PROTOCOL TITLE: Interstage right ventricular functional assessment as a prognostic measure of morbidity/mortality in patients with single ventricle physiology

Example: Research Protocol Retrospective Review of Records
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1) Protocol Title
   Interstage right ventricular functional assessment as a prognostic measure of morbidity/mortality in patients with single ventricle physiology.

2) IRB Review History*
   NA

3) Objectives*
   The objective of this study to evaluate the use of Tricuspid Motion Annular Displacement (TMAD) measures and lateral annular displacement versus conventional measurements from pre and post first stage palliation (Norwood) surgery and pre Glenn surgery to evaluate them as prognostic measures of patient morbidity and/or mortality.

   1. Examine the relationship between pre Stage I Norwood echocardiographic function tests and clinical outcomes during the first interstage period (between the Stage I Norwood and Glenn).
   2. Examine the relationship between post Stage I Norwood echocardiographic function tests and clinical outcomes during the first interstage period (between the Stage I Norwood and Glenn).
   3. Examine the relationship between pre Stage II Glenn function and postoperative clinical outcomes for patients who had the Glenn.

4) Background*
   Hypoplastic left heart syndrome (HLHS) is a congenital birth defect wherein the left sided structures of the heart do not develop as properly. There are several variants where the left ventricle (LV), the mitral valve, the aortic valve and the aortic arch may be underdeveloped or malformed to varying degrees and in various combinations. The cause of such defects is largely unknown but is attributed to a combination of genes and maternal environmental factors (2). This is the most common cause of single ventricle physiology, where there is only one adequate systemic pumping chamber. Other conditions, like unbalanced atrioventricular canal, can lead to single ventricle physiology. It is also possible to have a single LV, but this is less common. Repair and outcomes of that condition
are different than patients with a single right ventricle (RV). Patients with a single RV are palliated in a common manner. There are currently three stages of surgical palliation: the first stage palliation usually involves the Norwood procedure (with a BT shunt or with the Sano shunt) (referred to as Stage I Norwood throughout protocol) to ensure unobstructed outflow from the pumping chamber to the body via an aorta. The second stage is the Bidirectional Glenn procedure (referred to as Glenn throughout protocol) which connects the superior vena cava to the pulmonary arteries to provide blood flow to the lungs via venous return rather than a high pressure shunt. The final stage is the Fontan procedure which involves connecting the inferior vena cava to the pulmonary arteries, thus removing mixing, with all venous blood returning to the lungs prior to going to the heart.

Improved surgical techniques and perioperative care have led to lower morbidity and mortality in patients with HLHS who have single ventricle palliative surgeries. Early mortality after the Stage I Norwood procedure has been reported to be as low as 6%. The first interstage period between the Stage I Norwood and Glenn poses the highest risk, with mortality between 9 - 19% (3). Despite improved outcomes, multiple morbidities are encountered in the interstage period including emergent readmissions and slow growth. Independent risk factors for morbidity and mortality include tricuspid valve regurgitation (TR) and depressed function of the RV. There is consensus that RV function is an important determinant of single ventricle palliative surgery outcomes. In a study published in 2011, Khoo et al (5), found that reduced RV function was consistently seen before the Glenn. The LV is hypoplastic or not well formed, so the RV becomes the systemic single ventricle. Hence, RV function is an important determinant of clinical status in these patients. At this point in time, there is a paucity of published reports on measurement of RV function in the interstage period as it relates to outcomes and no consensus on how to measure RV function.

Altmann et al (7), in 2000, used two-dimensional echocardiography to assess RV function and used it as a predictor of outcome in HLHS. In a cohort of 60 patients, if patients had pre-Stage I Norwood RV dysfunction, then they had significantly greater mortality before Glenn. Survival at 18 months after Stage I Norwood surgery was 93% for patients with normal RV function preoperatively and only 47% for those with abnormal function (p = <0.005). The relative risk for later mortality was 11 times greater for patients with initial RV dysfunction. Another showed that measurements of function decrease after the Stage I Norwood operation, but did not assess mortality outcomes (4). Finally, worsening function before Glenn compared to pre-Stage I Norwood measurements has been
demonstrated (5, 6). These data, taken as a whole, suggest that there is ventricular dysfunction in this group and that it affects outcomes.

While RV function remains an important prognostic indicator of morbidity and mortality, there are limitations to accurately measuring it due to its asymmetry and there is no widely accepted method to accomplish this. This asymmetry makes estimating ejection fraction very difficult to calculate reliably. In contrast, LV function can be measured more easily because it is symmetric so a few measurements can be used to estimate the ejection fraction.

