Heart Rate Is the Major Determinant of Diastolic Filling Pattern During Growth: A Radionuclide Ventriculography Assessment

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Abstract. Left ventricular diastolic filling is a fundamental constituent of cardiac performance. Diastolic function in both adults and children can be routinely assessed by radionuclide ventriculography (RNV). It has previously been shown that factors such as heart rate (HR) and age can significantly modify diastolic performance in adults, thus limiting the clinical applicability of RNV diastolic indices. The aim of this study was to investigate various factors that may affect diastolic function in childhood. Seventy-nine children, aged 40 days to 15 years, were enrolled in the study; their HR ranged from 45 to 160 beats per minute (bpm). All had intact cardiac function and were submitted to baseline RNV prior to chemotherapy initiation for malignancies. Using stepwise linear regression analysis, HR was identified as the major factor affecting RNV diastolic indices during growth. Applying univariate regression models, diastolic indices were corrected for a reference HR of 100 bpm; this substantially reduced variability of RNV diastolic indices along age increments, allowing for the establishment of reference ranges. In conclusion, HR was shown to be the major determinant of RNV diastolic indices during growth. Adjustment for this variable alone can offer reference ranges for the assessment of left ventricular filling in childhood.

Key words: Heart rate — Diastolic filling — Radionuclide ventriculography

Diastolic filling plays a significant role in global cardiac performance [20, 31]. Left ventricular filling is a complex process, reflecting the interaction of a variety of factors, such as myocardial relaxation, passive mechanical properties of the myocardium, loading conditions, and uniformity of activation and inactivation [4, 12, 19]. The pattern of left ventricular filling can be noninvasively assessed by equilibrium radionuclide ventriculography (RNV); Doppler echocardiography (D-echo), and magnetic resonance imaging [1, 10, 24]. Currently, semiquantitative diastolic function indices are used for clinical purposes, but their wide application may be limited by inherent methodological problems.

The role of diastolic function is less well recognized in pediatric populations [26]. Limited data exist on diastolic filling pattern in infants and children from D-echo flow velocity measurements at the mitral orifice [6, 15, 17, 28]. No normal ranges for RNV diastolic indices have been reported for clinical use in pediatrics, despite the fact that this technique has been applied in children [25, 30].

In this retrospective study the diastolic filling pattern is assessed by RNV in a pediatric population with intact heart function. In particular, the importance of some potentially influencing factors, such as age, heart rate (HR), body size, heart size, and systolic function, is investigated.

Patients and Methods

Population Recruitment

The population studied consisted of 79 children (49 boys, 30 girls) referred for baseline RNV study before initiation of potentially cardiotoxie chemotherapy. Their ages ranged from 40 days to 15 years (mean 7.0 ± 4.5 years) and their HR ranged from 45 to 160 beats per minute (bpm) (mean 101.8 ± 25.4 bpm). The underlying disease was acute lymphocytic leukemia in 36 cases, lymphoma in 14, sarcomas in 10, Wilms’ tumor in 9, and other less common conditions in 12.
types of tumors in 10. Their cardiac performance was judged intact on the basis of history, physical examination, electrocardiography, and echocardiographic evaluation, as needed. No febrile patients were included and time was given to crying children to calm down. Cases with neural crest tumors were not enrolled to exclude potential chronic catecholamine influence. Height (H) and body weight (W) were measured in all cases and the body surface area (BSA) was calculated according to the Dubois and Dubois’ formula [9]: BSA = H0.725 W0.425 71.84.

Radionuclide Ventriculography

The in vivo labeling technique was used to label autologous red blood cells with 99mTcO₄⁻. The administered pertechnetate activity dose was escalated according to the European Association of Nuclear Medicine Pediatric Task Group schedule [27]. Acquisition was performed at rest in the supine position. The gamma detector, equipped with a general-purpose parallel hole collimator, was positioned at best septal view and the photopoint of the gamma camera was set at 140 keV with a 20% window. R-R interval was divided in 24 frames and a dynamic filtration mode acquisition was used, with rejection of R-R intervals out with ±10% of the mean interval. Typically, 5000 kcounts per study were acquired. Tail frames were automatically corrected for loss of counts due to R-R variation. Using a second derivative edge detection technique regions of interest (ROIs) were automatically generated for each of the 24 frames. These ROIs were subsequently manually corrected where obvious errors were noted. A background ROI was drawn at the inferolateral edge of the left ventricle. The background-subtracted time–activity curve (TAC) was generated and it was approximated by a fourth-order Fourier transformation. The first derivative of the latter, representing the rate of left ventricular volume changes, was supplementary used for accurate measurement of both the timing of diastolic events and the diastolic parameters (Fig. 1).

Ejection fraction (EF) was calculated in the usual manner. Ejection time (ET) was designated as the period from the start of the heart cycle to the lowest TAC point, with filling time (FT) being the rest of the R-R interval. Peak filling rate (PFR) was defined as the peak of the first derivative curve at the first half of diastole and it was expressed in both end diastolic volumes per second (EDV/sec) and stroke volumes per second (SV/sec). The interval from the lowest TAC point to the time when PFR occurred was defined as time to peak filling rate (TPF). The late positive deflection of the first derivative curve was attributed to the atrial contraction, and from the corresponding TAC deflection the atrial component to diastolic filling (A/V) was measured and expressed as percentage of SV. The first third filling fraction (1/3FF) was designated as the percentage of left ventricular filling during the first third of FT. All these parameters for diastolic function assessment have been previously described [1, 16]. EDV and ESV (and hence SV) were calculated using a previously validated count ratio-based method [22].

Statistics

Descriptive statistics are presented as mean ± 1 standard deviation (SD). Normal curve plots were fitted over data histograms for normal distribution assessment. The explanatory power of each individual variable on diastolic parameters was sequentially assessed by forward stepwise regression analysis. Dependence of various diastolic indices on HR was modeled by univariate regression analysis and the best fitting linear or polynomial equation was selected using statistical criteria. The goodness of fit of the regression equations to the data was assessed by Pearson’s correlation coefficient (r). The nonparametric Kruskall–Wallis test was used for comparisons of more than two independent groups followed by Dunnett’s C-test for pairwise comparisons between groups. Statistical significance was accepted for p values <0.05.

Results

The late TAC deflection, allowing atrial kick identification and A/V assessment, was detectable in 50 cases. The rest of diastolic indices were easily measured in all cases, even in the presence of high HR.

A negative correlation between age and HR was found (HR = 0.27 age⁻³–7.54 age + 134, r = –0.61, p < 0.0001). HR declined with increasing age and the rate of change was progressively decelerated (Fig. 2). No appreciable change was noted beyond the age of 14 years.

Time variables, diastolic indices, and ejection fraction values of the entire population are listed in Table 1. HR, EF, PFR (EDV/sec), PFR (SV/sec), TPF, TPF/FT, A/V, and the 1/3FF values were normally distributed.

The effect of age, EF, HR, EDV, SV, and BSA on diastolic filling indices, investigated by forward stepwise regression analysis, was as follows: PFR (EDV/sec) was significantly affected by only HR (adjusted r² = 0.519). PFR (SV/sec) was also significantly affected by HR (adjusted r² = 0.569), the addition of EF in the model being of minimal importance (adjusted r² = 0.597). TPF was significantly affected by only HR (adjusted r² = 0.291), as was