Interpretation of Left Ventricular Diastolic Dysfunction in Children with Cardiomyopathy by Echocardiography: Problems and Limitations

Dragulescu et al: Classification of Diastolic Function in Children

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Abstract

Background—Left ventricular diastolic dysfunction (DD) is a key determinant of outcomes in pediatric cardiomyopathy (CM), but remains very challenging to diagnose and classify. Adult paradigms and guidelines relating to DD are currently applied in children. However, it is unknown whether these are applicable to children with CM. We investigated the assessment of DD in children with CM using adult and pediatric echocardiographic criteria and tested whether recent adult guidelines are applicable to this population.

Methods and Results—Three investigators independently classified diastolic function in 4 study groups: controls; dilated (DCM), hypertrophic (HCM) and restrictive (RCM) cardiomyopathy. Agreement between investigators, failure to classify DD and the reasons for diagnostic failure were determined. The usefulness of individual echo parameters to diagnose and classify DD was assessed. 175 children (0-18yrs) were studied. DD diagnostic criteria were discrepant in the majority of patients. Delayed relaxation was diagnosed in only 14% of HCM patients and never in DCM and RCM, with 50% of those patients having co-existing findings of elevated filling pressures. Many key parameters, such as mitral and pulmonary venous Doppler were not informative. Agreement between investigators for grading of diastolic dysfunction was poor (36% of CM patients).

Conclusions—Assessment of DD in childhood cardiomyopathy seems inadequate using current guidelines. The large range of normal pediatric reference values allows diagnosis of diastolic dysfunction in only a small proportion of patients. Key echo parameters to assess DF are not sufficiently discriminatory in this population and discrepancies between criteria within individuals prevent further classification and result in poor inter-observer agreement.

Key Words: diastolic dysfunction, pediatric, cardiomyopathy
Diastolic dysfunction (DD) is a major determinant of prognosis and survival in several pediatric cardiomyopathies (CM)\textsuperscript{1-3}. Although left ventricular (LV) ejection fraction (EF) correlates with patient outcomes in adults and children, echo parameters of DD are most predictive of outcome in pediatric dilated (DCM)\textsuperscript{1,2}, non-compaction\textsuperscript{4} and hypertrophic (HCM) cardiomyopathy\textsuperscript{3,5,6}. Therefore echo diagnosis and grading of DD in childhood CM is important.

The diagnosis of DD is difficult due to a lack of a clinical “gold standard”\textsuperscript{7}. Even invasive measurements obtained during cardiac catheterization have important shortcomings and provide only partial information on ventricular diastolic properties. Atrial pressures and LV end-diastolic pressure are generally used as surrogate measures of ventricular stiffness and compliance but both are influenced by other confounding factors. Ventricular relaxation is even more difficult to assess invasively as this is a fast event requiring the use of high-fidelity catheters which are not routinely used in the clinical setting. Apart from methodological concerns, in many institutions, including our own, pediatric CM patients do not routinely undergo diagnostic cardiac catheterization. Therefore, echocardiography serves as the main imaging modality for evaluation and follow-up of these children. Echocardiographic assessment is based on integration of information obtained from mitral inflow, pulmonary venous Doppler and tissue Doppler imaging\textsuperscript{8}. Echocardiographic studies in adult patients describe a progression of DD along a continuum of increasing severity ranging from normal, through delayed relaxation, pseudo-normal filling to restrictive filling\textsuperscript{9-11}. Based on this patho-physiological paradigm, the American Society of Echocardiography (ASE) has recently published guidelines for evaluation of DD\textsuperscript{8}. However, these guidelines do not inform on their application to children and adolescents. Moreover, there are very few studies investigating DD in childhood CM and these involve relatively small numbers of patients\textsuperscript{1-3,12}. Consequently, diagnosis and grading of
DD in childhood CM remains poorly defined.

The aim of this study was to define problems in classification of DD in children with CM using echocardiography and to assess whether published adult echo guidelines for classification and grading of DD are applicable to this population. We further investigated the usefulness of individual echocardiographic diastolic parameters to diagnose and classify DD in children.