The traditional, and most widely used, method of assessing right ventricular function is two dimensional echocardiographic qualitative evaluation (‘eyeballing’). More quantitative methods include tracing the RV endocardial border or measuring RV dimensions (this is cumbersome and inter-observer variability is high) (17). Three dimensional echocardiography and magnetic resonance imaging are more sophisticated methods of measuring right ventricular function. However, both of these methods are very time-consuming and have limited availability.

Two easier and faster methods of right ventricular function assessment are tricuspid lateral annular excursion which is similar to tricuspid annular plane systolic excursion (TAPSE) and tricuspid motion annular displacement (TMAD).

TAPSE estimates the systolic excursion at the lateral annulus of the tricuspid valve. TAPSE is normally assessed with M-mode in an apical four-chamber view, placing the M-mode cursor on the lateral tricuspid annulus (8). Maximum systolic excursion of the lateral annulus is measured on M-mode. This can also be done now using speckle tracking software that allows us to track the annulus from two dimensional images and measure how far it moves. This measure gives the longitudinal shortening of the RV which estimates global function. An excellent correlation between the TAPSE and RV ejection fraction as assessed by radionuclide angiography was shown by Kaul et al and Kjaergaard et al (9, 10) and with Simpson’s RVEF by Miller et al (11). This approach appears reproducible and proved to be a strong predictor of prognosis in heart failure (12).

TMAD is similar to TAPSE in that it measures tricuspid valve annular displacement in the longitudinal direction. However, in contrast to TAPSE which measures the absolute displacement of the lateral tricuspid valve
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TMAD measures the amount of systolic excursion of both the medial and lateral tricuspid annulus in relation to a point on the RV apex. From this, a percent shortening of the whole ventricle is calculated using speckle tracking technology to track portions of the ventricle through systole. This method only takes a few minutes so is much easier than other methods. As part of calculating TMAD, lateral tricuspid annular displacement is also measured (though this is theoretically not TAPSE as it is not done on M-mode) because one of the tracked points is the lateral annulus of the tricuspid valve. Hugues et al, Smith et al and Ueti et al, in three independent studies, found that the RV ejection fraction positively correlated with tricuspid annular displacement compared with other 2-D and 3-D techniques (13), with MRI (14) and with radionuclide angiography (15).

We know that there are certain variables that are predictive of outcome in single ventricle patients including initial right ventricular function prior to the Norwood operation. Ultimately, right ventricular dysfunction determines long term prognosis for patients with hypoplastic left heart syndrome, so it is essential to accurately assess/measure right ventricular function. We do not currently have a widely used, accessible and fast way to assess RV function and correlate that with outcomes. However, as shown by several recent studies, TMAD and TAPSE can be accurate and reliable assessors of this important prognostic variable. TMAD improves upon the shortcomings of traditional modalities. As part of our study, we will include two more traditional measures of RV function.

Research is lacking on tying these measures of RV function to outcomes in the interstage period. Previous studies have not associated TMAD to clinical outcomes in our population. Determining this association may make TMAD more meaningful for future clinical use.

In our study, we will use the retrospective record of TMAD, lateral annular displacement, RV ejection fraction and fractional area change to assess echocardiographic function tests and correlate that with clinical outcomes. We believe TMAD and lateral annular displacement will perform better at predicting clinical outcomes. Specific study aims are to:

4. Examine the relationship between pre Stage I Norwood echocardiographic function tests and clinical outcomes during the first interstage period (between the Stage I Norwood and Glenn).

5. Examine the relationship between post Stage I Norwood echocardiographic function tests and clinical outcomes during the first interstage period (between the Stage I Norwood and Glenn).

6. Examine the relationship between pre Stage II Glenn function and postoperative clinical outcomes for patients who had the Glenn.
If our hypothesis is proven, this will identify TMAD and lateral annular displacement as useful measures of right ventricular function and help prognosticate interstage and post-Glenn morbidity in patients with single ventricle physiology.

5) **Inclusion and Exclusion Criteria***

A list of all patients who underwent the Stage I Norwood and the Glenn in the last four years will be obtained from the cardiovascular surgery team. From this list, the PI will screen based on the criteria below.

**Inclusion criteria:**
- Children diagnosed with single ventricle physiology with RV dominance (HLHS, Unbalanced AVC, mitral stenosis/atresia, aortic stenosis/atresia)
- Had at least one echocardiogram of sufficient quality for TMAD analysis prior to and within a month after the Stage I Norwood or within six weeks prior to the Glenn.

**Exclusion criteria**
- Glenn performed after 18 months
- Children who subsequently underwent a two ventricle repair

6) **Study-Wide Number of Subjects***

Between 2009 and 2013 there were 146 patients in our age range who had single ventricle palliations. We estimate 20% of those will not meet our inclusion criteria. We further estimate from previous experience that 10% will not have adequate echocardiographic images for our analysis. This will leave approximately 100 patients for our analysis. Additional patients through May 2014 will be included so we anticipate the number of enrolled subjects to be 130.

