Prognostic Implications of the Systolic to Diastolic Duration Ratio in Children With Idiopathic or Familial Dilated Cardiomyopathy

Tapas Mondal, MD; Cameron Slorach, RCDS; Cedric Manlhiot, BSc; Wei Hui, MD; Paul F. Kantor, MBCh, DCH; Brian W. McCrindle, MD, MPH; Luc Mertens, MD, PhD; Mark K. Friedberg, MD

Background—Childhood dilated cardiomyopathy (DCM) carries high morbidity and mortality. The echocardiographic systolic to diastolic (S:D) duration ratio, an indicator of global cardiac performance, is elevated in DCM; however, its prognostic implications have not been investigated in this population.

Methods and Results—We investigated systolic and diastolic durations and the resultant S:D ratio using pulsed tissue Doppler imaging in children with idiopathic or familial DCM. We studied serial echocardiograms from presentation until the last follow-up echo. Results were compared with heart rate–matched controls and between DCM subgroups based on an acute or insidious presentation. The association between S:D ratio and death or need for transplant was analyzed. All analyses were adjusted for repeated measures per patient. We studied 200 serial echocardiograms of 48 children with DCM (7.0±6.0 years) and 25 controls. Adjusted for repeated measures through a compound symmetry covariance structure, the S:D ratio was higher in DCM patients (−0.425 [0.072]; P<0.001) because of shortened diastole. A S:D ratio >1.2 at presentation and on serial evaluation was associated with a hazard ratio of 10.5 (95% confidence interval, 3.9–27.8; P<0.001) for death or transplant. In combined multivariable analysis, a S:D ratio >1.2 remained significantly associated with hazard of death/transplant (hazard ratio, 9.1; P=0.04) after adjustment for ejection fraction (hazard ratio: 2.2 per −10%; P<0.001).

Conclusions—A high S:D ratio is associated with increased risk for death or need for transplant in children with DCM across the spectrum of heart rates and may be a useful prognostic index for serial evaluation of children with DCM.

Key Words: cardiomyopathy, dilated ■ echocardiography ■ pediatrics ■ prognosis

Clinical Perspective on p 780
The systolic to diastolic (S:D) duration ratio is an indicator of global left ventricular (LV) performance, which is elevated in cardiac dysfunction because of prolonged systolic duration and shortened diastolic duration.4 Using Doppler interrogation of mitral regurgitation (MR), we have previously demonstrated that in children with DCM, systolic duration is abnormally prolonged and diastolic duration correspondingly shortened, further compromising cardiac filling and function.4 However, the S:D ratio has not been studied in relation to transplant-free survival in this population. Accordingly, the aim of this study was to investigate the relationship of S:D ratio, as measured by tissue Doppler imaging (TDI), with the need for cardiac transplant or death in children with DCM. We hypothesized that an elevated S:D ratio is associated with increased risk for death or need for cardiac transplantation in pediatric DCM.

Methods

Patient Population
All children, 0 to 18 years of age, registered in the pediatric heart failure database with a diagnosis of idiopathic, genetic, or familial DCM and who received their initial echocardiogram at our institution...
between June 2004 (when digital echocardiography was instituted in our laboratory) and 2010 were included. Patients were eligible for inclusion if they had a dilated LV with decreased systolic function as defined by a LV end-diastolic dimension (LVEDD) z score >2 based on institutional z scores and a LV ejection fraction (EF) <50% from the biplane method of discs. Patients with structural heart disease or those who had undergone previous surgery were excluded. As the exact time of disease onset is unknown in most children, the date of the initial echocardiogram at the time of presentation to our institution was taken as the disease onset for the purposes of survival analysis. We performed offline measurements on digitally stored images from 4 serial echocardiograms for each patient: at presentation to our center, 2 intermediate follow-up studies, and the last follow-up echo or the last echo before heart transplant or death. Although there is a strong correlation between age and heart rate, some children with DCM may have heart rates that are disproportionate for age, either fast because of the disease or slow when on β-blocker therapy. Because heart rate is the main determinant of cardiac cycle intervals, controls were matched first for heart rate, then by age, then by sex. Controls consisted of children who underwent echocardiography for evaluation of a murmur or healthy volunteers in whom the medical history, physical examination, and echocardiogram were all normal.

