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Measures of dyssynchrony in the left ventricle of healthy children and young patients with dilated cardiomyopathy

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Abstract

Background—Doppler tissue imaging (DTI) may help identify children with dyssynchrony who could benefit from resynchronization therapy. However, few studies have quantified dyssynchrony measures in children, no study has investigated the relationship between age, heart rate and dyssynchrony measures in children, and no study has quantified cross-correlation delay in children. We *hypothesized* that measures of left ventricular dyssynchrony would correlate with age primarily due to correlation between heart rate and age, and that children with cardiomyopathy would have left ventricular dyssynchrony.

Methods—Sixty healthy children and 11 children with dilated cardiomyopathy were prospectively enrolled. Seven dyssynchrony measures were quantified: septal-lateral delay (SLD), peak velocity difference (MaxDiff), SD of times-to-peak in 12 segments in systole (Ts-SD) and diastole (Te-SD), and cross-correlation delay in systole (XCD_{systole}), diastole (XCD_{diastole}) and the whole-cycle (XCD_{whole}).

Results—The 7 dyssynchrony measures were either *not* correlated with age or only weakly correlated with age after correcting for heart rate using Bazett's formula. SLD, MaxDiff and Ts-SD showed dyssynchrony in 57–85% of normals compared to 20% for XCD_{whole} and 3% for Te-SD. XCD_{systole}, XCD_{diastole}, XCD_{whole}, and Te-SD were elevated in children with dilated cardiomyopathy compared to controls.

Conclusion—Echocardiographic dyssynchrony measures should be corrected for heart rate using Bazett's formula in children. Time-to-peak DTI dyssynchrony measures classify many healthy children as having an abnormality with the timing of left ventricular contraction, which suggests the methodology is not accurate in children. In preliminary studies, cross-correlation dyssynchrony measures show elevated systolic and diastolic measures of dyssynchrony in children

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with dilated cardiomyopathy compared to controls, which deserves further investigation to help identify children who may benefit from resynchronization therapy.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a class 1A treatment for adults with stable, New York Heart Association (NYHA) class III/IV heart failure with prolonged QRS duration and low left ventricular ejection fraction (EF) despite optimal medical therapy.[1] The success of CRT in adults has led to children with heart failure undergoing CRT.[2–4] However, criteria for selecting children who will most likely benefit from CRT are not yet well-defined. The few pediatric patients who have received and benefitted from CRT differ substantially from adults who receive CRT in their etiology (71% had congenital heart disease), symptoms (only 38% were NYHA class III/IV), and objective ventricular measures (only 54% had an EF $\geq$ 35% and a QRS duration $\geq$ 120ms).[2] Thus, adult criteria for CRT implantation are not likely to apply to pediatric patients.

Doppler tissue imaging (DTI) has been used in adult patients with heart failure to diagnose left ventricular (LV) dyssynchrony, which is thought to be the primary therapeutic target of CRT.[5] Thus, DTI may likewise play an important role in the development of criteria to select children for CRT.[6] In fact, DTI has already been used in multiple studies to identify dyssynchrony in children with heart disease.[7–14]

However, only two studies have reported normal ranges of DTI dyssynchrony measures in large, prospective groups of normal children.[11, 15] Studies using DTI in adults have largely ignored effects of heart rate on DTI dyssynchrony measures, and no study has investigated the relationship between age, heart rate and measures of LV dyssynchrony in normal children. Additionally, no study has reported normal ranges of cross-correlation delay (XCD) in healthy children, which is a new DTI dyssynchrony measure that has shown promise in adults[16], and therefore should be evaluated in children. Moreover, recent reports have shown that DTI dyssynchrony measures may be falsely abnormal in a large proportion of normal adults[17], and have poor reproducibility and controversial utility in predicting response to CRT[18], which may limit their utility in children.

Thus, our objectives were to 1) investigate the relationship between age, heart rate and measures of LV dyssynchrony in a large, prospective cohort of normal children; 2) report normal values including estimates of reproducibility for XCD parameters in normal children; and 3) quantify measures of dyssynchrony in a group of children with dilated cardiomyopathy for comparison to the normal subjects. We *hypothesized* that 1) measures of left ventricular dyssynchrony would correlate with age due primarily to the correlation between heart rate and age in children and 2) children with dilated cardiomyopathy have left ventricular dyssynchrony as quantified with XCD.

METHODS

The study was approved by the Institutional Review Boards of Emory University and Children's Healthcare of Atlanta. All subjects and their parents provided informed consent/assent.