**Methods**

**Study population**

Children and adolescents diagnosed with dilated, hypertrophic or restrictive cardiomyopathy were identified retrospectively from the institutional database. The study was approved by the institutional ethics board. We included a group of normal controls consisting of healthy children with no history of cardiovascular disease and a normal echocardiogram. Children diagnosed with DCM were included if they had an EF of less than 50% and a LV end diastolic dimension z-score >2 (based on institutional z-scores)\textsuperscript{13}. Children diagnosed with HCM were included based on an increased wall thickness (interventricular septal thickness z score >2) and the presence of a normal or increased EF\textsuperscript{14}. Children diagnosed with restrictive cardiomyopathy (RCM) were included if they had clinical symptoms of growth restriction, dyspnea, exercise intolerance, emesis and/or other symptoms of heart failure with restrictive left ventricular physiology with dilated atria, normal EF and normal LV dimensions and wall thickness\textsuperscript{15}.

**Echocardiography**

One echocardiogram was selected for each patient at a time when the patient was clinically stable, i.e. the first outpatient study or last echocardiogram before discharge from initial hospitalization depending on availability. Our standardized clinical functional protocol includes
a comprehensive diastolic assessment. Diastolic parameters were re-measured from the stored
digital data by a single investigator (AD). These included (Figure 1): mitral inflow early to late
diastolic flow (E/A) ratio, mitral E wave deceleration time (DT), isovolumic relaxation time
(IVRT), pulmonary venous (PV) systolic to diastolic peak velocity ratio (S/D), PV A wave
reversal (Ar) amplitude and duration, time difference between PV Ar and mitral A duration,
mitral lateral and septal peak early diastolic tissue velocities (E’lat, E’med), mitral E to mean E’
ratio and left atrial volume (by the area length method) indexed to body surface area (LAVi). All
measurements were performed offline from standard views, according to current ASE
recommendations\(^8\) using a commercially available workstation (Syngo Dynamics, Siemens,
Mountain View, California).

**Classification of DD**

Three investigators independently interpreted the measurements. To assess practical application
and interobserver variability of DD classification by current paradigms, each observer was asked
to classify each patient as having either normal diastolic function, delayed relaxation,
pseudonormalization, restrictive physiology or indeterminate DD. Each patient was classified
using three different classification criteria. The first method used the diagnostic flowchart
recently published in the ASE guidelines using adult cut-off values suggested in the guidelines\(^8\).
The second method also used the ASE guidelines diagnostic flowchart but adult cut-off values
were substituted with published pediatric reference values by age group. Parameters were
classified as abnormal if outside 2 standard deviations (SD) for age\(^16-18\). We did not adjust
parameters for heart rate as published data are presented without heart rate correction. Each
investigator was then asked to classify DF for a third time based on their subjective assessment
of the diastolic parameters. Due to the lack of pediatric guidelines this is likely the method most
commonly used in daily clinical practice. In addition, the investigators were asked to assess whether they thought LV filling pressures were normal or elevated based on the measurements provided.

In each patient, the agreement in DD classification between investigators for each of the three classification methods was assessed. Interobserver agreement was also evaluated for the assessment of LV filling pressures. In addition, we evaluated the percentage of patients defined by the three observers as having normal diastolic function and those in whom it could not be classified. We further defined the reasons for failure to classify DF. In order to assess which diastolic parameters may be useful to diagnose DF, we assessed whether individual diastolic parameters were able to discriminate healthy controls from children with CM.

Determination of failure to classify DD

The current ASE guidelines allow diagnosis of ‘normal’, ‘constrictive pericarditis’ or ‘athletes heart’ when the LA is dilated (>34 ml/m2) in the presence of a normal E’. As none of the patients in our study were athletes; and all had an obvious CM diagnosis without constriction, failure to classify DF was determined when there was discordance between the early diastolic tissue Doppler velocity and the LAVi: i.e. a normal E’ in the presence of a dilated LA or, an abnormally low E’ in the presence of a normal LAVi. Failure to grade DD was also determined when diagnostic criteria between two adjoining grades of diastolic dysfunction (based on the ASE guidelines flowchart) were present. For example when criteria existed for both delayed relaxation and for pseudonormal filling; or, when criteria existed for both pseudonormal and restrictive filling. Failure to diagnose DD was also determined when mitral inflow and/ or diastolic tissue velocities were blended thereby precluding analysis by the ASE guideline’s flowchart.
Statistical analysis