Echocardiography
Echocardiography was performed on Philips or General Electric ultrasound systems, during quiet respiration (as breathhold is not consistently feasible in young children), using probes with frequencies appropriate for patient size. Images were obtained with simultaneous electrocardiographic tracing on the ultrasound display. Pulsed-wave TDI was obtained at the lateral mitral annulus.

S:D Ratio Measurement
Systolic and diastolic durations were measured from pulsed tissue Doppler sampled at the lateral mitral annulus (Figure 1). Systolic duration was defined as the interval from the ECG QRS onset to the end of the TDI S’ wave. Diastolic duration was defined as the remainder of the cardiac cycle (the interval between S’ termination to QRS onset in the subsequent cardiac cycle; Figure 1). Because cardiac time intervals can be measured by M-mode, we further compared intervals by TDI to those measured by M-mode where systolic duration was defined as the interval between QRS onset to aortic valve closure with the M-mode cursor placed through the aortic valve.

Statistical Analysis
Data are presented as means with SDs. Because children with DCM may present with an acute or more insidious (chronic) course and these groups may differ in their characteristics and outcomes, we further analyzed results based on an acute versus chronic presentation. An acute presentation was arbitrarily defined as a presenting history of <2 weeks of symptoms or who required mechanical ventilation or inotropic support at diagnosis. Patients with a longer and/or more gradual initial history, usually referred for outpatient evaluation, were defined as chronic presentation. The outcome for each group was determined as survival versus death or need for cardiac transplantation (acute presentation [total of 72 echocardiograms analyzed] versus chronic presentation [110 echocardiograms analyzed]). Linear regression models adjusted for repeated measures per patient using a compound symmetry covariance structure, with the study group as the independent variable modeled as a categorical variable, were used to assess the difference in mean echocardiographic values between the 2 subgroups and to test the association between functional echo parameters and outcome. The F test was used to determine the statistical significance of group effect. The association between heart rate and S:D ratio, and between other clinical or echo parameters and S:D ratio, was assessed by linear regression models adjusted for repeated measures per patient using a compound symmetry covariance structure. These associations are expressed as parameter estimates and SE, where the parameter estimates expresses the magnitude and direction of change in the dependent variable for each unit change in the independent variable. Independent variables were log-transformed. The primary outcome was listing for cardiac transplant or death, which was estimated using Kaplan–Meier methods; because of the limited number of events, we were not able to model death and transplantation separately. For the purpose of this analysis, patients’ medical history was subdivided into multiple periods based on the timing of S:D ratio measurements, in which a new period started at each echocardiogram and follow-up was censored at the following echocardiogram or end of follow-up (negative censored) or death/transplantation listing (event). Autocorrelation between the separate periods on the same patient was adjusted for using an exchangeable covariance structure to calculate hazard ratio. Generalized estimating equations were used to model repeated-measures data over time. The log-rank method was used to calculate the confidence interval of the hazard ratio for survival stratified by S:D ratio. Intra- and interobserver reliability for measurement of TDI systolic and diastolic durations was assessed using Bland–Altman analysis in 10 randomly chosen DCM patients and 10 controls. Bland–Altman analysis was also used to compare time intervals and the S:D ratio measurement by TDI versus M-mode. A P value <0.05 was accepted as statistically significant. Statistical analysis was performed using SAS statistical software v9.3 (SAS Institute, Cary, NC). The institutional review board approved the study and waived requirement for individual patient consent.

Clinical Characteristics
Forty-eight children diagnosed with idopathic, familial, or genetic DCM were studied. Their characteristics are shown in Table 1. DCM and controls were similar in age and sex. Children with DCM had clinical signs and symptoms of heart failure, including abdominal pain, emesis, exercise intolerance, shortness of breath, and failure to thrive. Patients were receiving treatment for heart failure, including diuretics, angiotensin-converting enzyme inhibitors, and β-blockers. The effect of β-blockers on heart rate is accounted for by comparison to heart rate–matched controls and was entered as a variable in the subgroup multivariable analysis. Because most patients were on a combination of anti–heart failure medications, because medications other than β-blockers do not directly affect heart rate, beyond their affect on heart failure or loading, and because subgroups would be too small to further study the effects of individual medications, other medical therapy was not accounted for in the data analysis. Seventeen patients (35%) experienced the adverse outcome of death/listing for transplant.
Table 1. Comparison of Echo Parameters Between Dilated Cardiomyopathy Patients and Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DCM (n=48)</th>
<th>Control (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>7.7±6.6</td>
<td>6.5±6.1</td>
<td>0.47</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>48</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>33±16</td>
<td>68±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EDD, cm</td>
<td>4.98±1.65</td>
<td>3.83±0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EDD, Z score</td>
<td>5.6±2.4</td>
<td>0.4±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>564±146</td>
<td>599±155</td>
<td>0.38</td>
</tr>
<tr>
<td>Systolic duration, ms</td>
<td>312±54</td>
<td>297±57</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic duration, ms</td>
<td>245±99</td>
<td>305±98</td>
<td>0.02</td>
</tr>
<tr>
<td>S:D duration ratio</td>
<td>1.41±0.43</td>
<td>1.01±0.17</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

