Boston Children's Hospital

Sept 30 2022

TITLE: Assessment of Patterns of Ventricular Contraction Using 3-Dimensional Echocardiography in Children with Functional Single Right Ventricles Palliated to Fontan Circulation

A. Specific Aims/Objectives

Aim 1. Do right ventricular (RV) contractile patterns in single RV patients with Fontan physiology differ from age–matched controls?
Aim 2. What is the strength of correlation between traditional 2-dimensional echo assessments of ventricular function and novel 3-dimensional echo/ReVISION assessments of RV function in this population?
Aim 3. What is the reproducibility of RV volumes estimated from RV endocardial surface detection in patients palliated to Fontan circulation?

B. Background and Significance

Echocardiography has been the primary diagnostic tool in the single ventricle population but remains significantly limited with respect to the assessment of ventricular function. More novel, three-dimensional techniques may offer significant improvement over traditional, 2D echo assessments of RV function. Recently, software (the ReVISION program) has been developed that is able to decompose 3D RV datasets into separate components of RV function, representing the three primary components of RV contraction – longitudinal movement of the base toward the apex, radial inward movement of the free wall toward the septum and antero-posterior traction of free wall insertion points to the septum (Appendix).[1,2] This method has been used to study variations in contraction patterns in subjects with repaired congenital heart disease, including tetralogy of Fallot and heart disease with a systemic right ventricle in a biventricular circulation (i.e. D-transposition of the great arteries status post atrial switch, L-transposition of the great arteries).[3,4] By using this technique in the single ventricle population, we hope to gain new insights into the alterations of systemic right ventricular function in the Fontan circulation, compared to normal patients.

C. Preliminary Studies

As described above, this technique has been utilized to study right ventricular function in adults with both congenital and non-congenital heart disease. More recently, we used the ReVISION method to analyze RV function in cohort of 166 healthy, pediatric subjects (data to be presented at the American Society of Echocardiography Scientific Sessions in June 2022). In this population of healthy children with structurally normal hearts, the anteroposterior and radial shortening appeared to contribute as much as longitudinal shortening to overall RV function. We also observed an overall decrease in global RV function with age in children, with decreases in REF and AEF driving that maturational change. We aim to build on this work by assessing the components of contractile function in the single, systemic RV in patients with hypoplastic left heart syndrome.

D. Design and Methods

(1) Study Design

Single center, prospective cohort.

(2) Patient Selection and Inclusion/Exclusion Criteria

Study subjects include those age ≤18 years with functional single ventricle with systemic RV (i.e. hypoplastic left heart syndrome including mitral stenosis/aortic stenosis, mitral stenosis/aortic atresia, and mitral atresia/aortic atresia, and right-dominant complete atrioventricular canal defect) palliated to Fontan circulation who are scheduled to undergo echocardiography for routine clinical reasons. Subjects with arrhythmia at the time of image acquisition will be excluded from analysis.

Control subjects will be selected by age-matching (within 12 months of age at the time of echocardiogram) from a historical cohort of patients who presented to cardiology clinic for evaluation, underwent echocardiography with 3D acquisition of the RV and were ultimately deemed free of cardiac disease with normal physical examination, EKG and echo.

(3) Description of Study Treatments or Exposures/Predictors

Aim 1: Patient group (Fontan vs normal)
Aim 2: Traditional 2D parameters of RV function: 2D strain (longitudinal free wall, total global strain), S', fractional area change (FAC); qualitative assessment of RV systolic function

(4) Definition of Primary and Secondary Outcomes/Endpoints

Aim 1: Global 3D RV ejection fraction (RVEF), and: longitudinal EF (LEF), radial EF (REF), anteroposterior EF (AEF), as well as these 3 parameters indexed to the global EF to assess their relative contribution to the overall ejection fraction (e.g. LEFi, REFi, AEFi)

Aim 2: Global 3D RV EF, and ReVISION measures as above (RVEF, AEF, LEF, REF, AEFi, LEFi, REFi), Global circumferential strain, global longitudinal strain, global area strain.