Results are expressed as mean ± SD or percentages as appropriate. An unpaired Student t-test was used for comparison between the different CM groups and controls. Kappa statistics was used to assess the interobserver agreement for classification of DF. A p value <0.05 was considered statistically significant. Analysis was performed using IBM SPSS Statistics software version 19.

Results

Characteristics of the study population are presented in Table 1. Overall there were 18 subjects less than 1 year of age including 1 neonate. The DCM group had higher heart rates and lower EF. The HCM group was slightly older than the other groups and, as expected, had thicker ventricular walls and higher EF. The RCM group had normal EF, slightly smaller LV dimensions compared to controls and significantly dilated atria (mean LAVi: 80±38ml/m2 vs. controls 24.8±6ml/m2). The individual diastolic parameters for each of the patient groups are shown in the supplemental table. Most DCM and RCM patients had one or a combination of heart failure medication including betablockers (63%), ACE inhibitors (70%), diuretics (70%), digoxin (13%). Five DCM patients were on milrinone awaiting heart transplantation. In the HCM group, 60% had no medication while the rest were on betablockers, associated with disopyramide in five.

Interpretation of individual diastolic parameters

We calculated the percentage of each individual diastolic parameter values falling within the normal range based on published adult and pediatric normal data (Table 2). In all groups, including the CM groups with overt cardiac dysfunction, a significant proportion of individual
diastolic parameter values fell within the normal range.

For the control group, most diastolic parameters fell within normal range according to pediatric reference data. As expected, some values fell outside the normal control range defined by +/-2SD. Overall, published pediatric diastolic reference data successfully classified normal controls as having normal diastolic function, while adult criteria classified 10 to 30% of individual diastolic parameters as abnormal, mostly in younger children. However, these were often discrepant in individual patients. For example some controls had short DT and IVRT but otherwise normal data, while some had an E/A ratio >2 with or without a short DT. Using adult definitions of normal, only 12(24%) controls had all criteria within the normal range; while 11(22%) had 3 or more abnormal criteria using the ASE guidelines flowchart. Nine of these 11 individuals were 7 years of age or younger. This confirms that adult cutoff values would incorrectly classify normal children as having DD.

Overall, in the study population as a whole and using age appropriate reference values, individual parameters were often not informative. The most consistently abnormal and discriminating parameter was the mitral DT, which was normal in 90% of controls and abnormal in ~70% of RCM and DCM patients. The mitral DT was abnormal in a lower percentage of HCM patients, possibly due to a pseudonormal pattern in some patients (Figure 2). For tissue Doppler velocities, as a group, CM patients had significantly lower values compared to controls (p<0.001). Still, up to 50% of values were within the normal range for age (Table 2). Analysis of the tissue velocity scatter plots showed that a septal peak E’ of 11 cm/s discriminated fairly well between patients and controls (Figure 3B). LAVi values were abnormal in all RCM patients (by definition) but also in many DCM and HCM patients, while mild to moderate mitral regurgitation was present in 14% of patients. Overall, the isovolumic relaxation time, mitral E/A
ratio and pulmonary venous velocities were within normal range in most cardiomyopathy patients by adult and pediatric criteria, limiting the use of these parameters for the interpretation of diastolic function. (Table 2, Figure 2 and 4).

