Left Ventricular Diastolic Function in Infants, Children, and Adolescents. Reference Values and Analysis of Morphologic and Physiologic Determinants of Echocardiographic Doppler Flow Signals During Growth and Maturation

LOTHAR SCHMITZ, MD, HEIKE KOCH, MD, GEORG BEIN, MD, KONRAD BROCKMEIER, MD

Berlin, Germany

Objectives. The aim of this study was to set up reference values for Doppler flow-derived left ventricular filling parameters and to evaluate physiologic determinants of changes in signal expression related to maturation.

Background. In left ventricular diastolic function studies, age-related modulations in signal expression are observed. Assuming degenerative myocardial changes to be absent during childhood and adolescence, the determinants of these modulations must be different from those suspected in adults.

Methods. Pulsed wave Doppler signals from the mitral valve tip region were recorded in 329 healthy subjects aged 2 months to 39 years. Multiple linear regression was used to evaluate statistical relations between Doppler flow signals and stroke volume in the mitral valve area.

Results. Increasing early filling time velocity integral throughout maturation caused a decrease in atrial filling fraction from 0.34 ± 0.06 to 0.24 ± 0.04 (p < 0.005). Peak flow velocities during atrial systole decreased from infancy to adolescence (66 ± 15 to 41 ± 10 cm/s). Main effects on signal modulation were caused by heart rate, stroke volume and mitral ring area with a linear model fit (R²) of 0.79 for early filling phase (E)-time velocity integral, 0.6 for atrial filling phase peak velocity 0.84 for total E duration and 0.73 for E deceleration time. Atrial filling phase-time velocity integral, albeit significantly dependent on heart rate, was stable throughout growth.

Conclusions. During infancy and childhood, the stroke volume crossing the mitral valve is a main modulator for early filling phase (E)-time velocity integral and diastolic time intervals during early filling, whereas atrial filling phase parameters are mainly dependent on heart rate. This results in a more pronounced atrial filling during infancy and childhood.

(J Am Coll Cardiol 1998;32:1441–8)

©1998 by the American College of Cardiology

In healthy adults, diastolic parameters of left ventricular filling undergo changes with aging (1,2) that are attributed to physiologic degenerative myocardial processes and which have to be taken into account in the judgment of diastolic function (3). Apparent modulations in echocardiographic diastolic flow pattern and flow duration have also been observed from fetal life throughout infancy and childhood (4–7). It has been shown that maturational modulations in early filling time integral and peak flow velocity during atrial systole can be correlated to body surface area, age and heart rate, but the basic physiologic and morphologic determinants for the expression of diastolic flow parameters have not yet been evaluated systematically. With the assumption that in healthy subjects at least from late infancy through the second decade of life intrinsic myocardial factors do not change greatly, the driving forces of the observed changes in signal expression must be different from those reported in adults.

Therefore, beyond the drawing up of centile charts for echocardiographic left ventricular flow parameters from infancy to young adulthood, the objectives of the study were the evaluation of anatomic and physiologic determinants related to changes in signal size and duration during maturation. In this study, we tested the hypothesis that changes in the stroke volume crossing the mitral valve play a significant role in signal expression.

Methods

Out of 320 prospectively investigated healthy subjects aged 2 months to 19 years, 281 data sets fulfilled qualitative standards to be entered in a database for reference values of diastolic left ventricular function. All healthy subjects visited our outpatient department for the final clearing up of innocent heart murmurs. Exclusion criteria were any abnormalities in the patient’s history possibly interfering with normal circulatory function, as well as pathologic findings during physical examination in the electrocardiogram or in the echocardiographic examination. Furthermore, data sets were rejected due
to incomplete data acquisition and the lack of qualitative criteria defined by the inability to adjust the Doppler volume to a position as defined below. Probands were examined in a quiet resting state without prior sedation. Infants were allowed to be bottle fed during the examination. A further 48 data sets of 50 examinations performed in healthy volunteers aged 20 to 39 years were investigated to observe data continuity into adulthood. The same exclusion criteria were applied to this group. These probands had additional uneventful bicycle stress testing and Holter monitoring. Informed consent was obtained from the participants and/or their parents.

**Data acquisition**. All investigations were performed on a Hewlett Packard cardiologic ultrasound system 77020AC using transducers of 2.5 MHz, 3.5 MHz or 5 MHz as appropriate for the given patient. The examination procedure was restricted to three well-trained investigators (LS, HK, KB). Measurements were recorded on videotape for off-line evaluation. Investigations from parasternal long axis view, short axis view and apical 4-chamber view were performed in a recumbent left lateral position. The aortic arch was examined from the suprasternal notch, the atrial septum and the venous and arterial vessel situs from substernal view. Color Doppler imaging was performed to detect more than physiologic valvular regurgitation or vessel stenoses. The mitral valve ring diameter during diastole was measured from the apical 4-chamber view.