Normal controls

Sixty healthy children ranging in age from 0–18 years were prospectively recruited by our research nurses through word of mouth and recruitment flyers and were *not* referred for routine echocardiography. Inclusion criteria were: (1) age 0–18 years (2) QRS duration less than 95th percentile on standard 12-lead electrocardiogram and (3) no history of heart

disease. Exclusion criteria included: (1) structural abnormality or abnormal function on echocardiogram, (2) history of systemic hypertension, metabolic, genetic, neuromuscular or lung disorders, and (3) history of any rhythm abnormality.

Patients with dilated cardiomyopathy

Eleven children with dilated cardiomyopathy were prospectively recruited to participate in the study for comparison to the normal controls. Inclusion criteria were: (1) age 0 – 18 years and (2) diagnosis of dilated cardiomyopathy by the patient's attending physician. Patients were excluded if they had a history of heart surgery or congenital heart disease. We defined cardiomyopathy as an enlarged ventricle (Z-score >2) with decreased ventricular function (fractional shortening <28%) without anatomical or other known cause such as coarctation, aortic stenosis, history of congenital heart disease or heart surgery or suspected myocarditis.

DTI data acquisition

Apical 2-, 3- and 4-chamber DTI of the myocardium was acquired using a 5S or M3S probe (Vivid 7, GE Vingmed, Horten, Norway) as appropriate for patient size. The myocardial walls were aligned parallel to the Doppler beam to minimize the angle of insonation, and frame rate was optimized to a minimum of 100 Hz. Pulsed Doppler images of the aortic outflow tract were acquired to enable definition of systole during post-processing. All studies were done *without* the use of sedation, and images were acquired during end-expiration when possible.

DTI dyssynchrony measures

Postprocessing software (EchoPAC PC, Version 6.0.0, GE Vingmed) was used to export velocity curves from the DTI data for calculation of 7 published dyssynchrony measures:

Systolic dyssynchrony measures

1. basal septal-to-lateral delay in time-to-peak systolic velocity (SLD)[19]
2. maximum difference in times-to-peak systolic velocity between any 2 of the basal septal, lateral, anterior and inferior LV segments (MaxDiff)[20]
3. the standard deviation (SD) of times-to-peak systolic velocity in the 12 basal and mid-wall segments of the LV (Ts-SD)[21]
4. systolic cross-correlation delay ($XCD_{systole}$)[22]

Diastolic dyssynchrony measures

1. the standard deviation of times-to-peak diastolic velocity in the 12 basal and mid-wall segments of the LV (Te-SD)[23]
2. diastolic cross-correlation delay ($XCD_{diastole}$)[22]

Whole cycle dyssynchrony measure

1. whole cycle cross-correlation delay (XCD_{whole})[16]

Quantification of XCD_{whole} , $XCD_{systole}$ and $XCD_{diastole}$ have been described previously. [16, 22] Figure 1 shows an example calculation of these cross-correlation parameters for a set of velocity curves from a child with dilated cardiomyopathy. Briefly, a cross-correlation function was used to calculate the time delay which resulted in maximum correlation between velocity curves from opposing ventricular segments. One velocity curve was shifted relative to the other curve, and the normalized cross-correlation value was computed for each time shift (the normalized correlation coefficient ranges from 1 = perfect synchrony

to (-1) = perfect dyssynchrony). The time shift between the two curves resulting in the maximum correlation value was defined as the cross-correlation delay (XCD) between the two curves. The entire velocity curves were used to calculate XCD_{whole} while the systolic (from mitral valve closure to aortic valve closure) and diastolic (from aortic valve closure to mitral valve closure) portions, respectively, were used to calculate XCD_{systole} and XCD_{diastole} .

Regions of interest were sized to encompass the entire LV segment of interest which has previously been shown to minimize variability.[24] An average velocity curve was generated from three cardiac cycles of velocity data prior to quantifying the measures of dyssynchrony. This averaging was done with the cine-compound function in the EchoPAC software to improve the signal-to-noise ratio of the extracted velocity curves.[25] All velocity data was exported using stationary regions of interest. Pulsed Doppler of the aortic outflow tract was used to define systole for identification of the peak systolic velocity.

Times-to-peak systolic velocities were automatically identified by a computer program written in MATLAB quantitative analysis software (Version 7.10, MathWorks Inc, Natick, MD). This program imported velocity curves and valve timings from the echocardiogram postprocessing software (EchoPAC PC, Version 6.0.0, GE Vincmed) and exported the time from the Q wave to the maximum velocity in the ejection phase. Peaks were checked by an expert observer to ensure accuracy.