**Discordant parameters within individual patients**

Using the recommended guidelines, individual parameters were often discordant in individual patients, precluding classification of DF. Given that E’, LAVi and DT appeared to be the best discriminatory parameters to differentiate CM patients from controls, we further analyzed their characteristics in children with CM. E’ and LAVi were discordant in 37% of CM patients overall, most commonly in HCM patients (Table 3). Twenty-five patients had normal tissue velocities in the presence of a dilated LA. Of these, DT was normal in 8 of 10 HCM, 2 of 5 RCM and 2 of 10 of DCM patients (5 had blended inflow). A smaller proportion of patients had low E’ in the presence of a normal LAVi (18 cases). Most of these were associated with an abnormal DT: 8 of 10 HCM patients with prolonged DT and 4 of 7 DCM patients with short DT. When both E’ and LAVi were normal, all HCM patients had a normal DT whereas in the DCM group there were 6 patients with short DT and 3 who had blended mitral inflow pattern. All 3 parameters were abnormal in 11/50 (22%) HCM, 15/50 (30%) DCM and 7/16 (44%) RCM patients.

**Agreement between investigators for classification of DF and filling pressures**

Agreement between investigators was poor for the grading of DD as well as for the estimation of filling pressures (Table 4). Interobserver agreement was highest in the RCM group (76% for diastolic grading and 88% for filling pressures), and lowest in the DCM group (<50%). Interobserver agreement was improved in older patients, those with slower heart rates and those with higher EF (p<0.05). Only 7 patients had criteria consistent with delayed relaxation, all
adolescents with HCM.

Tissue velocities and LAVi, which represent the focal point in the ASE classification flowchart for DD, were often discrepant in individual patients by both adult and pediatric criteria. This led to high failure rate to classify DD (Table 4) and to poor interobserver agreement. A clear DD grading was assigned in only 37% of CM patients. Of these, approximately half (23 of 43 patients) were diagnosed by all 3 observers as having normal diastolic function. Conversely, a DD grade could not be assigned in 27% of patients due to overlapping or discrepant criteria in individual patients (Table 3). This occurred regardless of whether adult or pediatric cut-off values were used in the ASE diagnostic flowchart.

**Discussion**

Diagnosis of DD in children with CM is challenging. Despite the availability of reference values for individual DF parameters, there is little available guidance for the practicing clinician on diagnosis and grading of DD in children with CM. As a consequence, the pediatric cardiologist has to rely on existing guidelines and recommendations derived from adult studies. In the current study, we undertook a detailed descriptive analysis of the usefulness of individual echocardiographic parameters and their application to pediatric CM population, within the framework of current available guidelines.

The main findings of our study are: 1. There is a high percentage of normal diastolic parameters in children with overt and often severe cardiac dysfunction. 2. There is frequent discordance between E’ and LA volume criteria, hindering the use of diagnostic flowcharts published in the adult recommendations. 3. Discordant and/or overlapping criteria preclude more precise grading of DD in the majority of patients. 4. These and other factors lead to overall poor
agreement between observers, even in a research setting.

Is the adult paradigm of DD progression applicable to children?

The aforementioned problems raise the question whether adult paradigms of DD are applicable to children, beyond simple differences in age or heart-rate related cut-off values. The classification of diastolic dysfunction in adults is based on a paradigm of progression of abnormalities along a continuum of increasing severity from normal, through delayed relaxation, evolving through a phase of pseudo-normalization to a pattern of restrictive filling\textsuperscript{10}. This paradigm has not been proven conceptually in infants and children. While the current study cannot verify or reject this paradigm due to lack of a reference standard and its cross-sectional, retrospective nature, there are several important observations that can be made from our data that suggest that this paradigm may not apply to the pediatric population. In our experience, criteria consistent with delayed relaxation are distinctly uncommon in children. Only 7 HCM patients (6.4\% of all CM patients), presented criteria consistent with delayed relaxation, while no DCM or RCM patients had sufficiently concordant criteria to classify delayed relaxation or pseudo-normal filling. There are several possible explanations for this. One is that children present in more advanced stages of DD and therefore milder degrees of DD were not diagnosed in our cohort. However, almost half of the DCM patients where investigators agreed on DD grading had diastolic parameters within the normal range. These patients demonstrated severe systolic dysfunction and some degree of diastolic dysfunction would be expected\textsuperscript{19}. Alternatively, it may be that isolated delayed relaxation is uncommon in children and that decreased compliance exists in the absence of impaired relaxation; or even without prior development of delayed relaxation. If this postulate is subsequently confirmed in future studies, it questions the applicability of adult paradigms and current recommendations to diagnose and grade diastolic dysfunction in children.
Difficulties in diagnosing DD in childhood CM