EDD indicates end-diastolic dimension; LV, left ventricle; and S:D, systolic to diastolic.

Echocardiography

At baseline, children with DCM had larger LV dimensions, reduced EF, similar heart rate, and an increased S:D ratio compared with controls (Table 1). Eleven DCM children had no MR, 24 had trace or mild MR, 9 moderate MR, and 2 severe MR. MR was not assessed in 2. Thirty-five had qualitatively good right ventricular (RV) function, 10 had qualitatively mildly decreased RV function, and 1 had moderately decreased RV function. RV images were inadequate in 2.

Analysis by DCM Presentation

The average time between the first and last echocardiogram was 1.2±1.3 years, with a median of 0.6 years (interquartile range, 0.18–2.1 years). Table 2 compares the S:D ratio, time intervals, and other functional parameters by an acute versus chronic DCM clinical presentation. In a series of separate univariable linear regression models adjusted for repeated measure through a compound symmetry covariance structure, DCM with an acute presentation had a trend toward an elevated S:D ratio versus DCM with a chronic presentation. These patients also had worse EF versus those with chronic presentation and worse TDI cardiac cycle timing intervals (Table 2).

Relation Between S:D Ratio, Age, Heart Rate, and Outcome

Table 3 shows the relation between functional echo parameters, including the S:D ratio and the outcome of death or transplant. LV dimensions, EF, systolic duration, diastolic duration, S:D ratio, and isovolumic relaxation and contraction times were associated with outcome. In linear regression models adjusted for repeated measure through a compound symmetry covariance structure, the S:D ratio decreased with age in children with DCM, likely because of the association between age and heart rate (Figure 2). Regardless of age, the S:D ratio increases with increasing heart rates (Figure 3).

Association Between S:D Ratio and Survival

A S:D ratio >1.2 was associated with increased death or transplant (hazard ratio, 10.5; 95% confidence interval, 3.9–27.8; P<0.001) <2 years of echocardiography (Figure 4A and 4B). The 1.2 cut point represents the natural inflection point in this distribution. A S:D ratio >1.2 was associated with death or need for heart transplant <2 years after echocardiography with 0.94 sensitivity, 0.64 specificity, a negative predictive value of 0.99, and a positive predictive value of 0.28. In multivariable analysis, a S:D ratio >1.2 remained significantly associated with hazard of death/transplant (hazard ratio, 9.1; 95% confidence interval, 1.1–74.1; P<0.001) after adjustment for EF (hazard ratio, 2.2; 95% confidence interval, 1.4–3.4 per −10%; P<0.001). When entering LVEDD expressed as a Z score into the model, the S:D ratio lost its significance (P=0.08), because of the small sample size (P value for LVEDD Z score, 0.19). The sample size was too small to enter MR and RV function as additional variables into the model. We also investigated survival stratified by the S:D ratio at the initial study using the 1.2

Table 2. Difference Between Dilated Cardiomyopathy Patients With an Acute Versus Chronic Presentation in Separate Univariate Linear Regression Models Adjusted for Repeated Measures Through a Compound Symmetry Covariance Structure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute vs Chronic (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF, %</td>
<td>−12 (−19 to −4)</td>
<td>0.003</td>
</tr>
<tr>
<td>LV EDD, cm</td>
<td>+0.20 (−0.61 to +1.00)</td>
<td>0.63</td>
</tr>
<tr>
<td>LV EDD, Z score</td>
<td>+0.83 (−0.65 to +2.31)</td>
<td>0.27</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>−76 (−191 to −39)</td>
<td>0.20</td>
</tr>
<tr>
<td>Systolic duration</td>
<td>+5 (−23 to +34)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diastolic duration</td>
<td>−70 (−158 to +19)</td>
<td>0.12</td>
</tr>
<tr>
<td>S:D duration ratio</td>
<td>+0.34 (−0.05 to +0.73)</td>
<td>0.08</td>
</tr>
<tr>
<td>TDI ICT, ms</td>
<td>+23 (−5 to +41)</td>
<td>0.01</td>
</tr>
<tr>
<td>TDI IVRT, ms</td>
<td>+9.7 (−1.3 to +18.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>TDI ET, ms</td>
<td>−8.0 (−59.1 to +43.1)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EDD, end-diastolic dimension; EF, ejection fraction; ET, ejection time; ICT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; S:D, systolic to diastolic; and TDI, tissue Doppler imaging.