During pulsed wave Doppler examinations of diastolic left ventricular filling, the sample volume was positioned in the mitral valve tip region. No angle correction was applied and the Doppler sample was positioned to within ±15° of the central inflow stream verified by color Doppler imaging. No wall filter was applied and the signal amplification switch was set to be optimized automatically by the echocardiography system. An electrocardiographic trace was recorded simultaneously with the echocardiogram at a "chart speed" of 100 mm/s.

**Data evaluation**. Measurements were performed from video recorded signals using the software of the echocardiography system. Data were examined by a single investigator (LS). For the assessment of intraobserver variability, 20 of the original data sets were randomly chosen for reinvestigation. These 20 data sets were also examined in a blinded manner by another investigator (HK) to assess interobserver variability. To assure that identical signals were reinvestigated we used the videotape time tracks and visual comparison of paper off-prints concurrently. For Doppler tracings in the mitral valve area, the measurements of six consecutive heart cycles were averaged, regardless of the proband’s respiratory cycle. Doppler indices were calculated using the averaged data of its constituents.

**Diastolic function parameters**. Peak flow velocities and time velocity integrals during early ventricular filling and during atrial filling, total time of early filling and atrial filling, the acceleration time and deceleration time of early filling were measured from signals of the same cardiac cycle. Ratios were calculated for peak flow velocities and for time velocity integrals. The relation of atrial to total ventricular filling was calculated as: \( \text{AFF} = e\text{-TVI}/(E\text{-TVI} + A\text{-TVI}) \), where \( \text{AFF} \) = atrial filling fraction, \( e\text{-TVI} = \) atrial filling phase time velocity integral \( E\text{-TVI} = \) early filling phase time velocity integral \( A\text{-TVI} = \) atrial filling phase time velocity integral and \( E\text{-TVI} + A\text{-TVI} = \) early filling phase time velocity integral.

- **E-** and **A-wave parameters** were measured and calculated using the implemented software of the echocardiography system by manually tracing digitized envelopes around the Doppler flow signal starting and ending at zero flow level. In case of signal superimposition, the E-TV and the according time intervals were measured by manual extrapolation of the deceleration slope through the A wave or through diastasis flow to the zero flow line. When E and A waves were separated, the onset of the A-TV was defined either as the visible intercept of the Doppler shift signal on the zero flow line or by manual extrapolation of the signal through diastasis flow to the zero flow line. In the case of signal superimposition, the A wave was not extrapolated backward through the E wave, but the point on the x-axis corresponding to the Doppler shift intersection was then defined as the onset of atrial filling. To measure A-TV, a normal-to-the-zero flow line was plotted through the early flow signal starting at the signal intersection and, after reaching the free Doppler shift signal, the trace was completed as usual. The technique for obtaining time velocity integrals and time intervals is illustrated in Figure 1.

**Data reproducibility**. Interobserver variability expressed as correlation coefficients between measurements of two investigators yielded \( R = 0.98 \) for early filling phase peak velocity \( (E_{\text{max}}) \), \( R = 0.94 \) for E-TV, \( R = 0.99 \) for atrial filling phase peak velocity \( (A_{\text{max}}) \), \( R = 0.95 \) for A-TV, \( R = 0.9 \) for early filling acceleration time, \( R = 0.93 \) for early filling deceleration time and \( R = 0.89 \) for atrial filling time. The error was random and no systematic trend was observed. Intraobserver variability was generally lower than interobserver variability with correlation coefficients \( R = 0.98 \) for \( E_{\text{max}} \), \( R = 0.96 \) for E-TV, \( R = 0.99 \) for \( A_{\text{max}} \), \( R = 0.97 \) for A-TV, \( R = 0.95 \) for early filling acceleration time, \( R = 0.95 \) for early filling deceleration time and \( R = 0.93 \) for atrial filling time. Thus overall reproducibility was sufficient in our echocardiographic laboratory.