Published normal data for diastolic parameters in children are based on relatively small populations, especially when sub-divided by age, and present a wide range of normal values\textsuperscript{16-18}. We found that pediatric reference data successfully defined normal controls, but due to the wide range of normal values, diastolic dysfunction was classified in only a small proportion of our cohort of patients with overt CM. Although in the absence of a reference standard we cannot determine with certainty that these patients had DD, based on the phenotypic disease severity, both in DCM and in HCM patients, we believe that diastolic dysfunction of some degree must be present in a substantial proportion of patients. Therefore, our results indicate that current echo criteria are inadequate to diagnose and classify DD in pediatric CM. Moreover, our results show that when DD is diagnosed or suspected, discrepancies between diastolic parameters or diagnostic criteria within individual patients are common. This adversely affects interpretation of DF, the ability to grade DD and interobserver agreement. These problems are not exclusive to the pediatric population. A recent study in adults showed important discordance between investigators in classifying pseudo-normal and restrictive DD, while relative agreement was noted for normal and delayed relaxation patterns. Agreement was moderate for the estimation of filling pressures\textsuperscript{20}.

Assessment of DF in children

Our results suggest that among the various DF echo parameters, $E'$, DT and LAVi are likely to be the most useful in the evaluation of DF in children with CM. Still, even these parameters were often discrepant in the individual child. Consequently, the two-level decision tree flowchart recommended by current ASE guidelines for DD classification\textsuperscript{8} appears to be poorly applicable in children. This suggests that new diagnostic criteria for diagnosis and grading of DD are
needed in children. Early diastolic tissue velocities, particularly E’med, seemed to differentiate patients from controls better than E’lat or E/mean E’ ratio (Figure 3) implying decreased recoil or possibly delayed relaxation\textsuperscript{21}. DT also seemed to differentiate patients from controls, albeit with considerable overlap, possibly related in part to pseudo-normalization (Figure 2). Combining septal E’ with DT appears to best differentiate patients from controls (Figure 5). However, using either of these two parameters alone is inadequate to grade DD. The discrepancies between E’ and LAVi, especially in the younger group, raises the question if age related cutoff values for these parameters should be determined. Conversely, the IVRT does not appear to be useful in any of the CM patients groups included in this study. Likewise, the E/A ratio, despite its traditional central position in the assessment of diastolic function, was not useful in our population, except in a small number of adolescents with HCM.

**Agreement between observers for classification of DD**

Despite a-priori agreement between investigators on the methodology to classify DD and a structured research setting, agreement between observers was poor. This further demonstrates the difficulties in application of current recommended guidelines to the pediatric population and emphasizes the need for further investigation into whether current paradigms of progression of DD derived from adult populations are applicable in children. Our data also emphasize the need for specific pediatric recommendations.

**Limitations**

As previously mentioned, this is a retrospective study without invasive reference data. CM patients in our institution do not routinely undergo cardiac catheterization and information such as filling pressures was not consistently available, even retrospectively. Current recommendations are based on echo criteria and this study focused on this application. The
number of patients is relatively small, especially for the RCM group. In this group, data was further limited by the lack of tissue Doppler in some patients. There were no missing data other than the PV Doppler in one HCM patient. The DCM group was relatively younger and some patients, although stable, were in severe heart failure. This reflects the reality of the patients encountered in clinical practice. We analyzed a single echocardiogram for each patient. Although we strictly defined the timing of echocardiography (the discharge echo of initial admission or first outpatient echo), patients may have been at different time points in the disease process. This is a limitation of a retrospective study and of not knowing at what point in the disease process the patient presented to the referral center. Likewise, it is difficult to determine when the disease process actually starts in relation to when the patient becomes symptomatic and is referred for evaluation. Importantly, our study does not define the prognostic value of individual diastolic echo parameters. This requires further prospective study.