Relationship between age, heart rate and measures of dyssynchrony

The relationship between each dyssynchrony measure and age was determined with a Pearson's linear correlation coefficient. A value of $p < 0.05$ was considered a statistically significant correlation. This correlation was explored using both raw data and data corrected for heart rate according to Bazett's formula[26–28]:

$$Dyssynchrony_{\text{corrected}} = \frac{Dyssynchrony_{\text{uncorrected}}}{\sqrt{RR}} \quad (1)$$

where “ $Dyssynchrony_{\text{corrected}}$ ” is the final corrected value in milliseconds for each dyssynchrony measure for a given volunteer, “ $Dyssynchrony_{\text{uncorrected}}$ ” is the dyssynchrony measure in milliseconds derived from that individual volunteer for the dyssynchrony measure of interest, and RR is the time in seconds between two consecutive electrocardiogram R waves.

Comparison between normal controls and patients with dilated cardiomyopathy

Each of the 7 DTI dyssynchrony measures was quantified in the 60 normal controls and the 11 patients with dilated cardiomyopathy. Mean values for each of the 7 dyssynchrony measures was compared between the normal controls and patients with dilated cardiomyopathy using an unpaired student's t-test. A value of $p < 0.05$ was considered statistically significant.

Thresholds to diagnose dyssynchrony

Published adult threshold values were investigated to determine the percentage of both normal children and patients with dilated cardiomyopathy who had values for dyssynchrony measures above levels considered to be diagnostic of dyssynchrony in adult patients. The threshold values were defined as:

1. SLD above 60 milliseconds[19]
2. MaxDiff above 65 milliseconds[29]

3. Ts-SD above 34.4 milliseconds[30]
4. Te-SD above 34 milliseconds[31]
5. XCD_{whole} above 31 milliseconds[16]

Note that XCD_{systole} and XCD_{diastole} do not have published thresholds considered to be diagnostic of dyssynchrony, so these parameters were excluded from this analysis.

Interobserver reproducibility

Interobserver reproducibility was performed on 12 randomly selected echocardiograms by two independent observers. Reproducibility was displayed graphically with Bland-Altman plots. A coefficient of variation (CoV) was calculated for each dyssynchrony measure using the following equation:

$$CoV = \frac{\overline{\sigma_i}}{M} \quad (2)$$

$$\overline{\sigma_i} = \frac{\sum_{i=1}^{12} \sqrt{\frac{D_{i,1} + D_{i,2}}{2}}}{12} \quad (3)$$

where $\overline{\sigma_i}$ is the mean standard deviation defined by equation 3, M is the group mean dyssynchrony for all 24 calculations (two calculations from each observer for each of the 12 studies), $D_{i,1}$ is the value calculated by observer number 1 on subject i , and $D_{i,2}$ is the value calculated by observer number 2 on subject i .

Additionally, Cronbach's alpha was calculated as a measure of inter-observer reliability as follows[32]:

$$\alpha = 2 \cdot \left(1 - \frac{\sigma_A^2 + \sigma_B^2}{\sigma^2(m_i)} \right) \quad (4)$$

where σ_A^2 = the variance of the 12 measurements (on 12 different patients) performed by observer "A", σ_B^2 = the variance of the 12 measurements performed by observer "B", $\sigma^2(m_i)$ = the variance of the sum of the measurements done for each of the 12 patients where $m_i = m_A + m_B$ = the sum of the measurements done by each observer on subject i .

RESULTS

Basic characteristics of the normal controls and patients with dilated cardiomyopathy are shown in Table 1. The patients with dilated cardiomyopathy had significantly reduced left ventricular ejection fraction and increased heart rate with no significant difference in age or QRS duration. Etiology of the cardiomyopathy in the patients included idiopathic (8 patients), metabolic (1 patient), neuromuscular (1 patient), and chemotherapy-induced (1 patient). Most of the patients (7/11) were enrolled within 2 months of diagnosis and most (8/11) were symptomatic and hospitalized. All patients were receiving therapy for heart failure.

Relationship between age, heart rate and dyssynchrony

A significant positive correlation was found between age and 6 of the 7 measures of dyssynchrony when using data *not* corrected for heart rate (Figure 2 and Table 2). No

significant correlation was found between age and 5 out of the 7 DTI measures of dyssynchrony after correcting for heart rate using Bazett's formula (Figure 3 and Table 2). After correcting for heart rate, MaxDiff showed a weak, positive correlation with age ($R = 0.38$). Similarly, XCD_{systole} showed a weak, positive correlation with age after correcting for heart rate ($R = 0.35$).

