The Effect of the Superior Cavopulmonary Anastomosis on Ventricular Remodeling in Infants with Single Ventricle

Renee Margossian, MD, Victor Zak, PhD, Amanda J. Shillingford, MD, Anthony M. Hlavacek, MD, James F. Cnota, MD, Michael D. Puchalski, MD, Jami C. Levine, MD, Brian W. McCrindle, MD MPH, Meryl S. Cohen, MD, Karen Altmann, MD, Piers C. Barker, MD, Daphne T. Hsu, MD, and Steven D. Colan, MD, for the Pediatric Heart Network Investigators, *Boston and Watertown, Massachusetts; Milwaukee, Wisconsin; Charleston, South Carolina; Cincinnati, Ohio; Salt Lake City, Utah; Toronto, Ontario, Canada; Philadelphia, Pennsylvania; New York, New York; and Durham, North Carolina*

Background: Infants with single ventricular physiology have volume and pressure overload that adversely affect ventricular mechanics. The impact of superior cavopulmonary anastomosis (SCPA) on single left ventricles versus single right ventricles is not known.

Methods: As part of the Pediatric Heart Network placebo-controlled trial of enalapril in infants with single ventricular physiology, echocardiograms were obtained before SCPA and at 14 months and analyzed in a core laboratory. Retrospective analysis of the following measurements included single ventricular end-diastolic volume (EDV), end-systolic volume (ESV), mass, mass-to-volume ratio (mass/volume), and ejection fraction. Qualitative assessment of atrioventricular valve regurgitation and assessment of diastolic function were also performed.

Results: A total of 156 participants underwent echocardiography at both time points. Before SCPA, mean ESV and mass *Z* scores were elevated (3.4 ± 3.7 and 4.2 ± 2.9, respectively) as were mean EDV and mass/volume *Z* scores (2.1 ± 2.5 and 2.0 ± 2.9, respectively). EDV, ESV, and mass decreased after SCPA, but mass/volume and the degree of atrioventricular valve regurgitation did not change. Subjects with morphologic left ventricles demonstrated greater reductions in ventricular volumes and mass than those with right ventricles (mean change in *Z* score: left ventricular [LV] EDV, −1.9 ± 2.1; right ventricular EDV, −0.7 ± 2.5; LV ESV, −2.3 ± 2.9; right ventricular ESV, −0.9 ± 4.6; LV mass, −2.5 ± 2.8; right ventricular mass, −1.3 ± 2.6; $P \leq .03$ for all). Approximately one third of patients whose diastolic function could be assessed had abnormalities at each time point.

Conclusions: Decreases in ventricular size and mass occur in patients with single ventricle after SCPA, and the effect is greater in those with LV morphology. The remodeling process resulted in commensurate changes in ventricular mass and volume such that the mass/volume did not change significantly in response to the volume-unloading surgery. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Single ventricle, Systolic ventricular function, Diastolic ventricular function, Ventricular remodeling, Superior cavopulmonary anastomosis, Congenital heart disease

In neonates and infants with single ventricle (SV) heart disease, the functioning ventricle must support both the systemic and pulmonary circulations, resulting in volume and pressure overload. One major aim in the surgical management of these patients is to mitigate the impact of the chronic volume overload that can lead to ventricular dilation and hypertrophy and ultimately to decreased systolic function. One of the effects of the superior cavopulmonary anastomosis (SCPA) procedure is to decrease the ventricular volume overload

From the Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts (R.M., J.C.L., S.D.C.); New England Research Institutes, Watertown, Massachusetts (V.Z., S.D.C.); the Medical College of Wisconsin, Milwaukee, Wisconsin (A.J.S.); the Medical University of South Carolina, Charleston, South Carolina (A.M.H.); Cincinnati Children's Hospital, Cincinnati, Ohio (J.F.C.); the University of Utah, Salt Lake City, Utah (M.D.P.); The Hospital for Sick Children, Toronto, Ontario, Canada (B.W.M.C.); The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (M.S.C.); Columbia University, New York, New York (K.A., D.T.H.); and Duke University Medical Center, Durham, North Carolina (P.C.B.).

This work was supported by U01 grants from the National Heart, Lung, and Blood Institute (HL068269, HL068270, HL068279, HL068281, HL068285, HL068292, HL068290, HL068288, and HL085057) and the US Food and Drug Administration Office of Orphan Products Development. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Reprint requests: Renee Margossian, MD, Department of Cardiology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115 (E-mail: *renee.margossian@cardio.chboston.org*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.03.005

Abbreviations

AVV = Atrioventricular valve

AVVR = Atrioventricular valve regurgitation

EDV = End-diastolic volume

EF = Ejection fraction

ESV = End-systolic volume

ISV = Infant single ventricle

LV = Left ventricular

Mass/volume = Mass-to-volume ratio

RV = Right ventricular

SCPA = Superior cavopulmonary anastomosis

SV = Single ventricle

SVC = Superior vena cava

V_{fp} = Ventricular flow propagation

by directing systemic venous blood from the upper part of the body to the lungs, bypassing the SV. The SCPA procedure has been shown to reduce the incidence of systolic ventricular dysfunction in SV patients by providing an incremental decrease in volume overload early in infancy.[1-3]

Several investigators have attempted to define the changes in ventricular volumes, systolic function, and mass-to-volume ratio (mass/volume) in SV patients in small case series.[3-5] Others have made an effort to characterize changes in diastolic function.[6] Each of these studies has used different methods of assessment, precluding comparisons of the groups studied. Most reports focus on patients with left ventricular (LV) morphology, and if patients with LV and right ventricular (RV) morphologies are included, the results are typically combined for analysis.

