Nomograms for Blood Flow and Tissue Doppler Velocities to Evaluate Diastolic Function in Children: A Critical Review

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Interest in diastolic function in children has increased recently. However, the strengths and limitations of published pediatric nomograms for echocardiographic diastolic parameters have not been critically evaluated, especially in the neonatal population. A literature search was performed within the National Library of Medicine using the keywords *normal/reference values*, *power Doppler/tissue Doppler velocities*, and *children/neonates*. The search was further refined by adding the keywords *diastolic function*, *myocardial*, *mitral/tricuspid inflow*, *pulmonary vein*, and *Tei index*. Thirty-three published studies evaluating diastolic function in normal children were included in this review. In many studies, sample sizes were limited, particularly in terms of neonates. There was heterogeneity in the methodologies to perform and normalize measurements and to express normalized data (*Z* scores, percentiles, and mean values). Although most studies adjusted measurements for age, classification by specific age subgroups varied, and few addressed the relationships of measurements to body size and heart rate (especially with higher neonatal heart rates). Although reference values were reproducible in older children, they varied significantly in neonates and infants. Pediatric diastolic nomograms are limited by small sample sizes and inconsistent methodologies for the performance and normalization of measurements, with few data on neonates. Some studies do reveal reproducible patterns in diastolic function in older children. A comprehensive pediatric nomogram of diastolic function involving a large population of normal infants and older children and using standardized methodology is warranted and would have tremendous impact in the care of children with acquired and congenital heart disease. (J Am Soc Echocardiogr 2013;26:126-41.)

Keywords: Echocardiography, Children, Neonates, Diastolic function

The use of blood flow and tissue Doppler measurements to evaluate diastolic function in adults has been studied extensively for many years.[1] Similarly, interest in indices of diastolic function for children with congenital and acquired heart diseases has also grown, especially in the past 20 years.[2-5] However, there are still limitations to the echocardiographic evaluation of diastolic function in children, especially in neonates and infants.[6] Normal or expected Doppler velocities change significantly with increasing age and body size,[7-44] and they are frequently difficult to evaluate at the faster heart rates of children, especially during the neonatal period. In addition, the maturation of myocardial fibers, especially in terms of diastolic function, occurs primarily in the first few months of life,[8,9,15,32,35,36,39] and normal values for diastolic parameters in neonates and infants must definitely account for age.[6]

Many pediatric centers have published nomograms for indices of diastolic function,[7-44] though many of the earlier studies were fraught with limitations, particularly in terms of sample size,[25,30,31] adequate representation of neonates, study population, methodology, normalization approach, and expression of reference values. More recent studies have overcome many of the issues of sample size and variable methodology,[18-21] though limitations persist in data normalization and expression. Reference values appear to be reproducible in older children, though data in neonates and small children are still limited and often heterogeneous. For example, the mean value for the late diastolic flow velocity or A wave at the mitral valve for a 3-year-old child varies from 42 cm/sec[7] to 50 cm/sec[15] to 61 cm/sec.[19]

Classification of the severity of diastolic dysfunction has also been problematic, particularly because many studies have used adult criteria to grade diastolic dysfunction.[1] Although it may be reasonable to apply these standards to children >3 years old,[6,18] age and heart rate have significant effects on diastolic parameters in smaller children, especially during the neonatal period,[8-18,32,34-36,39] often precluding an accurate assessment of the severity of diastolic dysfunction. The aims of this study were to review the limitations of published pediatric nomograms for blood flow and tissue Doppler velocities at the mitral and tricuspid valves and at the pulmonary veins, especially in neonates, and to highlight the strengths in recent studies, especially in terms of eventually establishing the ideal pediatric nomogram for diastolic function.