Comparison between normal controls and patients with dilated cardiomyopathy

Systolic dyssynchrony measures—The systolic time-to-peak dyssynchrony measures SLD, MaxDiff and Ts-SD were similar in the controls and the patients with dilated cardiomyopathy (Figure 4 and Table 3). However, XCD_{systole} was significantly prolonged in the patients with dilated cardiomyopathy.

Whole-cycle dyssynchrony measure— XCD_{whole} was significantly prolonged in the patients with dilated cardiomyopathy compared to the controls (Figure 4 and Table 3).

Diastolic dyssynchrony measures—Both diastolic measures of dyssynchrony (Te-SD and XCD_{diastole}) were significantly prolonged in the patients with dilated cardiomyopathy compared to the controls (Figure 4 and Table 3).

Relationship between QRS duration and measures of dyssynchrony in children with dilated cardiomyopathy

XCD_{whole} correlated positively ($p = 0.006$, $R = 0.77$) with QRS duration in the children with dilated cardiomyopathy (Figure 5). No other parameters showed a significant correlation.

Thresholds to diagnose dyssynchrony

Between 57 and 85% of the normal controls had values above adult thresholds for diagnosing dyssynchrony according to the time-to-peak parameters SLD, MaxDiff and Ts-SD (Figure 6 and Table 3). These percentages were similar in the patients with dilated cardiomyopathy (64–91%). Only 3% of the normal controls had diastolic dyssynchrony quantified by Te-SD compared to 64% of the patients with dilated cardiomyopathy. Finally, 20% of the normal controls had whole-cycle dyssynchrony as quantified by XCD_{whole} compared to 82% of the patients with dilated cardiomyopathy. Velocity curves from a representative normal control are shown in Figure 7.

Interobserver reproducibility

Coefficients of variation for two independent observers quantifying the 7 dyssynchrony measures in 12 randomly selected echocardiograms ranged from 13 to 30% (Table 4). Bland-Altman limits of agreement are shown graphically in Figure 8. Additionally, Cronbach's alpha values ranged from a minimum of 0.64 for Ts-SD to 0.95 for XCD_{whole} and were higher in general for the three XCD parameters.

DISCUSSION

The major findings of this study include: 1) DTI measures of dyssynchrony are either *not* correlated with age or very weakly correlated with age after correcting for heart rate using Bazett's formula; 2) Over half of normal children are classified as having dyssynchrony according to published adult threshold values for time-to-peak DTI dyssynchrony parameters, suggesting that this methodology should be used with extreme caution in pediatrics due to potential inaccuracies; 3) In Preliminary studies, systolic, diastolic and whole-cycle cross-correlation delay (XCD) parameters are elevated in children with dilated cardiomyopathy compared to normal controls; 4) DTI measures of dyssynchrony show

limited inter-observer reproducibility in children, with coefficients of variation ranging from 13 to 30%.

Relationship between age, heart rate and measures of dyssynchrony

While previous studies have corrected dyssynchrony measures for heart rate using Bazett's formula, this is the first study to show that correcting dyssynchrony measures in children for heart rate according to Bazett's formula is necessary to facilitate comparisons across different age groups. Six of the seven measures of dyssynchrony were positively correlated with age prior to correcting for heart rate. After correcting for heart rate, these correlations were either eliminated (in 4 parameters) or reduced to a level that is clinically insignificant (in 2 parameters).

Our results are similar in concept to a study on 593 healthy children published by Cui et al. [33] The authors found that the DTI-derived uncorrected values of isovolumic contraction time, isovolumic relaxation time and Tei index all correlated with age. However, after correction for heart rate using Bazett's formula, these timing parameters were *not* correlated with age, similar to what we have shown with dyssynchrony measures. Importantly, of the 7 published studies we identified which quantify DTI dyssynchrony measures in healthy children or children with dilated cardiomyopathy, none of these studies corrected for heart rate using Bazett's formula (Tables 5 and 6). It is also notable that the larger mean values observed in our study compared to those in Tables 5 and 6 are at least in part due to correction for heart rate (The mean heart rates in our normal controls and patients with dilated cardiomyopathy were 97 and 121 beats per minute, respectively. Any dyssynchrony measure derived during a heart rate above 60 beats per minute will be prolonged when corrected using Bazett's formula).

Systolic “dyssynchrony” in healthy children

We have been careful to use the terminology “dyssynchrony measures” in our manuscript to describe a methodology for measuring regional heterogeneity in the timing of contraction or relaxation in the heart. We believe the word “dyssynchrony” alone is a diagnosis which should be defined as having a value for a dyssynchrony measure above a certain diagnostic or predictive threshold. Our results suggest that over half of healthy children have systolic “dyssynchrony” according to published adult thresholds for time-to-peak DTI dyssynchrony parameters (SLD, MaxDiff and Ts-SD). We believe this is mostly due to inaccuracies in the dyssynchrony parameters and does *not* suggest that normal children actually have dyssynchrony.