**Mitral valve size, cardiac output and left ventricular muscle mass**. To investigate the influence of the mitral valve size and cardiac output on flow parameters, the valvular ring diameter and total time velocity integral during diastole were measured from the apical 4-chamber view. Stroke volume (SV) and cardiac index were calculated both from the mitral valve Doppler signals, including diastasis flow (in all cases), and

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-TV</td>
<td>atrial filling phase velocity integral</td>
</tr>
<tr>
<td>A_{\text{max}}</td>
<td>atrial filling phase peak velocity</td>
</tr>
<tr>
<td>AFF</td>
<td>atrial filling fraction</td>
</tr>
<tr>
<td>E-TV</td>
<td>early filling phase velocity integral</td>
</tr>
<tr>
<td>E_{\text{max}}</td>
<td>early filling phase peak velocity</td>
</tr>
<tr>
<td>E/A</td>
<td>ratio of early to atrial filling phase velocity integrals</td>
</tr>
<tr>
<td>TVI</td>
<td>atrial filling phase time velocity integral</td>
</tr>
<tr>
<td>E/TVI</td>
<td>early filling phase time velocity integral</td>
</tr>
<tr>
<td>AFF</td>
<td>atrial filling phase peak velocity</td>
</tr>
<tr>
<td>MM</td>
<td>muscle mass</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
</tbody>
</table>
using the equation area = \( \pi \times r^2 \) where \( r \) is half the diameter. Cardiac index was calculated as SV \( \times \) heart rate/body surface area. Stroke volume derived from two-dimensional echocardiogram was calculated by subtracting end systolic volume (ESV) from the end diastolic volume (EDV) using the equation for EDV = \((8/3)\pi \times (\text{ventricular area in diastole}^2/\text{ventricular length in diastole})\) and for ESV = \((8/3)\pi \times (\text{ventricular area in systole}^2/\text{ventricular length in systole})\).

Stroke volume calculations from total time velocity integral and from two-dimensional echocardiogram showed a linear correlation with a correlation coefficient of 0.88. Comparing both methods in the abovementioned subset of the study group, a uniform 40% overestimation along the whole bandwidth of stroke volumes was obtained with the Doppler-derived volumes.

Left ventricular muscle mass (MM) was calculated from M-mode data following the recommendations of the American Society of Echocardiography with the exception that the correction factor (−14 g) was omitted, which is a common practice in infants and children to prevent underestimation of MM in the young (8,9): end diastolic MM = 1.04 \times [(\text{internal ventricular dimension} + \text{interventricular septum dimension} + \text{posterior wall thickness})^3 - \text{internal ventricular dimension}^3] \text{g}.

Statistical methods. Statistical Package for Social Sciences (SPSS) for Microsoft Windows 6.0 was used. Median values and percentiles or means and standard deviations were calculated for each parameter. After visual analysis of scatter plots and regression curves, the choice of an appropriate division of the study population into age-related subgroups was based on one-way analysis of variance (ANOVA). The statistical influence of underlying physiologic and morphologic parameters (independent variables) on diastolic flow parameters (dependent variables) was evaluated by multivariate ANOVA. Model fit was verified by joint multivariate Bonferroni tests. Multiple stepwise linear regression was performed to obtain regression equations (mean values and 95% confidence intervals) of all normally distributed diastolic flow parameters and time intervals. Normal distribution of parameters was tested by Kolmogorov–Smirnov’s goodness of fit test. A complete residual analysis including Durbin–Watson statistics was performed to reconfirm the validity of the applied model. Statistical significance was assumed at an error level of 5%.

Results

Age-related reference values of left ventricular filling.

Data of all 329 probands were analyzed to draw age-related centile charts. Most of the physiologic and anatomic determinants with presumed influence on diastolic function parameters are significantly different between subgroups from infancy through adolescence (Table 1).

E-TVI (Fig. 2) increases from the second month of life up to 19 years of age with statistically significant differences between adjacent age groups. E_{vmax} (Fig. 3) is stable between the age groups from infancy to adolescence. But E_{vmax} increases significantly (p < 0.01) from 62.9 ± 13 cm/s in infants younger than 4 months to 88 ± 11 cm/s in 7- to 24-month old infants. Increasing heart rate, and by this superimposition of E and A waves, has no significant impact on the expression of early filling signals.

A-TVI (Fig. 4) remains generally stable with slightly increasing tendency, but with statistically insignificant changes between adjacent age groups. Superimposition of early and atrial filling signals due to tachycardia cause a significant shift of A-TVI to the upper quartile level of the entire study population only in age groups 3 and 4. A_{vmax} (Fig. 5) falls significantly during infancy and childhood and then remains at a stable level up to 19 years of age. In age groups 3 and 4 the maximum velocity of atrial filling increases with higher heart rates to values beyond the upper quartile of the centile chart.

As a result of parameter modulations of their constituents, the ratios of early to atrial phase parameters (E/A-TVI, Fig. 6 and E/A_{vmax}, Fig. 7) and the atrial filling fraction (AFF, Fig. 8) undergo significant changes throughout maturation. The impact of heart rate on the atrial filling signal influences the percentile distances in age groups 3 and 4.