Conclusion

In conclusion, pediatric reference data for echo parameters to assess diastolic function successfully define normal controls, but due to the large range of normal values, diastolic dysfunction is classified in only a small proportion of CM patients, even when their disease is severe. Discrepancies between diagnostic criteria within individual patients are common, adversely affecting interpretation of diastolic function and inter-observer agreement. Isolated delayed relaxation is seen in only a minority of HCM patients, and not in DCM or RCM. These results suggest that pediatric diastolic dysfunction does not follow the progression seen in adult patients and that new diagnostic criteria are needed in children.
Disclosures

None.

References


Table 1. General and echo characteristics of the study population by cardiomyopathy type

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Controls (n=50)</th>
<th>DCM (n=50)</th>
<th>RCM (n=16)</th>
<th>HCM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>9.7±4.8</td>
<td>8.0±6.1</td>
<td>10.3±6.2</td>
<td>11.8±4.1*</td>
</tr>
<tr>
<td>BSA (m2)</td>
<td>1.2±0.45</td>
<td>0.94±0.53*</td>
<td>1.1±0.6</td>
<td>1.4±0.48*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>85.8±17.6</td>
<td>103±30*</td>
<td>86.5±11.3</td>
<td>70.8±13.2</td>
</tr>
<tr>
<td>LV EF(%)</td>
<td>58.2±7.8</td>
<td>27±13.6*</td>
<td>57±13</td>
<td>76.7±13.2*</td>
</tr>
<tr>
<td>LV EDD z-score</td>
<td>-0.08±1</td>
<td>6.04±2.4*</td>
<td>-0.88±1.7*</td>
<td>-2.23±1.5*</td>
</tr>
<tr>
<td>IVS thickness z-score</td>
<td>-0.2±0.8</td>
<td>-0.17±1.8</td>
<td>0.6±1.7*</td>
<td>7.8±2.7*</td>
</tr>
<tr>
<td>Blended mitral inflow</td>
<td>0</td>
<td>9 (6 &lt;1y old)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*p<0.05 compared to the control group

BSA – body surface area; DCM – dilated cardiomyopathy; EDD – end diastolic diameter; EF – ejection fraction; HCM – hypertrophic cardiomyopathy; IVS – interventricular septum; RCM – restrictive cardiomyopathy.

Table 2. Frequency of normal individual diastolic parameters in the study population by cardiomyopathy type according to adult cutoff values and pediatric reference data

<table>
<thead>
<tr>
<th>% of patients with normal values</th>
<th>Normal controls (n=50)</th>
<th>DCM (n=50)</th>
<th>RCM (n=16)</th>
<th>HCM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion</td>
<td>Adult</td>
<td>Pediatric</td>
<td>Adult</td>
<td>Pediatric</td>
</tr>
<tr>
<td>IVRT(%)</td>
<td>94</td>
<td>64</td>
<td>62</td>
<td>75</td>
</tr>
<tr>
<td>PV S/D ratio(%)</td>
<td>84</td>
<td>60</td>
<td>50</td>
<td>69</td>
</tr>
<tr>
<td>PV Ar(%)</td>
<td>92</td>
<td>86</td>
<td>84</td>
<td>62.5</td>
</tr>
<tr>
<td>Ar - A(%)*</td>
<td>92</td>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DT(%)</td>
<td>68</td>
<td>12</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>E/A(%)</td>
<td>58</td>
<td>30</td>
<td>86</td>
<td>25</td>
</tr>
<tr>
<td>E'(%)</td>
<td>100</td>
<td>30</td>
<td>46</td>
<td>25</td>
</tr>
<tr>
<td>E/E'(%)</td>
<td>90</td>
<td>26</td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td>LAVi score(%)</td>
<td>98</td>
<td>40</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

* a subset of patients in each group had uninterpretable results with abnormal pattern in 22% of DCM, 62.5% of RCM and 25% of HCM patients.