Our results are consistent with a study by Misra *et al* showing that roughly 40% of children had “dyssynchrony” when using the Ts-SD parameter.[15] One possible explanation for this result is that children have different levels of left ventricular dyssynchrony measures compared to adults. However, this conclusion is refuted by our data showing no relationship between dyssynchrony measures and age from infancy (age 0) to young adulthood (age 18). Additionally, between 40 and 68% of healthy adults have been shown to have dyssynchrony according to established threshold values for DTI time-to-peak dyssynchrony parameters. [17] Thus, the more likely explanation is that DTI time-to-peak dyssynchrony measures are not accurate.[34] A good example of this inaccuracy is shown in Figure 7 where, despite the velocity curves appearing synchronous in a normal control, the peak systolic velocity in the basal septum and lateral wall occur at very different times.

Cross-correlation measures of dyssynchrony

While most DTI dyssynchrony measures utilize “time-to-peak” analysis to quantify timing differences based on the dispersion of the timing of peak velocities throughout different

parts of the ventricle, cross-correlation dyssynchrony measures utilize all the points on the velocity curves. XCD measures were more accurate than time-to-peak DTI dyssynchrony measures in one study in adults.[16] Twenty percent of normal children in the current study had dyssynchrony according to the published adult threshold of 31 ms, which was significantly lower than the rates of 57–85% seen for the time-to-peak parameters. Thus, XCD may have promise in diagnosing dyssynchrony in children. However, further studies will be needed to determine the utility of XCD in this area and to define the “best” method for evaluating wall timing and diagnosing dyssynchrony in children.

It is notable that XCD is not limited to a specific imaging modality, and has in fact been shown to be more accurate than time-to-peak analysis when applied to other imaging modalities, including cardiac magnetic resonance imaging (MRI).[35] Additionally, XCD has been used by other groups to quantify mechanical dyssynchrony using DTI[36] and speckle-derived strain[37].

Measures of systolic dyssynchrony in children with dilated cardiomyopathy

Our results are conflicting on whether children with dilated cardiomyopathy suffer from systolic dyssynchrony. The time-to-peak systolic dyssynchrony measures showed no difference between children with dilated cardiomyopathy and normal controls, while $XCD_{systole}$ was significantly prolonged in the patients with dilated cardiomyopathy. Published studies comparing dyssynchrony using DTI in normal children and children with dilated cardiomyopathy have also shown conflicting results (Table 6). For example, Friedberg *et al* showed that Ts-SD was increased in children with dilated cardiomyopathy compared to normal controls, while SLD was similar between the two groups.[11] Similar discrepancies exist in the adult literature. For example, Lafitte *et al* evaluated six time-to-peak dyssynchrony measures in adults undergoing resynchronization therapy and showed that these parameters agreed on the diagnosis of dyssynchrony in only half of the patients.[38] Future studies will need to define a gold standard method for diagnosing dyssynchrony in children in order to resolve this discrepancy.[39]

Diastolic measures of dyssynchrony in children with dilated cardiomyopathy

Both measures of diastolic dyssynchrony (time-to-peak parameter Te-SD and $XCD_{diastole}$) were significantly elevated in the patients with dilated cardiomyopathy. Only 3% of the healthy controls in our study had diastolic dyssynchrony according to adult threshold values, consistent with a level of 2% reported by Friedberg *et al*. [11] Additionally, the percentage of patients with diastolic dyssynchrony found in our study according to Te-SD (64%) was identical to that reported by Friedberg *et al*. [11] This suggests that diastolic dyssynchrony is common in children with dilated cardiomyopathy. However, there is conflicting evidence in the literature on this topic also due to a previous study showing no difference in diastolic dyssynchrony measures between normals and children with dilated cardiomyopathy.[13] Thus, future work with larger numbers of patients will need to address this discrepancy.

Reproducibility

Poor reproducibility has been a significant problem for DTI dyssynchrony measures in the adult literature, as evidenced by the results of the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study.[18] It is therefore extremely important to document reproducibility of these measures in children prior to using them in the clinical setting. Unfortunately, of the 7 studies shown in Tables 5 and 6 using DTI dyssynchrony measures in children, only two of them quantified reproducibility.

To facilitate comparison with published studies, we quantified both coefficients of variation and Cronbach's α between two independent observers for each dyssynchrony measure.