Table 3. Association Between the Outcome of Death or Transplant and Echocardiography Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Association With Outcomes (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF (per 5%)</td>
<td>0.63 (0.53–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EDD, cm</td>
<td>1.66 (1.13–2.44)</td>
<td>0.009</td>
</tr>
<tr>
<td>LV EDD, Z score</td>
<td>1.65 (1.35–2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-R interval (per 50 ms)</td>
<td>0.58 (0.44–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic duration (per 50 ms)</td>
<td>0.57 (0.38–0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic duration (per 50 ms)</td>
<td>0.46 (0.32–0.365)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S:D duration ratio (per 0.1)</td>
<td>1.11 (1.06–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDI ICT, ms</td>
<td>1.14 (0.49–2.68)</td>
<td>0.76</td>
</tr>
<tr>
<td>TDI IVRT, ms</td>
<td>1.00 (0.86–1.16)</td>
<td>0.99</td>
</tr>
<tr>
<td>TDI ET, ms</td>
<td>0.90 (0.71–1.15)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Estimates are adjusted for repeated measures through a compound symmetry covariance structure. CI indicates confidence interval; EDD, end-diastolic dimension; EF, ejection fraction; ET, ejection time; ICT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; S:D, systolic to diastolic; and TDI, tissue Doppler imaging.
Table 5 shows the associations between age and various functional parameters and the S:D ratio. Larger LV dimensions and lower EF were associated with a higher S:D ratio. Age was also associated with the S:D ratio, likely through its association with heart rate. Statistically, the duration of diastole, but not systole, was significantly associated with the S:D ratio. Accordingly, mitral filling time was associated with the S:D ratio; isovolumic relaxation time trended toward a statistically significant association with the S:D ratio.

**Factors Associated With S:D Ratio**

We sought to additionally investigate the longitudinal impact of disease course on timing intervals and on the S:D ratio. However, both age and heart rate are correlated and play a central role in determining cardiac timing intervals. Therefore, we explored the associations between age (Table 5) and between time from the first echo (Table 6) with the various echo parameters and time intervals in linear regression models adjusted for repeated measure through a compound symmetry covariance structure. For each yearly increase in age, all timing intervals increased, presumably as a consequence of the decrease in heart rate. The composite effect of prolongation of both the systolic duration and diastolic duration was a mild, but statistically significant, decrease in the S:D ratio. This occurs because the increase in diastolic duration with age is much larger than the prolongation of systolic duration with age (Table 5). In addition, for each increase in the year of age, there was an increase in absolute LVEDD, but a small (and likely clinically insignificant) decrease in LV \( z \) score. In this context, the change in these parameters for serial echocardiograms largely paralleled the changes related to age. Accordingly, there was a strong increase in the R-R interval (signifying a lower heart rate), a lengthening of systolic and diastolic duration, and overall a slight decrease in the S:D ratio. These changes were accompanied by a prolongation of the mitral filling time.

**Effect of Age and Time Since First Echocardiography on Cardiac Cycle Timing Parameters**

We compared systolic and diastolic time intervals and the S:D ratio by TDI versus those obtained by M-mode. Results of Bland–Altman intraobserver reliability had a 3.9 ms bias (1.0%; \( P=0.18 \)) for systolic duration and 3.1 ms (0.6%; \( P=0.50 \)) for diastolic duration. Interobserver reliability in controls had a bias of 1.4 ms (0.4%; \( P=0.75 \)) for measurement of systolic duration and 3.1 ms (0.6%; \( P=0.50 \)) for measurement of diastolic duration.

