Assessment of Diastolic Function in Single-Ventricle Patients After the Fontan Procedure

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Background: Patients with functional single ventricles after the Fontan procedure have abnormal cardiac mechanics. The aims of this study were to determine factors that influence diastolic function and to describe associations of diastolic function with current clinical status.

Methods: Echocardiograms were obtained as part of the Pediatric Heart Network Fontan Cross-Sectional Study. Diastolic function grade (DFG) was assessed as normal (grade 0), impaired relaxation (grade 1), pseudonymization (grade 2), or restrictive (grade 3). Studies were also classified dichotomously (restrictive pattern present or absent). Relationships between DFG and pre-Fontan variables (e.g., ventricular morphology, age at Fontan, history of volume-unloading surgery) and current status (e.g., systolic function, valvar regurgitation, exercise performance) were explored.

Results: DFG was calculable in 326 of 546 subjects (60%) (mean age, 11.7 ± 3.3 years). Overall, 32% of patients had grade 0, 9% grade 1, 37% grade 2, and 22% grade 3 diastolic function. Although there was no association between ventricular morphology and DFG, there was an association between ventricular morphology and E′, which was lowest in those with right ventricular morphology ($P < .001$); this association remained significant when using Z scores adjusted for age ($P < .001$). DFG was associated with achieving maximal effort on exercise testing ($P = .004$); the majority (64%) of those not achieving maximal effort had DFG 2 or 3. No additional significant associations of DFG with laboratory or clinical measures were identified.

Conclusions: Assessment of diastolic function by current algorithms results in a high percentage of patients with abnormal DFG, but few clinically or statistically significant associations were found. This may imply a lack of impact of abnormal diastolic function on clinical outcomes in this cohort, or it may indicate that the methodology may not be applicable to pediatric patients with functional single ventricles. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Congenital heart disease, Single ventricle, Fontan, Diastolic function

Although surgical palliation of patients with functional single ventricles by the Fontan procedure has resulted in improved survival during childhood, long-term morbidity and mortality remain major concerns. In particular, the relationships of pre-Fontan variables to diastolic function and of diastolic function to long-term morbidity and mortality in this cohort are still largely unknown. In the National Heart, Lung, and Blood Institute–sponsored Pediatric Heart Network Fontan Cross-Sectional Study of 546 Fontan survivors, the majority of patients (73%) had normal ejection fractions (EFs) by echocardiography, but only 28% had normal indices of diastolic function.[1] Although patients with single-ventricle physiology have been described as having diastolic dysfunction with both reduced compliance and impaired relaxation,[2] associations with anatomic, clinical, and historical factors have not been described. Additionally, because an acutely increased mass-to-volume ratio immediately after a Fontan operation has been postulated by some to be detrimental to diastolic function,[3,4] we sought to assess correlations between diastolic function and current mass-to-volume ratio and to determine whether mass-to-volume ratio correlates with clinical characteristics.

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This work was supported by U01 grants from the National Heart, Lung, and Blood Institute (HL068269, HL068270, HL068279, HL068281, HL068285, HL068292, HL068290, HL068288). This work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the National Heart, Lung, and Blood Institute. ClinicalTrials.gov identifier: NCT00132782.

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2016.07.016

Abbreviations

ACE = Angiotensin-converting enzyme

AVV = Atrioventricular valve

BSA = Body surface area

DFG = Diastolic function grade

DT = Deceleration time

EDP = End-diastolic pressure

EDV = End-diastolic volume

EF = Ejection fraction

ESV = End-systolic volume

LV = Left ventricular

RV = Right ventricular

Vo_2 = Oxygen consumption

METHODS

The National Heart, Lung, and Blood Institute–sponsored Pediatric Heart Network Fontan Cross-Sectional Study characterized the health status of 546 Fontan survivors aged 6 to 18 years, enrolled by seven clinical centers in North America. Prospective data collection included two-dimensional and Doppler echocardiography, exercise testing, health status questionnaires, and laboratory tests. Full details of the study have been published.[1,5,6] Written informed consent and assent were obtained according to local guidelines, and the study protocol was approved by the institutional review board or research ethics board of each center.

Echocardiograms were obtained according to a predetermined study protocol. None were obtained under sedation. The echocardiograms were submitted to the data-coordinating center for initial quality control and then forwarded to the echocardiography core laboratory for analysis. Ventricular morphology was characterized as left ventricular (LV) dominant (e.g., tricuspid atresia), right ventricular (RV) dominant (e.g., hypoplastic left heart syndrome), or mixed (e.g., unbalanced atrioventricular canal defect). A single representative beat was selected for all systolic and diastolic measures. To determine ventricular size and EF, the ventricle was analyzed from the apical transverse plane (ventricular long-axis) and the parasternal short-axis views. End-diastolic volume (EDV) and end-systolic volumes (ESV) were calculated using the biplane modified Simpson algorithm.[7] Percentage EF was then determined as $[(EDV - ESV)/EDV] \times 100$. Ventricular mass was calculated as myocardial EDV (epicardial volume − endocardial volume) × myocardial density (1.05 g/mL).