XCD parameters were highly reproducible with Cronbach's α all 0.88. Ts-SD had particularly poor reproducibility with a Cronbach's α equal to 0.64, which is consistent with the value of 0.69 published by Friedberg *et al.*[11] The coefficients of variation for Ts-SD and MaxDiff in adults enrolled in PROSPECT were 33.7% and 31.9%, respectively. These values were better in our study at 13% and 16%, respectively, likely due to the fact that the two observers measuring data from our study were from the same institution while those in PROSPECT were at different institutions. SLD had the highest coefficient of variation in our study equal to 30% mostly due to problems with high variability in identification of the peak systolic velocity, which have been discussed extensively in the literature.[24, 40]

It is worth noting that XCD parameters are calculated automatically from DTI velocity curves, yet had similar coefficients of variability compared to the time-to-peak parameters. This is likely due to the fact that all DTI parameters, including XCD, require manual placement of regions of interest from which most of the variability likely arises. Future techniques to reduce this variability are needed. However, XCD did show values for Cronbach's α (another estimate of reproducibility) all close to or greater than 0.9, which is considered excellent reliability.

Future directions

Cardiac resynchronization therapy has been a highly successful treatment in adults with heart failure[1], and has shown promise in helping children with heart failure.[2–4] However, translating this therapy carefully into pediatrics requires 1) better methodologies for diagnosing dyssynchrony with both high accuracy and reproducibility in children and 2) a better understanding of the role of dyssynchrony in children with heart disease. The relationship between dyssynchrony and mortality in pediatric patients needs to be investigated in order to determine whether dyssynchrony is an important therapeutic target. Additionally, studies to address the discrepancies among methods used to diagnose dyssynchrony need to be completed.

Limitations

Additional methods for diagnosing dyssynchrony in children using echocardiography include 3-dimensional echocardiography and speckle tracking, which we did not utilize in our study. However, 3-dimensional echocardiography has already shown limitations in its ability to quantify dyssynchrony in adults with heart failure[41], and speckle tracking may have worse reproducibility than DTI dyssynchrony parameters.[42] Thus, future studies investigating these methods in children may be warranted, but will need to document feasibility and reproducibility. When discussing the quantification and reproducibility of measures of dyssynchrony from tissue Doppler versus speckle tracking, it is prudent to note: 1) tissue Doppler directly measures velocity; 2) speckle tracking directly quantifies displacement from which strain can be derived as a spatial derivative and velocity can be derived as a derivative in time; 3) derivatives amplify noise[43]. Thus, theoretically tissue Doppler should have less noise when quantifying velocity-based measures of dyssynchrony since no derivatives are required.

No threshold values exist for diagnosing dyssynchrony using $XCD_{systole}$ or $XCD_{diastole}$. We could have derived threshold values for these indices from the mean plus 2*SD of the normal controls in our study. However, determining thresholds using this analysis assumes that the two distributions of normals and patients with dyssynchrony are almost entirely non-overlapping, which may not be true. We believe that threshold values should be determined from carefully defined positive and negative control studies where the underlying state of dyssynchrony is known and controlled experimentally.

This study is a single-center, prospective study which utilized only one echocardiographic platform (GE Vivid 7). Inter-institutional studies utilizing multiple platforms to document feasibility and reproducibility of echocardiographic measures of dyssynchrony in children will be important in the future. Additionally, we included a small number of pediatric patients with dilated cardiomyopathy (11), and larger groups of patients from multiple centers should be studied in the future.

Threshold values from adult studies were not corrected for heart rate according to Bazett's formula prior to testing these threshold values in normal children. Correcting dyssynchrony measures for heart rate has likely been ignored in adult studies due to the fact that adults have heart rates close to 60 beats per minute which has no effect when normalizing measures using Bazett's formula. Only one of the studies[31] which define threshold values reported heart rates (mean of 70.5 beats per minute). If we were to correct the adult threshold values for this mean heart rate of 70, the threshold values would change by a factor of 0.93 (7%) and only change the classification of two normal subjects: one for MaxDiff and one for XCD_{whole}. It is also important to note that there are other published methods for correcting for heart rate, including expressing dyssynchrony measures as a percentage of the RR interval. However, we chose to use Bazett's formula for two reasons: 1) it is the most common method in the literature and 2) as discussed above, using Bazett's formula facilitates comparisons with adult values which are minimally affected by this correction due to heart rates being close to 60.

This study did not define values of dyssynchrony for predicting response to CRT in children. The fact that time-to-peak measures of dyssynchrony are high in normal children suggests these parameters will unlikely be useful in predicting response to CRT in children. Due to the fact that XCD parameters were low in normal controls and elevated in children with dilated cardiomyopathy suggests that XCD may play a role in future studies attempting to predict response to CRT using DTI.