**S:D Ratio by TDI Versus S:D Ratio by M-Mode**

We compared systolic and diastolic time intervals and the S:D ratio by TDI versus those obtained by M-mode. Results of Bland–Altman limits of agreement are presented in Figure 5 and summarized here. TDI measurements had poor agreement with M-mode measurements. For systolic duration, the bias was \(-0.63 \) ms (SD, 31; 95% limits of agreement, \(-61 \) to 59); for diastolic duration, the bias was \(-12 \) ms (SD, 54; 95% limits of agreement, \(-119 \) to 94); for the S:D ratio, the bias was \(-0.002 \) (SD, 0.40; 95% limits of agreement, \(-0.79 \) to 0.79).

**Discussion**

Childhood DCM is a condition that continues to carry high mortality. Therefore, risk stratification and prognostication are important to its management. Simple, noninvasive measures to assist in serial prognostication are especially germane, because they can be readily implemented in routine clinical practice. We investigated the echocardiographic S:D ratio during longitudinal follow-up in childhood DCM and its association with death or need for cardiac transplant in this population. The results of this study show that a S:D ratio >1.2, as measured from TDI, at initial presentation, and during serial assessment, is associated with increased risk for death or need for transplantation in children with DCM. Conversely, a low S:D ratio is associated with low risk of death or need for transplantation.

Heart rate is a major determinant of systolic and especially diastolic duration because of the linear relation between systole and heart rate and the exponential relation between...
At resting or low heart rates, systole constitutes ≈40% of the cardiac cycle in healthy children.6 Conversely, in ventricular dysfunction of various causes, including DCM, systole prolongs and concomitantly diastole shortens.4,10–12 This leads to an increased S:D ratio, which progressively worsens as heart rate increases.4,10 Indeed, the S:D ratio has previously been shown to predict systolic and diastolic dysfunction in a mixed population of children with acquired and congenital heart disease.13 We previously demonstrated the usefulness of the RV S:D ratio measured from tricuspid regurgitation Doppler to predict death or the need for transplant in children with pulmonary arterial hypertension.14 We now extend these findings to show that a higher S:D ratio is associated with increased risk of death or transplant in children with DCM.

Although the mechanisms driving mortality with an increased S:D ratio remain to be explored, several putative mechanisms seem possible. Because systole prolongs and diastole shortens, LV filling time is decreased.15 Our results are consistent with this mechanism because LV filling time was indeed decreased in association with the S:D ratio, which presumably would lead to reduced cardiac output, as well as reduced time available for LV coronary perfusion.15,16 Our results replicate well-known principles, in that a slower heart rate allows longer diastolic time and longer ventricular filling.15,16 Although the therapeutic implications of these results remain to be investigated, our results suggest that medications that slow heart rate, such as ivabradine, may be useful in the management of pediatric heart failure.17 This requires further study. Interestingly, recent studies have suggested that

Table 4. Results From a Series of Separate Univariable Models Investigating the Association Between Age, Echo Parameters, and S:D Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>EST* (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.056 (0.011)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EDD, cm</td>
<td>−0.047 (0.042)</td>
<td>0.26</td>
</tr>
<tr>
<td>LV EDD, z score</td>
<td>0.151 (0.021)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>−0.019 (0.003)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler isovolumic contraction time (per 10 ms)</td>
<td>−0.018 (0.036)</td>
<td>0.61</td>
</tr>
<tr>
<td>Tissue Doppler isovolumic relaxation time (per 10 ms)</td>
<td>−0.012 (0.066)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mitral filling time (per 10 ms)</td>
<td>−0.020 (0.004)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-R interval (per 10 ms)</td>
<td>−0.021 (0.003)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection time (blood Doppler; per 10 ms)</td>
<td>−0.062 (0.009)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection time (tissue Doppler; per 10 ms)</td>
<td>−0.039 (0.010)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler systolic duration (per 10 ms)</td>
<td>−0.012 (0.012)</td>
<td>0.31</td>
</tr>
<tr>
<td>Tissue Doppler diastolic duration (per 10 ms)</td>
<td>−0.032 (0.005)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All estimates are adjusted for repeated measures through a compound symmetry covariance structure. A positive parameter estimate (EST) signifies that a higher variable value is associated with a higher S:D ratio. A negative EST means that a higher variable value is associated with a lower S:D ratio. EDD indicates end-diastolic dimension; EF, ejection fraction; LV, left ventricle; and S:D, systolic to diastolic.