Due to E- and A-wave superimposition with higher heart rates, diastasis flow was absent in 87.5% of the infants, 65% of children aged 2 to 5 years, 35% of children aged 6 to 13 years and 21% of subjects aged 14 to 19 years.

Determinants of diastolic function. Using multivariate analysis (Table 2) and multiple stepwise linear regression (Table 3), we investigated the statistical influence of the six independent variables—heart rate, stroke volume, mitral ring area, left ventricular MM, age and body surface area—on
diastolic flow parameters and time intervals. When the study group was truncated at the age of 19 years, statistical analysis revealed a linear model to be appropriate for the description of parameter movements throughout growth and maturation. Linear regression was not performed with the ratios of time velocity integrals and peak velocities and in total diastole and diastasis duration because these variables were not normally distributed. Likewise, the acceleration time of early ventricular filling was eliminated due to its linear dependency on total early filling duration. For all the variables included, normalized residual plots closely followed the identity line with a maximum error of 5% observed in early filling peak velocity. Durbin–Watson coefficients had a mean of 2.03 (minimum 1.79, maximum 2.21), indicating the absence of autocorrelation.

With E-TVI and A max, correlation coefficients are high and the applied model explains 79% and 60% of the observed developmental changes, respectively (Table 3). Heart rate, SV and mitral ring area are factors of high impact on all flow parameters. Age, body surface area and left ventricular MM, although part of the model, are either completely excluded by regression analysis or exhibit a statistically negligible influence on flow variables.

A multiple linear regression model including only heart rate, age and body surface area as variables yielded R 2s with a maximum of 0.56 in E-TVI for the flow parameters and a maximum of 0.68 in early filling deceleration time for the diastolic time intervals.

Diastolic time intervals are mainly determined by heart rate (Table 2). Stroke volume influences to a moderate extent total duration and deceleration time during early filling, and mitral ring area influences considerably total early filling time and early filling deceleration time.

Discussion

This study provides reference values for age-related changes in diastolic left ventricular flow parameters from infancy to young adulthood. Furthermore, we were able to...
demonstrate that the observed changes in signal strength and duration are statistically correlated with parameters describing the flow-to-gate relationship at mitral valve level. The fact that heart rate in conjunction with mitral valve size and SV explains a high percentage of the observed signal modulations during early and atrial filling demonstrates their basic physiologic impact on left ventricular filling mechanics in children.

In adults a continuous shift from passive ventricular to active atrial ventricular filling can be observed. Most investigators attribute these changes to degenerative processes of the left ventricular myocardium with an apparent loss of compliance and increasing myocardial stiffness with aging. While in healthy adults there is little or no change in the morphologic (body surface area, heart size) and physiologic (heart rate, cardiac output) prerequisites (1,3), during infancy, childhood and adolescence both morphologic and physiologic conditions undergo permanent changes, and a shift in parameter expression with age opposite to that observed in adults has been reported by several investigators (3–6,10,11).

With our regression model all variables can be obtained simultaneously during the echocardiographic investigations and they are all directly or indirectly involved in left ventricular filling mechanics. We have been able to demonstrate that from infancy through adolescence the observed modulations in signal strength and duration are not only correlated with changes in heart rate, but also with changes in mitral valve size and SV if one accounts for the interaction of the parameters.
whereas a statistical model including heart rate, age and body surface area has only poor explanatory power.

**Early filling phase.** Early filling time velocity integral is most strongly directly related to SV and inversely related to mitral ring area. The SV per unit mitral ring area increases with age by almost 50%, and thus could be the physiologic prerequisite for the observed changes in signal expression. Assuming that beyond infancy myocardial stiffness and the end systolic volume index of the left ventricle remain stable, the higher SV crossing the atrioventricular junction explains most of the increase in time velocity integral. Weak influences are related to heart rate, which agrees with previous findings in healthy adults (10,11).

**Atrial filling phase.** Heart rate and cardiac output cause major contributions and are directly correlated with peak A velocity, whereas mitral ring area is inversely correlated with it, adding only moderate-to-weak contributions to the modulations of peak flow during atrial systole. This observation, especially the high impact of heart rate on peak flow velocity, is in accordance with previously published data in children and adults (7,12,13). In contrast to the early filling parameters, we could not observe different parameter slopes between early and late infancy.