Conclusions

Dyssynchrony measures quantified using Doppler tissue imaging in children should be corrected for heart rate according to Bazett's formula. Many healthy children have are classified as having systolic "dyssynchrony" using time-to-peak parameters and published adult threshold values, so this methodology is likely inaccurate in children. In preliminary studies, cross-correlation delay parameters show elevations in systolic and diastolic measures of dyssynchrony in children with dilated cardiomyopathy, which deserves further investigation to help identify children who may benefit from cardiac resynchronization therapy.

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Figure 1.

Example calculation of cross-correlation delays (XCD). A) Velocity curves from the septum and lateral wall of a patient with dilated cardiomyopathy. Valve timings including aortic valve opening (avo), aortic valve closure (avc), mitral valve opening (mvo) and mitral valve closure (mvc) are shown. B) The cross-correlation spectrum for XCD using the entire velocity curves from (A). C) The cross-correlation spectrum for XCD using just the systolic portion of the velocity curves in (A) from mvc to avc. D) The cross-correlation spectrum for XCD using just the diastolic portion of the velocity curves in (A) from avc to mvc.

Figure 2.

Prior to normalization, 6 of the 7 DTI dyssynchrony parameters are strongly correlated with age.

Figure 3.

After correcting for heart rate using Bazett's formula, DTI dyssynchrony parameters are either uncorrelated or only weakly correlated with age.

Figure 4.

Time-to-peak systolic dyssynchrony parameters show no difference between children with dilated cardiomyopathy (DCM) and healthy controls. However, XCD parameters and Te-SD show significantly increased systolic, diastolic and whole-cycle dyssynchrony in children with DCM.

Figure 5.
In the children with dilated cardiomyopathy, QRS duration correlated with XCD_{whole}.

Figure 6.

When using published adult threshold values for diagnosing dyssynchrony, over half of normal, healthy children have likely inaccurate “dyssynchrony” according to time-to-peak DTI dyssynchrony parameters, while only 3% have diastolic dyssynchrony by Te-SD and 20% have dyssynchrony by XCD_{whole}.

Figure 7.

Doppler tissue velocity curves from the basal septum and lateral wall of a representative normal control show dyssynchrony according to the time-to-peak parameters SLD (142ms), MaxDiff (137ms) and Ts-SD (78ms) while Te-SD (15ms) and XCD_{whole} (11ms) were normal. Note that MaxDiff is slightly less than SLD due to differences in the mean heart rate correction for MaxDiff which utilizes two different echocardiographic images (with two potentially slightly different heart rates). Peak systolic and diastolic velocities are marked with black circles. Doppler-derived valve timings are shown with vertical dashed lines (avo = aortic valve opening; avc = aortic valve closure; mvo = mitral valve opening; mvc = mitral valve closure).

Figure 8. Bland-Altman limits of agreement (mean $\pm$ 2*SD) for the 7 dyssynchrony parameters calculated independently by two observers for 12 randomly-selected echocardiograms.

Table 1

Basic characteristic of the normal controls and patients with dilated cardiomyopathy

Variable (units)	Normal Controls (n = 60)			Dilated Cardiomyopathy (n = 11)			p
	Mean	Range		Mean	Range		
Age (years)	6.8 ± 6	0.02 – 18		5.7 ± 6	0.02 – 16		0.58
Male gender (%)	35 (58%)	–		7 (64%)	–		0.33
Heart rate (beats per minute)	97 ± 25	51 – 183		121 ± 28	75 – 157		0.02
QRS duration (ms)	75 ± 11	48 – 94		96 ± 42	65 – 218		0.13
Left ventricular ejection fraction (%) *	57 ± 7	39 – 76		24 ± 9	13 – 38		<0.001
Left ventricular fractional shortening (%) *	33 ± 4	28 – 44		9 ± 4	4 – 17		<0.001
DTI frame rate (frames per second)	150 ± 8	100 – 155		145 ± 9	124 – 154		0.07

Values are means ± SD. Ventricular volumes and ejection fractions derived from Simpson's biplane analysis. P values comparing the two groups are from unpaired t-tests.

* Could not be calculated for 4 of the controls and 2 of the patients with dilated cardiomyopathy due to accidental loss of data which occurred *after* quantification of dyssynchrony parameters.