Assessment of diastolic function typically involves a multiparametric approach, predominantly using spectral Doppler velocities and tissue Doppler velocities. Lester *et al.*[8] described a practical approach to diastolic function assessment that involved assessments of mitral inflow characteristics, tissue Doppler early diastolic velocities, atrial size, pulmonary vein flow, isovolumics relaxation time, and mitral inflow propagation velocity. Some of these parameters were not assessable in single-ventricle anatomic variants, particularly atrial size, because of the markedly abnormal and variable geometries of the atrial chambers in the various iterations of single-ventricle circulations.

Therefore, our diastolic assessment was based on the following measurements: Doppler parameters of atrioventricular valve (AVV) inflow (ratio of early mitral inflow velocity [E] to atrial wave inflow [A] velocity [E/A ratio] and deceleration time [DT] of early inflow), tissue Doppler assessment of peak AVV annular velocities in early diastole (E′), and mitral inflow propagation velocity using M-mode color Doppler across the AVV inflow. For E′ values, we used the average of the velocities of the two walls bounding the systemic ventricle (septum and AVV annulus for single ventricles, right and left lateral walls of unbalanced atrioventricular canal systemic ventricle). Two grading systems were used. First, a diastolic function grade (DFG) was assigned to each study on the basis of an algorithm proposed by others.[8,9] For application to a pediatric cohort, an E/E′ Z score of 3 was used, the equivalent of an absolute value of E/E′ ratio of 10 in adults:

grade 0: normal = [(1 < E/A ≤ 2) and (DT ≥ 140 msec) and (E/E′ Z ≤ 3)];
grade 1: impaired relaxation = [E/A ≤ 1];
grade 2: pseudonormalization = {(1 < E/A ≤ 2) and [(DT < 140 msec) or (E/E′ Z > 3) or (mitral inflow propagation velocity < 55 cm/sec)]}; and
grade 3: restrictive = [E/A > 2].

Second, studies were classified as having restrictive pattern present or absent; a restrictive pattern was considered to be present if E/A > 2 or if 1 < E/A < 2 and DT < 140 msec. Because determination of both the DFG and presence or absence of a restrictive pattern required E/A ratios, 84 studies with E-wave and A-wave fusion (either partially or fully, as demonstrated in Figure 1) were excluded from analysis.

Historical factors were obtained from medical chart review, including pre-Fontan catheterization variables, history of coarctation requiring intervention at the time of the pre-Fontan catheterization, history of superior cavopulmonary anastomosis (e.g., bidirectional Glenn shunt, hemi-Fontan), and type of Fontan procedure (e.g., lateral tunnel connection, direct right atrial–to–pulmonary artery connection). Clinical data obtained at the time of echocardiography included B-type natriuretic peptide level, Child Health Questionnaire (CHQ) parental report[10] physical and psychosocial summary scores, and medications, including history of and current angiotensin-converting enzyme (ACE) inhibitor use. Subjects also underwent exercise stress testing, and the following parameters were recorded: peak oxygen consumption (Vo_2), ventilatory anaerobic threshold, percentage predicted peak Vo_2, percentage predicted ventilatory anaerobic threshold, maximal oxygen pulse/body surface area (BSA), maximal work rate, percentage predicted maximal oxygen pulse, percentage predicted maximal work rate, and percentage predicted maximal heart rate.

Statistical Analysis

Descriptive statistics are reported as mean ± SD or as median (interquartile range). Logistic regression was used to model the presence versus absence of a restrictive pattern as a function of age, and a generalized additive model was used to assess potential nonlinearity between age and restrictive pattern. Spearman correlation coefficients were used to examine the association between continuous diastolic function measures and age. Cumulative logistic regression was used to model the relationship between DFG and age. An interaction was fit between age and ventricular morphology to determine whether associations between DFG and age were dependent on anatomy. Similarly, tests of interaction were fit to assess whether associations of DFG and other clinical measurements depended on ventricular morphology. We used a χ^2 test to assess the association of DFG and categorical patient and clinical variables. Analysis of variance and Kruskal-Wallis tests were used to compare parameters of systolic function (EF, ESV, EDV, and mass/volume Z scores[11]), current AVV or semilunar valve regurgitation, current use of ACE inhibition, exercise performance, and functional status by DFG. Multivariate modeling was not conducted, because few variables were associated with DFG. Analysis of variance was used to compare the distributions of E/E′ ratio and other continuous diastolic function parameters and