METHODS

Diastolic Indices

This study focused on the following echocardiographic parameters of diastolic function: (1) peak blood flow velocities at the mitral and

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Abbreviations
BSA = Body surface area
DT = Deceleration time
IVRT = Isovolumic relaxation time
LA = Left atrial
LV = Left ventricular

tricuspid valves during early filling (E wave) and in late diastole (A wave), the E/A ratio, the E-wave deceleration time (DT), and the isovolumic relaxation time (IVRT); (2) peak forward flow velocities during systole (S wave) and diastole (D wave) and peak reverse flow velocity during atrial contraction (Ar wave) in the pulmonary veins; (3) peak myocardial velocities at the lateral mitral annulus, at the basal interventricular septum, and at the tricuspid annulus in early (e′) and late diastole (a′); and (4) the Tei index (or myocardial performance index) for the left ventricle and right ventricle, calculated as the sum of isovolumic contraction time and IVRT divided by ventricular ejection time, measured using both blood flow and tissue Doppler echocardiography (this index is considered to be a measure of combined systolic and diastolic function).

Search Strategy

Potential publications were identified from a systematic search in the National Library of Medicine (PubMed access to MEDLINE citations; http://www.ncbi.nlm.nih.gov/PubMed/) conducted in July 2012. The search strategy included a mix of Medical Subject Headings and free-text terms for the key concepts, starting from *normal/reference values*, *power Doppler/tissue Doppler velocities*, and *children/neonates*. The search was further refined by adding the keywords *diastolic function*, *myocardial*, *mitral/tricuspid inflow*, *pulmonary vein*, and *Tei index*. In addition, we identified other potentially relevant publications using a manual search of references from all eligible studies and review articles as well as from the Science Citation Index Expanded on the Web of Science. All identified reports were assessed independently by two reviewers, and a consensus was reached for inclusion into the present study. Titles and abstracts of all articles identified by the search strategy were evaluated and excluded if (1) the studies included populations other than normal subjects or mixed adults with children and (2) the reports were written in languages other than English.

RESULTS

Search Results

Thirty-nine publications were identified in the search for potential inclusion into the study. Six studies were excluded on the basis of the criteria listed above, leaving 33 publications for analysis.

General Methodologic Limitations

A standardized methodology based on international consensus to measure blood flow and tissue Doppler velocities in the pediatric population is not currently available. Hence, measurements are performed using different echocardiographic views[7,9-12,35] and in different myocardial segments.[30,31] In addition, a recent study evaluating the reproducibility of functional echocardiographic measurements revealed fairly significant percentage error and poor reproducibility associated with some diastolic parameters (including E-wave DT, the duration of pulmonary venous flow reversal during atrial contraction, and the Tei index), decreasing their usefulness in daily practice.[45]

Table 1A Published regression equations for peak mitral valve inflow velocities and E-wave DT adjusted for age, heart rate, mitral valve area, stroke volume, and/or other systolic parameters

Study	Subject age	*n*	E (cm/sec)	A (cm/sec)	DT (msec)
Harada *et al.* (1995)[10]	7 d to 195 mo	226	*y* = 64.984 + 17.777 × log(age)	*y* = 51.011 − 0.069995 × age	
Schmitz *et al.* (2004)[13]	Preterm: 138 ± 70 d	25	*y* = 37.1 + 15.9 × SV − 59.3 × MVA	*y* = 44.2 + 8.34 × SV − 43.4 × MVA	
Schmitz *et al.* (2004)[14]	1 d to 2 y	238	*y* = −49.3 + 0.40 × HR + 8.28 × SV/MVA + VCFc/PSWS137	0–6 mo: *y* = −36.2 + HR × 0.32 + SV/MVA × 0.30 + 1.23 7–24 mo: *y* = −68.5 + HR × 0.79 + SV/MVA × 3.14	*y* = −20.4 + 0.18 × HR + 0.80 × SV/MVA
Schmitz *et al.* (1998)[15]	2 mo to 19 y	329		*y* = −4.220 + 0.539 × HR + 0.339 × SV − 4.052 × MVA	*y* = 0.175 + 0.00272 × HR + 0.00064 × SV − 0.0075 × MVA

HR, Heart rate; *MVA*, mitral valve area; *PSWS*, peak systolic wall stress; *SV*, stroke volume; *VCFc*, rate-corrected mean velocity of fiber shortening.