Additional descriptive data to be collected:

Demographic and clinical data (at the time of echocardiogram): Age; sex; weight; height; BSA; BMI; heart rate; SBP; DBP; native anatomy/variant of HLHS; prior number of surgeries; medications.

2D echocardiographic variables: TR grade; neo-AR grade; aortic arch obstruction grade (note that grades will be taken from the echo reports, and characterized as mild, moderate, severe); presence of fenestration; gradient across fenestration; arch obstruction.

Additional 3D echo variables: RVEDVi, RVESVi

(5) Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

Echocardiograms of the Fontan patients will be performed by a group of sonographers trained in 3D volume acquisition, using a breath-hold technique for 3D acquisition to minimize stitch artifact. The limited echo images obtained for research purposes will be obtained at the end of the clinical echo obtained as part of routine clinical care for subjects. Clinical images obtained as part of routine clinical care will be stored as a single study on the clinical PACS server. The sonographer will then create a separate study that will include only the several images needed for research purposes. After image acquisition, this separate research study will be transferred and stored on the separate, PACS research server. As such, the research images will not be interpreted by the reading cardiologist nor the results incorporated into the medical record. Documentation and details of verbal consent will be stored in the REDCap database. Subjects will be matched 1:1 with historical controls (previously obtained data) by age (within 12 calendar months at the time of echocardiogram).

After completion of the echo, the 3D echocardiographic data will be cleaned of any patient identifiers and uploaded into the TomTec 4D RV function imaging software. This software allows for contouring of the right ventricular borders to generate a 3D voxel. This voxel is de-identified and then downloaded and saved on a BCH workspace on the secure BCH server. Finally, the de-identified voxel is uploaded into the online, freely available ReVISION program. Each dataset is de-identified within the program and can only be accessed through a user-specific account that is password-protected. The ReVISION software outputs the primary outcomes specified above for aims 1 and 2.

In addition to the 3D data analysis detailed above, the 2-dimensional, demographic and clinical variables will be abstracted from the clinical medical record and clinical echocardiogram report by select investigators (Christopher Valle, Alessandra Ferraro).

(6) Study Timeline (as applicable)

Study recruitment: starting from time of IRB approval (ideally summer/early Fall 2022) and continuing for approximately 1 year or until target recruitment population is attained.

Data acquisition and analysis: will correspond with period of study recruitment

Final data analysis, abstract formation and manuscript drafting: anticipated this period will take up to 6 months following close of study recruitment period (through Winter/Spring 2024)

E. Adverse Event Criteria and Reporting Procedures

Given that there is no risk to the acquisition of a few additional echo images, we do not foresee adverse events nor the need to report adverse events.

F. Data Management Methods

All research data will be entered in a REDCap (Research Electronic Data Capture) database housed on the Boston Children's Hospital server. REDCap is a secure, password-protected database. REDCap's "Logging" feature allows for a timestamped audit trail for the study. Study staff may gain REDCap access only after completing training in the technology and data entry procedures for this study.
The REDCap database includes features of a quality management system. REDCap field validation includes appropriate field types, text field validation types, and ranges. The REDCap Data Quality and Issue Resolution functions will be used to monitor data quality. The standard data quality rules as pre-defined in REDCap's Data Quality module will be utilized for edit checks.

G. Quality Control Method

At the level of data acquisition, quality control will be ensured by using only a select (i.e. 3-4 individuals) group of sonographers trained and skilled in 3-dimensional echocardiographic image acquisition. Additionally, sonographers will be instructed to obtain images using a breath-hold technique to limit stitch artifact. Finally, sonographers will be provided an imaging protocol to follow for each subject (see Appendix).

At the level of data interpretation, only a single investigator (Christopher Valle) will perform contouring of the right ventricular borders using TomTec 4D RV imaging software to limit interobserver variability.

As a safety check of the validity of measurements, two additional investigators (David Harrild, Alessandra Ferraro) will perform repeat contouring of the right ventricular borders in a randomly selected subset to estimate intra- and inter-observer variability (see analysis plan below).