*EST is the change in S:D ratio for corresponding increase in independent variable.
Table 6. Association Between Echocardiographic Parameters and Time Since First Echocardiogram (in Years)

<table>
<thead>
<tr>
<th>Echo Parameter</th>
<th>EST* (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDD, cm</td>
<td>0.24 (0.09)</td>
<td>0.01</td>
</tr>
<tr>
<td>LV EDD, z score</td>
<td>−0.1 (0.21)</td>
<td>0.64</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>4.50 (1.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>41.26 (15.69)</td>
<td>0.009</td>
</tr>
<tr>
<td>Ejection time (blood Doppler; ms)</td>
<td>21.62 (5.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection time (tissue Doppler; ms)</td>
<td>26.99 (4.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue Doppler isovolumic contraction time, ms</td>
<td>−0.95 (5.28)</td>
<td>0.86</td>
</tr>
<tr>
<td>Tissue Doppler isovolumic relaxation time, ms</td>
<td>−2.65 (2.70)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mitral TDI systolic duration</td>
<td>9.82 (4.50)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral TDI diastolic duration</td>
<td>30.64 (11.57)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mitral TDI S:D ratio duration</td>
<td>−0.12 (0.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mitral filling time, ms</td>
<td>39.30 (18.46)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*EST is the change in echocardiographic parameter for each additional year since presentation.

All estimates are adjusted for repeated measures through a compound symmetry covariance structure. EDD indicates end-diastolic dimension; EF, ejection fraction; EST, parameter estimate; LV, left ventricle; S:D, systolic to diastolic; and TDI, tissue Doppler imaging.

Figure 5. Bland–Altman limits of agreement between tissue Doppler imaging and M-mode measurements for systolic duration (A), diastolic duration (B), and the S:D ratio (C). See text for quantitative details.

The S:D ratio may be useful as a screening parameter to exclude a substantial risk of death or need for cardiac transplant at the time of evaluation.

Beyond the intuitive effects on LV function, we have recently shown that in pulmonary arterial hypertension, an increased S:D ratio affects ventricular–ventricular interactions because prolonged RV contraction continues into LV diastole, thereby contributing to reduced LV filling.\textsuperscript{14,22} Similarly, in DCM, prolonged LV systole may extend into RV diastole, thereby impairing RV filling. Because RV function is a key prognostic factor in DCM, prolonged LV systole may be an important contributor to adverse ventricular–ventricular interactions and RV dysfunction and requires further study.

Our study cohort included a large proportion of infants. This reflects the patients with DCM treated at our center. Indeed, in the pediatric population, a large percentage of children with DCM (41%) and specifically in the idiopathic DCM subgroup (49%)\textsuperscript{1} are infants.\textsuperscript{1} However, the high number of neonatal data points does not affect the regression models because regression lines represent the average S:D ratio at each time point and in itself does not complicate analysis.

### S:D Ratio in DCM Subgroups

Because of the variable presentation of DCM in children, we further investigated timing intervals and the S:D ratio according to an acute versus chronic presentation. The S:D ratio was associated with outcome in both these groups and trended toward being worse in the acute group. Kaplan–Meier survival analysis showed that a higher S:D ratio was associated with worse survival regardless of an acute or insidious presentation. This stemmed from a shortened diastole in these patient groups, consistent with our speculation discussed above that a short diastole drives reduced filling and perhaps coronary perfusion.\textsuperscript{15,16} This, however, was not investigated in this study and as such remains a speculation worthy of further investigation. The S:D ratio captures the relative relationship between the fundamental intervals of cardiac function and may further relate to the coupling between systolic and diastolic function. Other known risk factors followed a similar pattern in that LVEDD \textit{z} score and LV EF were associated with adverse outcome. Nonetheless, our multivariable analysis revealed that an elevated S:D ratio was independently associated with death or transplant and, therefore, may have additive prognostic value. Of note, multivariable modeling of the S:D ratio with both LV EF and LV end-diastolic volume \textit{z} score in the model is limited by the small sample size and serves predominantly for hypothesis-generating purposes.
Measurement of S:D Ratio From TDI