Table 2

Correlation between age and dyssynchrony in the uncorrected data and the data corrected for heart rate using Bazett's formula (equation 1)

Variable	Uncorrected		Corrected	
	R	p	R	p
SLD	0.30	0.018	0.20	0.123
MaxDiff	0.55	<0.001	0.38	0.003
Ts-SD	0.30	0.021	-0.02	0.876
Te-SD	0.31	0.016	0.05	0.727
XCD _{whole}	0.37	0.365	-0.08	0.556
XCD _{systole}	0.49	<0.001	0.35	0.006
XCD _{diastole}	0.30	0.019	0.05	0.722

Table 3

Mean dyssynchrony values, corrected for heart rate using Bazett's formula (equation 1), in the normal controls and patients with dilated cardiomyopathy

Variable	Normal Controls (n = 60)		Dilated Cardiomyopathy (n = 11)		p
	Mean (ms)	Above threshold (%)	Mean (ms)	Above threshold (%)	
SLD	77 ± 49	57%	88 ± 67	64%	0.55
MaxDiff	105 ± 45	78%	118 ± 50	91%	0.38
Te-SD	54 ± 16	85%	55 ± 25	82%	0.82
Te-SD	16 ± 7	3%	50 ± 30	64%	<0.001
XCD _{whole}	22 ± 13	20%	111 ± 93	82%	<0.001
XCD _{systole}	43 ± 24	*	64 ± 32	*	0.016
XCD _{diastole}	14 ± 8	*	61 ± 46	*	<0.001

* No published threshold values exist, so percentages cannot be determined. Threshold values for diagnosing dyssynchrony are as published in the adult literature and equal to 60ms for SLD, 65ms for MaxDiff, 34.4ms for Te-SD, 34ms for Te-SD and 31ms for XCD_{whole}. P values shown are for comparing the group means and were calculated with an unpaired t-test.

Table 4

Inter-observer reproducibility

Variable	Coefficient of variation	Cronbach's α
SLD	30%	0.83
MaxDiff	16%	0.87
Ts-SD	13%	0.64
Te-SD	17%	0.81
XCD _{whole}	18%	0.95
XCD _{systole}	17%	0.90
XCD _{diastole}	21%	0.88

Table 5

Comparable data from the literature for normal children

Variable	Study	Mean ($\pm$ SD)	Percent with dyssynchrony	Bazett's heart rate correction?
SLD	[11]	27 $\pm$ 24	Not done	No
	Current	77 $\pm$ 49	57%	Yes
MaxDiff	[44]	40 $\pm$ 16	Not done	No
	Current	105 $\pm$ 45	78%	Yes
Ts-SD	[15]	30 $\pm$ 15	40%	No
	[11]	26 $\pm$ 11	Not done	No [*]
	[13]	20 $\pm$ 7	Not done	No [†]
	[14]	20 $\pm$ 8	Not done	No
	Current	54 $\pm$ 16	85%	Yes
Te-SD	[11]	9 $\pm$ 4	2%	No [*]
	Current	16 $\pm$ 7	3%	Yes
XCD _{systole}	[22]	49 $\pm$ 28	N/A [‡]	No
	Current	43 $\pm$ 24	N/A [‡]	Yes
XCD _{diastole}	[22]	11 $\pm$ 13	N/A [‡]	No
	Current	14 $\pm$ 8	N/A [‡]	Yes

* Reported uncorrected values due to the fact that correcting for heart rate did not change the results (did not investigate effect of correcting for heart rate on correlation between age and dyssynchrony)

[†] Reported values corrected by dividing by R-R interval, not Bazett's formula

[‡] Threshold values for diagnosing dyssynchrony have not been published

Table 6

Comparable data from the literature for children with dilated cardiomyopathy

Variable	Study	Mean ($\pm$ SD)	Percent with dyssynchrony	Bazett's heart rate correction?	Elevated in DCM vs controls?
SLD	[11]	37 $\pm$ 40	Not done	No [*]	No
	Current	88 $\pm$ 67	64%	Yes	No
Ts-SD	[10]	45 $\pm$ 11 (QRS 120) 32 $\pm$ 9 (QRS<120)	55%	No	Not done – no control group
	[11]	43 $\pm$ 22	Not done	No [*]	Yes
	[13]	44 $\pm$ 25	Not done	No [†]	Yes
	[14]	45 $\pm$ 24	65%	No	Yes
	Current	55 $\pm$ 25	82%	Yes	No
Te-SD	[11]	28 $\pm$ 18	64%	No [*]	Yes
	[13]	26 $\pm$ 20	Not done	No [†]	No
	Current	50 $\pm$ 30	64%	Yes	Yes

^{*} Reported uncorrected values due to the fact that correcting for heart rate did not change the results (did not investigate effect of correcting for heart rate on correlation between age and dyssynchrony)

[†] Reported values corrected by dividing by R-R interval, not Bazett's formula