H. Data Analysis Plan

Hypothesis: Subjects with Fontan circulation have a higher contribution of radial EF to global ejection fraction compared to age-matched controls with structurally normal hearts

Descriptive statistics will include mean ± SD or median (IQR) for continuous variables and frequencies with percentages for categorical data. For aim 1, differences in all outcome variables will be compared between the Fontan population and historical controls using Student's t-test for normally distributed data and the Wilcoxon rank sum test for non-normally distributed data. Between-group differences for categorical variables (e.g., systolic function grade) will be assessed using the Mantel-Haenszel test for linear trend and a Fisher exact test.

For aim 2, correlations between ReVISION RV functional parameters and 2D echocardiographic functional parameters (i.e. 2D strain, FAC, S', qualitative function) will be assessed using Pearson or Spearman correlation coefficient, as appropriate. Correlation analyses will be performed separately for the Controls and the group of subjects with Fontan circulation. To assess whether the magnitude of correlation is similar for Controls and subjects with Fontan circulation, linear regression with a test of diagnosis X 2DE predictor interaction will be performed.

To test reproducibility of computation of RV volumes, RV endocardial surface detection will be repeated in randomly selected Fontan patients by the same observer and by a second independent observer, both blinded to all prior measurements. The intraclass correlation coefficient (ICC) will be estimated to assess intra-observer and inter-observer agreement of independent measurements of RV volumes (RVEDV and RVESV).

I. Statistical Power and Sample Considerations

Aim 1: Assuming a mean REF 25.1 ± 7 % in the healthy controls (previous study, data not yet published), then with 49 subjects in each group and a two-sided 0.05-level test will have 80% to detect a mean group difference of 4% (0.6 SD) or larger in REF. Assuming a 70% rate of successful analysis (pilot study), then we would need to enroll 70 patients with HLHS.

Aim 2: With N=64 subjects with Fontan circulation, there is 80% power to detect a correlation of 0.35 or larger between a novel reVISION measure and a traditional 2D echo measure.

Aim 3: For the reproducibility aim, observer measurements on the studies of N=31 Fontan patients will yield a 95% confidence interval of maximum width 0.20 if agreement is high (ICC=0.85). If agreement is lower (ICC=0.70), then this sample size will be less precise, yielding a wider confidence interval, of width 0.37.

J. Study Organization

The principal investigator, David Harrild, MD, PhD, will have overall responsibility for the conduct of the study. Sub-investigators are cardiologists and cardiology researchers in the Heart Center at BCH, with appropriate credentialing. Dr. Harrild has responsibility for training and delegating tasks to study staff. Dr. Harrild's delegation of responsibilities follows Boston Children's Hospital guidance.

K. References

1. Ishizu T, Seo Y, Atsumi A, et al. Global and Regional Right Ventricular Function Assessed by Novel Three-Dimensional Speckle-Tracking Echocardiography. *J Am Soc Echocardiogr*. Published online 2017. doi:10.1016/j.echo.2017.08.007
2. Lakatos B, Tősér Z, Tokodi M, et al. Quantification of the relative contribution of the different right ventricular wall motion components to right ventricular ejection fraction: the ReVISION method. *Cardiovasc Ultrasound*. Published online 2017. doi:10.1186/s12947-017-0100-0
3. Surkova E, Kovacs A, Bispo D, et al. Mechanical contraction patterns of the systemic right ventricle: a 3D echocardiography study. *Eur Hear J - Cardiovasc Imaging*. 2021;22(Supplement_1). doi:10.1093/ehjci/jeaa356.412
4. Bidviene J, Muraru D, Kovacs A, et al. Global and regional right ventricular mechanics in repaired tetralogy of Fallot with chronic severe pulmonary regurgitation: a three-dimensional echocardiography study. *Cardiovasc Ultrasound*. 2021;19(1). doi:10.1186/s12947-021-00260-3