to peak systolic longitudinal strain was shorter in the septum than in the lateral wall, which is in accordance to previous reports. Zwanenburg et al. (71) showed an opposite spatial pattern of the onset of longitudinal deformation. As a result, duration of deformation was longest in the lateral wall, for which it is known that peak strains are largest (43, 71).

Our results demonstrate that increased age is associated with a greater extent of variation in timing of deformation among various left ventricular segments, indicating that patterns of regional nonuniformity of myocardial deformation are altered with age. These findings are in agreement with previous studies describing ventricular synchrony in healthy adult cohorts as well as animal studies, with the exception of a study performed by Ng et al. (51), which did not find decreased synchronicity with advanced age (27, 38, 53, 57, 68).

Several possible explanations for a decreasing extent of synchronicity with advancing age have been suggested previously. A study by Kitzman et al. (35) demonstrated age-related alterations in left ventricular diastolic function as an intrinsic biologic effect of aging, irrespective of other physiologic and pathologic changes that frequently accompany the aging process such as hypertension, coronary artery disease, and diabetes. Others (38, 68) described an age-associated increase in the dynamic stiffness of the left ventricle in addition to prolonged contraction duration due to a slower removal of calcium from the contractile proteins, independent of myocardial catecholamine content. In the elderly, delayed myocardial contraction and dys synchrony may result from myocardial fibrosis. Especially in hypertensive patients with silent ischemia or infarction, potentially contributing to further electromechanical uncoupling (42). Importantly, increased ventricular dyssynchrony and prolonged duration of contraction may impinge on early diastolic relaxation through increased postsystolic shortening and dys coordinate myocardial strain (62).

**Study limitations.** A technical limitation is that speckle-tracking echocardiography is dependent on frame rate, as well as image resolution and image quality. Low frame rates result in a too high frame to frame change of the speckle pattern, which prevents the precise characterization of regional myocardial deformation. However, since in this study we are primarily interested in time to reach peak strain, low frame rates only result in less resolution of the timing values but not in incorrect estimation. The optimal frame rate for precise detection of myocardial deformation has been reported to be ~70–100 Hz (23, 36, 40, 63). We used custom-made software that is not commercially available. The custom-made software was specially developed to improve the reliability of timing and peak estimations by averaging strain curves, as well as to include peak systolic strain measurements that occur (shortly) before aortic valve closure. This custom made software uses Q-Q intervals instead of the R-R interval used by commercially available software. Although the custom-made software is not commercially available, this method can be implemented in generally available software such as Matlab (see APPENDIX for instructions). However, when the strain curves are not averaged before calculating maximum strain and the time to reach these values, but the timing parameters are calculated from the individual curves and are averaged afterwards, similar values will be obtained. Comparison with an independent external technique, such as tagged MRI, was not performed in the

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**Table 6. Coefficient of determination \( R^2 \)**

<table>
<thead>
<tr>
<th>Predictor Outcome Variable Corrected for Heart Rate</th>
<th>Age</th>
<th>BSA</th>
<th>BMI</th>
<th>LV Mass/BSA</th>
<th>LVIDs</th>
<th>LVESV</th>
<th>ESWS</th>
<th>QRS Duration</th>
<th>QTc</th>
<th>Syx/BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diff. Sep-Lat S-L/R-R</td>
<td>0.45a</td>
<td>0.28a</td>
<td>0.26a</td>
<td>0.15b</td>
<td>0.18b</td>
<td>0.20b</td>
<td>0.01</td>
<td>0.12b</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>SD T2P S-L/R-R</td>
<td>0.40a</td>
<td>0.30a</td>
<td>0.21a</td>
<td>0.12b</td>
<td>0.24b</td>
<td>0.27b</td>
<td>0.04b</td>
<td>0.13b</td>
<td>0.04b</td>
<td>0.07b</td>
</tr>
<tr>
<td>SD T2P S-RP/R-R</td>
<td>0.49d</td>
<td>0.36d</td>
<td>0.26d</td>
<td>0.14d</td>
<td>0.23d</td>
<td>0.23d</td>
<td>0.01</td>
<td>0.15d</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>SD T2P S-RM/R-R</td>
<td>0.42d</td>
<td>0.22d</td>
<td>0.13d</td>
<td>0.14d</td>
<td>0.20d</td>
<td>0.13d</td>
<td>0.01</td>
<td>0.14d</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>SD T2P S-CP/R-R</td>
<td>0.33d</td>
<td>0.23d</td>
<td>0.13d</td>
<td>0.08d</td>
<td>0.17d</td>
<td>0.14d</td>
<td>0.01</td>
<td>0.17d</td>
<td>0.03d</td>
<td>0.03d</td>
</tr>
<tr>
<td>SD T2P S-CM/R-R</td>
<td>0.42d</td>
<td>0.34d</td>
<td>0.29d</td>
<td>0.24d</td>
<td>0.34d</td>
<td>0.32d</td>
<td>0.01</td>
<td>0.15d</td>
<td>0.04b</td>
<td>0.05b</td>
</tr>
</tbody>
</table>

Each \( R^2 \) is based on the linear model that uses all subjects with known values for the predictor used in that particular model. LVIDs, left ventricular end-diastolic volume; ESWS, end-systolic wall stress. All outcome variables are corrected for heart rate by dividing the timing measurements by the square root of the R-R interval of that particular subject. *\( P < 0.05; \) **\( P < 0.01; \) ***\( P < 0.001; \) ****\( P < 0.0001.\)
current study, primarily because the validation of speckle-tracking software has already been compared with MRI previously with excellent results (8, 19). In addition, the frame rate of tagged MRI cannot be as high as in echocardiography, which is of importance in children in whom heart rate is higher compared with adults. Furthermore, in the case of (young) children it often indicates a need for sedation and anesthesia, which might influence the established exam results. Further prospective studies are needed to compare the usefulness and prognostic value of dyssynchrony quantification through 2DSTE in children.

Conclusion. The present study provides reference values for timing of deformation assessed with 2DSTE in children and young adults. Our findings indicate that aging resulted in a decrease of synchronicity of left ventricular systolic deformation. The results of the present study should be further used to assess mechanical dyssynchrony in children with various (non-)cardiac conditions. Since the currently used selection criteria for CRT appear not very suitable for application in the pediatric age groups, it is possible that 2DSTE indexes could provide valuable additional information on myocardial synchrony and systolic function, which could be of assistance in selecting patients which could benefit from CRT.

APPENDIX

Three consecutive cardiac cycles were analyzed. Results from all views and segments were separately digitally stored into text files on the local hard drive of the GE workstation (with disabled drift compensation). The data files then were exported from the system and stored on the network for further analysis in a custom-made software package “CardiacCurveAnalysisTool” (CCAT) using Matlab version 7.4.0.287 (r2007a). Custom-made software: step-by-step: 1) automatic load of the three consecutive cardiac cycles results; 2) update sampling (cubic spline) to 2,000 samples per cardiac cycle (to be able to select precise time stamps for the QQ-definition); 3) interactive QQ-onset defining (on the three consecutive cardiac cycles); 4) curve length check (if length difference is >10%; then delete longest cycle); 5) deletion data of before and after the selected QQ timestamps; 6) padding zeros (NaN’s) at the end of the diastolic phase for the shortest cycles (to generate equal data lengths); 7) drift compensation [using Matlab detrend (linear) function]; 8) curve averaging (using Matlab mean function); 9) maximum detection; and 10) estimation of averaged peak values per segment.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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