Ar – A - time difference between pulmonary venous A reversal and mitral A wave duration; DCM – dilated cardiomyopathy; DT – mitral E wave deceleration time; E/A – mitral inflow peak E to A wave velocities ratio; E/mean E’ – mitral inflow peak E to mean septal and lateral tissue velocities E’ ratio; E’ lat – peak early diastolic tissue velocity at lateral mitral annulus; E’ sep - peak early diastolic tissue velocity at medial mitral annulus; HCM – hypertrophic cardiomyopathy; IVRT – isovolumic relaxation time; LAVi – left atrial volume indexed to body surface area; PV Ar - pulmonary venous A wave reversal peak velocity; PV S/D - pulmonary venous peak systolic to diastolic velocity ratio; RCM – restrictive cardiomyopathy.
**Table 3.** Reasons for failed classification, disagreement or mixed classification criteria

<table>
<thead>
<tr>
<th></th>
<th>DCM (n=50)</th>
<th>RCM (n=16)</th>
<th>HCM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
<td>Pediatric</td>
<td>Adult</td>
</tr>
<tr>
<td>Discordant E’/LAVi criteria (E’ abn-LAVi N/ E’ N -LAVi abn)</td>
<td>19/12/7</td>
<td>16/7/9</td>
<td>5/1/4</td>
</tr>
<tr>
<td>Unclear grading (grade 1 ↔ 2/ 2 ↔ 3/ blended mitral inflow)</td>
<td>10/3/6</td>
<td>15/3/8/4</td>
<td>5/1/4</td>
</tr>
<tr>
<td>Clear classification (N / abn)</td>
<td>21/7/14</td>
<td>19/12/7</td>
<td>6/0/6</td>
</tr>
</tbody>
</table>


**Table 4.** Subjective classification of diastolic dysfunction severity and filling pressures by the three investigators (A, B, C)

<table>
<thead>
<tr>
<th></th>
<th>DCM (n=50)</th>
<th>RCM (n=16)</th>
<th>HCM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
<td>Pediatric</td>
<td>Adult</td>
</tr>
<tr>
<td>Investigator subjective classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement(%)</td>
<td>23(46%)</td>
<td>10(62.5%)</td>
<td>32(64%)</td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Abnormal (grade 1/2/3)</td>
<td>11 (0/1/10)</td>
<td>9 (0/0/9)</td>
<td>14 (7/7/0)</td>
</tr>
<tr>
<td>Disagreement(%)</td>
<td>27(54%)</td>
<td>6(37.5%)</td>
<td>18(36%)</td>
</tr>
<tr>
<td>Kappa statistics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-B</td>
<td>0.509</td>
<td>0.462</td>
<td>0.592</td>
</tr>
<tr>
<td>A-C</td>
<td>0.549</td>
<td>0.647</td>
<td>0.812</td>
</tr>
<tr>
<td>B-C</td>
<td>0.334</td>
<td>0.352</td>
<td>0.507</td>
</tr>
<tr>
<td>Assessment of filling pressures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement(%)</td>
<td>24(48%)</td>
<td>13 (81.2%)</td>
<td>37(74%)</td>
</tr>
<tr>
<td>Normal / High</td>
<td>5/17</td>
<td>2/11</td>
<td>26/11</td>
</tr>
<tr>
<td>Disagreement(%)</td>
<td>26(52%)</td>
<td>3(18.7%)</td>
<td>13(26%)</td>
</tr>
<tr>
<td>Kappa statistics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-B</td>
<td>0.464</td>
<td>0.823</td>
<td>0.714</td>
</tr>
<tr>
<td>A-C</td>
<td>0.411</td>
<td>0.642</td>
<td>0.782</td>
</tr>
<tr>
<td>B-C</td>
<td>0.239</td>
<td>0.678</td>
<td>0.518</td>
</tr>
</tbody>
</table>

Figure Legends

**Figure 1.** Assessment of diastolic parameters in a patient with hypertrophic cardiomyopathy. A. Mitral valve inflow with measurements of the early and late diastolic waves and the E wave deceleration time. B. Pulmonary venous Doppler with measurement of the systolic, diastolic and atrial reversal waves amplitude and atrial reversal wave duration. C. Tissue velocities measured at the base of the interventricular septum. D. Left ventricular inflow and outflow for measurement of the isovolumic relaxation time. E - F. Left atrial area and length in apical four and two chamber views for the estimation of atrial volume.