**Ratios and atrial filling fraction.** During infancy, E/A<sub>max</sub> and E/A-TV1 are of a magnitude comparable to those in healthy 50- to 70-year-old adults. The strongest and virtually only determinant of these changes is heart rate, which is inversely related to both quotients. Atrial filling fraction exhibits a mirror image of the two quotients with a strong positive influence of heart rate. In infants, active atrial contribution to ventricular filling is physiologically higher than in adolescents. This fact is of importance for the treatment of heart failure during infancy. The coincidence of pump failure and cessation of normal sinus rhythm, which is frequently encountered at least temporarily after cardiac surgery, will therefore be poorly tolerated by infants and younger children.

**Diastolic time intervals.** Diastolic time intervals have strong correlations with heart rate. Stroke volume and mitral ring area are directly correlated to the total duration, acceleration and deceleration time of early ventricular filling, whereas the atrial filling time is an exclusive function of heart rate. The observation that total duration and relaxation time of early ventricular filling are partly dependent on mitral ring area and SV agrees with theoretical considerations and fits previously reported computer simulation studies (14).

**Early infancy and parameter expression.** In the first 6 months of life, intrinsic myocardial changes may probably play a major role in early filling signal expression. A rapid shift of both peak velocity and time velocity integral has also been observed in human fetuses between 18 and 38 weeks of gestation (15). Our results demonstrate a continually increasing early filling peak velocity up to an age of 6 months when a steady-state level is reached up to adolescence. This observation could in part be explained by changes in myocardial relaxation or other diastolic properties of the left ventricle. Atrial filling phase parameters in healthy infants obviously do not depend on these presumed changes in myocardial performance. Surprisingly, for all other parameters, including E/A ratios and AFF parameters, variability is lower in early and late infancy as compared to older subjects. Thus, studies in the infant are not at all less reliable when the investigation can be performed properly.

**Limitations of the study.** The fact that 41 out of 370 data sets had to be rejected was due to the inability to fulfill our measurement standards in regard to proper positioning of the sample volume or the inability to record clearly distinguishable E- and A-wave signals. Almost exclusively this situation was
encountered in infants and toddlers due to a combination of high heart rate and unstable Doppler sample position.

The measurement technique for filling time velocity integrals in the case of signal superimposition has been used in many different ways. Because it is impossible to decide which part of the signal truly belongs to early or atrial filling, we had to make arbitrary decisions. The extrapolation of the early filling time velocity integral through the atrial filling signal can be justified by the fact that median values and percentiles in the subgroups with and without superimposition of the signals are identical. Our approach to atrial time velocity integrals was led by technical considerations. The time velocity integral is by definition the integral of velocities during a physiologically defined flow period and implies that a measurement starts and ends with zero flow. Therefore, with the use of the commercially implemented software packages in echocardiography machines, tracing the A-TVI back along the extrapolated downslope of E-TVI is impossible. On the other hand, if there are arguments for the extrapolation of E-TVI through A-TVI, we had to choose the smallest measurement error in favor to E-TVI, being aware that signal superimposition implies a systematic error in the measurement of true A-TVI.

Comparing SV calculations made by the Doppler method with those derived from a single plane area length method, we found a uniform overestimation along the whole bandwidth of SVs. This is due to the inability of simultaneous time velocity integral recordings at mitral ring level and at the mitral valve tip region. We are also aware that the mitral ring area is not identical with the functional mitral valve opening area. But, as these combined systematic errors only lead to a parallel shift of the regression curves without affecting their gradients, it would not prevent using either volume for multiple regression. Consequently, we decided to use Doppler-derived volumes because only they allow simultaneous flow-to-signal correlation.

The probands were investigated in a quiet, nonedsedated state. Therefore, the reference values are representative only for this typical clinical situation. Special attention should be paid to excesses in heart rate which will very probably influence the expression of atrial flow parameters. No attention could be paid to triggering the signals to distinct phases of the respiratory cycle (16). As we have averaged signals from six consecutive heart cycles for the evaluation of each parameter, our values represent a random choice of signals representative for an intermediate position between the end points of the respiratory cycle. We strongly recommend performing this averaging procedure when the centile charts are used.

**Conclusions.** This study provides age-related reference values of left ventricular diastolic flow parameters in childhood and adolescence. The advantage of the age reference lies in the continuity of data observation into adult age. Beyond infancy up to the age of 20 years there is little evidence that intrinsic factors of myocardial function play a major role in diastolic left ventricular function. Statistical evidence supports our hypothesis that the changing flow-to-gate relationship during maturation plays a major role in the modulation of signal strength and duration. Cardiac output and mitral ring area are significant determinants, especially relevant in modulating the time velocity integral during early ventricular filling. To a lesser degree these determinants also influence peak flow velocities during atrial filling, which is mainly correlated with heart rate.

**References**