The National Heart, Lung, and Blood Institute–sponsored Pediatric Heart Network completed a multicenter randomized placebo-controlled trial of the angiotensin-converting enzyme inhibitor enalapril in infants with single ventricular physiology, the Infant Single Ventricle (ISV) study.[7] Clinical and echocardiographic data were prospectively gathered on all subjects. No difference was found in the primary outcome of weight-for-age *Z* score or in ventricular volumes, mass, or ejection fraction (EF) between the placebo and enalapril-treated groups. Using this large, well-characterized cohort, we sought to describe the changes in LV and RV geometry and systolic function that occur in response to SCPA surgery, to explore factors that are associated with those changes, and to characterize diastolic function in infants with single ventricular physiology.

METHODS

Details of the study design and main results of the ISV trial have been published.[7,8] In brief, infants with single ventricular physiology were enrolled between 7 and 45 days of age, across 10 North American centers, between August 2003 and May 2007. Subjects were included if they had stable hemodynamics and if they were anticipated to undergo SCPA surgery. The trial followed subjects through the SCPA surgery to the final study visit at 14 months of age. Written informed consent was obtained from a parent or guardian. The study was approved by the institutional review or ethics board at each participating institution.

Patient data collected included detailed anatomic diagnosis, age at enrollment and at SCPA surgery, gestational age, gender, race, medication history, and medical and surgical data from the SCPA procedure. Ventricular morphology was characterized as LV dominant (e.g., tricuspid atresia) or RV dominant (e.g., hypoplastic left heart syndrome). Patients with indeterminate or mixed ventricular morphology (e.g., unbalanced atrioventricular canal defects with two ventricles present) were not included in the RV-LV comparison analyses for this report.

Echocardiographic Data

A detailed quantitative echocardiographic evaluation was performed, including ventricular volumes and systolic and diastolic function, at two time points during the study: before SCPA and at 14 months (final study visit). Sedation was used according to local practice. Echocardiography was performed according to a prospective, standardized imaging protocol, and studies were sent to the echocardiographic core laboratory for interpretation by a single reader.

The systemic ventricle was imaged from the apical (ventricular long-axis) and parasternal short-axis planes. The endocardial border was traced at end-diastole and end-systole; the epicardial border was traced at end-diastole in both planes. End-diastolic volume (EDV), end-systolic volume (ESV), and mass were then calculated using a modified Simpson biplane method.[9] The percentage ventricular EF was calculated as [(EDV − ESV)/EDV] × 100. Ventricular mass was calculated as myocardial EDV (epicardial volume − endocardial volume) × myocardial density (1.05 g/mL). Inter- and intraobserver variabilities for this method of assessing morphologic SVs have been reported previously.[9] The degree of atrioventricular valve (AVV) regurgitation (AVVR) was qualitatively assessed and grouped as none/mild or moderate/severe.

Doppler assessment of AVV inflow was performed for E, A, early deceleration time, and a-wave duration. If the AVV inflow demonstrated partially fused E and A waves, which is common at infant heart rates, only the E velocity was recorded. If the waveforms were completely fused, no Doppler measurements were used. Doppler tissue imaging of annular myocardial velocities recorded E′ and A′ diastolic velocities at the two walls, which were averaged. Similar to AVV inflow assessment, if the tissue Doppler tracing demonstrated partial E′ and A′ fusion, only E′ velocity was recorded, and no measurements were used if E′ and A′ were completely fused. Figure 1 depicts examples of AVV inflow waveform fusion, and Figure 2 shows examples of Doppler tissue imaging waveform fusion. Figure 3 demonstrates the effect of the R-R interval on fusion of the waveforms. Duration of pulmonary vein flow reversal and ventricular flow propagation (V_{fp}) were also recorded. E/E′ values > 10 and V_{fp} values > 45 were considered abnormal.[10]

Echocardiographic data were reviewed and measurements made using custom software (Marcus Laboratories, Boston, MA).

Statistical Analysis

The data used in the analyses were obtained in a prospective manner; the analyses reported here were retrospectively proposed and implemented. To adjust echocardiographic measurements to account for the effect of body size (volume, mass) and age (EF, Doppler variables), *Z* score values were used.[11] *Z* score calculations were derived from the systemic left ventricle in a group of normal control subjects; the ventricular size and function *Z* scores used are therefore based on systemic LV measurements.

Data are described as frequencies, medians with 25th and 75th percentile values, and means with SDs as appropriate. For some of the evaluations below, echocardiograms with partial data were included; each section lists the number of subjects included for subanalysis. Echocardiographic measurements of the LV and RV groups were compared using Student's *t* test for nonskewed variables and the Wilcoxon rank sum test for other measures. In the subset of