**Figure 2.** Diastolic parameters in the study population by age and cardiomyopathy type. A: Mitral valve E to A ratio. B: Mitral valve E wave deceleration time. C: Left atrial volume indexed to body surface area.

**Figure 3.** Tissue Doppler diastolic parameters in the study population by age and cardiomyopathy type. A. Lateral mitral valve early diastolic tissue velocities. B. Medial mitral valve early diastolic tissue velocities. C. Mitral valve peak early diastolic inflow velocity to mean early diastolic tissue velocities ratio.

**Figure 4.** Pulmonary venous (PV) Doppler derived diastolic parameters in the study population. A: PV systolic to diastolic velocity ratio. B: PV A wave reversal peak velocity (Ar). C: Time difference between PV Ar duration and mitral A wave duration.

**Figure 5.** Added value of septal E’ and mitral deceleration time in differentiating patients from controls.
Interpretation of Left Ventricular Diastolic Dysfunction in Children with Cardiomyopathy by Echocardiography: Problems and Limitations
Andreea Dragulescu, Luc Mertens and Mark K. Friedberg

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SUPPLEMENTAL MATERIAL

Supplemental Table

Table. Individual diastolic parameters in the study population by cardiomyopathy type.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Normal controls (n=50)</th>
<th>DCM (n=50)</th>
<th>RCM* (n=16)</th>
<th>HCM (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVRT (ms)</td>
<td>60±9.7</td>
<td>56±16</td>
<td>63±19</td>
<td>74.2±22.5</td>
</tr>
<tr>
<td>PV S/D</td>
<td>0.8±0.2</td>
<td>0.9±0.4</td>
<td>1±0.4</td>
<td>1±0.4</td>
</tr>
<tr>
<td>PV Ar (cm/s)</td>
<td>23±5.9</td>
<td>24.6±8</td>
<td>34±11</td>
<td>31.6±12.5</td>
</tr>
<tr>
<td>Ar - A (ms)</td>
<td>-23±18</td>
<td>8.9±26</td>
<td>36.4±31</td>
<td>-6±32</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>153±28</td>
<td>113±34</td>
<td>94±27</td>
<td>197±43</td>
</tr>
<tr>
<td>E/A</td>
<td>2±0.6</td>
<td>2.3±1.1</td>
<td>2.6±1.6</td>
<td>1.8±0.6</td>
</tr>
<tr>
<td>E’ sep (cm/s)</td>
<td>14±2.4</td>
<td>7.2±2.8</td>
<td>7.1±2.9</td>
<td>8±3.2</td>
</tr>
<tr>
<td>E’ lat (cm/s)</td>
<td>18.3±4</td>
<td>10±5</td>
<td>9.2±3.8</td>
<td>12±4.7</td>
</tr>
<tr>
<td>E/ mean E’</td>
<td>6.6±1.7</td>
<td>13.2±4.7</td>
<td>12.3±6</td>
<td>11.4±5.4</td>
</tr>
<tr>
<td>LAVi score (ml/m²)</td>
<td>24.8±6</td>
<td>47.4±29</td>
<td>80.4±38</td>
<td>39±14.4</td>
</tr>
</tbody>
</table>

* tissue Doppler data available in 16 RCM patients.

Ar – A - time difference between pulmonary venous A reversal and mitral A wave duration; DCM – dilated cardiomyopathy; DT – mitral E wave deceleration time; E/A – mitral inflow peak E to A wave velocities ratio; E/mean E’ – mitral inflow peak E to mean septal and lateral tissue velocities E’ ratio; E’ lat – peak early diastolic tissue velocity at lateral mitral annulus; E’ sep - peak early diastolic tissue
velocity at medial mitral annulus; HCM – hypertrophic cardiomyopathy; IVRT – isovolumic relaxation time; LAVi – left atrial volume indexed to body surface area; PV Ar - pulmonary venous A wave reversal peak velocity; PV S/D - pulmonary venous peak systolic to diastolic velocity ratio; RCM – restrictive cardiomyopathy.