The S:D ratio was initially measured from Doppler interrogation of mitral or tricuspid regurgitation. Cui et al demonstrated in a large population of healthy children that timing intervals including the S:D ratio can be measured by TDI. Their data also provide normal reference values. Likewise, although we initially measured the S:D ratio in children with hypoplastic left heart syndrome using Doppler flow, Bellsham-Revell et al measured the S:D ratio in this population using TDI. Similarly, the myocardial performance index has been measured in children using TDI. The most obvious advantage of using TDI compared with regular pulsed Doppler of mitral or tricuspid regurgitation is that TDI will be feasible in most patients, whereas MR is not universally present. In some patients, MR may not be pan-systolic, thereby potentially underestimating systolic duration. However, TDI measurements are sampled at a specific region and unlike MR may not be indicative of global events. Nonetheless, the mitral annulus TDI is well established as an index of systolic and diastolic function, including in children with DCM. Moreover, TDI time intervals correlate well with pulsed Doppler flow intervals in children. However, there was poor agreement between time intervals and the S:D ratio measured by M-mode versus TDI in the DCM population, which may result from the local versus global nature of the measurements, different frame rates, perhaps different subintervals included in the systolic period, and other factors. Likewise, the Blandr Altman plot of diastolic duration suggests that the difference between TDI and M-mode decreases as the average increases, and that for the S:D ratio increases with increasing S:D magnitude. All these suggest that the 2 methods are not interchangeable. Comparison with the S:D ratio obtained by Doppler flow will require further study. Importantly for its implementation in clinical practice, the TDI S:D ratio is a reasonably simple and reproducible parameter easily obtained in most settings.

There are important limitations to TDI methodology as well as to the S:D ratio itself. As with all Doppler techniques, TDI measures only the vector of motion in the direction of the ultrasound beam. In addition, TDI measures absolute tissue velocity and is unable to discriminate passive motion (related to translation or tethering) from active shortening. As with any Doppler signal, identifying the termination of the pulsed TDI S′ wave can be challenging. This can lead to inaccuracies in measuring time intervals. Our results showed a low sensitivity for the S:D ratio in predicting death or transplant. Therefore, the S:D ratio should be challenging. This can lead to inaccuracies in measuring time intervals. Our results showed a low sensitivity for the S:D ratio in predicting death or transplant. Therefore, the S:D ratio should enhance prognostication regarding the risk for death or need for transplant in children with DCM. Further validation of the S:D ratio in larger, prospective, and optimally multicenter studies is warranted.

Conclusions

In conclusion, the S:D ratio is higher in children with DCM with adverse outcome across the pediatric age range. The S:D ratio, readily measured by TDI, may be a useful index to enhance prognostication regarding the risk for death or need for transplant in children with DCM. Further validation of the S:D ratio in larger, prospective, and optimally multicenter studies is warranted.

Disclosures

None.

References

15. Plehn G, Vormbrock J, Perings C, Machnick S, Zuehkle C, Trappe HJ, Meissner A. Loss of diastolic time as a mechanism of...
Childhood dilated cardiomyopathy (DCM) carries high morbidity and mortality, although some children improve. Echocardiography is commonly used for serial evaluation of children with DCM; however, there is a need for prognostic echocardiography indices. The echocardiographic systolic to diastolic (S:D) duration ratio, an indicator of global cardiac performance, is elevated in DCM. However, its prognostic implications have not previously been investigated in this population. In this study, we investigated systolic and diastolic durations and the resultant S:D ratio using pulsed tissue Doppler imaging in children with idiopathic or familial DCM. We studied 200 serial echocardiograms of 48 children with DCM, from presentation until the last follow-up echo, and compared results to heart rate–matched controls. We analyzed associations between the S:D ratio and death or need for transplant. The S:D ratio was higher in DCM patients because of shortened diastole. A S:D ratio >1.2 at presentation and on serial evaluation was associated with increased risk for death or transplant, independent of ejection fraction. Our results suggest that the S:D ratio may be a useful prognostic index for serial evaluation of children with DCM, expanding the available armamentarium to assess these patients.
Prognostic Implications of the Systolic to Diastolic Duration Ratio in Children With Idiopathic or Familial Dilated Cardiomyopathy
Tapas Mondal, Cameron Slorach, Cedric Manlhiot, Wei Hui, Paul F. Kantor, Brian W. McCrindle, Luc Mertens and Mark K. Friedberg

Circ Cardiovasc Imaging. 2014;7:773-780; originally published online August 19, 2014; doi: 10.1161/CIRCIMAGING.114.002120
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/7/5/773

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/