7) **Study-Wide Recruitment Methods***

We will not actively recruit subjects, but will review their medical records for the data of interest. Potential subjects will be identified using the cardiovascular surgical database. This study does not require any interventions or data collection beyond what is routinely collected and documented in the delivery and care of children.
8) Study Timelines*

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<tr>
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<td>Data analysis</td>
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9) Endpoints

Primary Study Endpoints:

- Correlations between echocardiographic measurements (e.g. TMAD, lateral displacement, fractional area change and RV ejection fraction) pre Stage I Norwood and clinical outcome measures (e.g. growth, mortality, hospital readmissions, presence of moderate atrio-ventricular valve dysfunction, end diastolic ventricular pressure, cardiac index).

- Correlations between echocardiographic measurements (e.g. TMAD, lateral displacement, fractional area change and RV ejection fraction) post Stage I Norwood and clinical outcome measures (e.g. growth, mortality, hospital readmissions, presence of moderate atrio-ventricular valve dysfunction, end diastolic ventricular pressure, cardiac index).

- Correlations between echocardiographic measurements (e.g. TMAD, lateral displacement, fractional area change and RV ejection fraction) pre Glenn and clinical outcome measures (e.g. time to extubation, time to chest tube removal, total inotrope score, time to negative fluid balance, ICU and hospital LOS and mortality).

10) Procedures Involved

This study will be a retrospective study that will compare cardiac function and outcomes during single ventricle palliation. Once IRB approval is obtained, we will begin the review of medical records for eligible subjects who received care between 1/1/2009 - 8/1/2014.

The specific procedures we will use during this study are as follows:

A list of children who have had the Stage I Norwood or Glenn surgeries between January 1st, 2009-August 15th, 2014 will be obtained from our cardiovascular surgery database. From this list, we will determine a group of subjects based on the inclusion/exclusion criteria listed previously. At this point, the subjects will be separated into group 1.
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(having undergone Stage I Norwood) and group 2 (having undergone Glenn). Most of these patients will be in both groups, but data from group 1 will be analyzed completely separately from group 2.

Apical four chamber clips from echocardiograms performed during standard care will be used to assess function. Specifically, we will use Q lab, part of Phillips software our echocardiographic laboratory to derive TMAD and lateral tricuspid annular displacement values. A single investigator will calculate all RV functional values.

In order to ensure accuracy, S. Javed H. Zaidi and Vivian Cui will measure TMAD and lateral tricuspid annular displacement on 15 echocardiograms randomly selected from those included in the study. Measurements will be compared between two observers (inter-observer variability). Another set of measurements on the same studies will be done by S. Javed H. Zaidi one month after the first set and those measurements will be compared with his first set (intra-observer variability).

Group one will have RV functional measures (TMAD, lateral annular displacement, RV ejection fraction and fractional area change) calculated from echocardiograms pre and post Stage I Norwood. Group two will have RV functional measures calculated from an echocardiogram done within six weeks prior to the Glenn. All echocardiographic calculations done during this study will be based upon images stored in the Xcelera program in our pediatric echocardiography lab.

A detailed chart abstraction will be performed to record the end points listed below. Clinical data will be obtained from our Care Connection EMR. Catheterization data if needed will be obtained from our Merge software.

Data to be recorded:
  o  Demographics (age, gender, weight, weight percentile)

For group one subjects (echocardiographic measurements pre and post Norwood)
  • Growth until Glenn procedure assessed by Z score for weight at time of procedure
  • Prematurity (<37 wga)
  • Mortality
  • Number of unexpected readmissions prior to Glenn
  • Development of at least moderate atrio-ventricular valve dysfunction assessed by pre-Glenn echocardiogram by time of Glenn as determined by the final report on that echocardiogram
  • End diastolic ventricular pressure assessed at pre-Glenn catheterization
  • Cardiac index assessed at pre-Glenn catheterization
  • Cardiopulmonary bypass time
  • Presence of an extracardiac anomaly or genetic syndrome

For group two subjects (echocardiographic measurements prior to Glenn)
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- Time to extubation
- Time to chest tube removal
- Total inotrope score post-procedure
- Time to negative fluid balance
- Total hospital and pediatric surgical heart unit (PSHU) length of stay
- Hospital mortality
- Presence of elevated pulmonary artery pressure
- Pre-bidirectional Glenn AV valve regurgitation that is greater than mild
- Low weight for age z score at time of surgery

11) Data and Specimen Banking*

NA

12) Data Management

Data Management
Data will be collected from the electronic medical record and recorded by study investigators. Data will be stored in an electronic password protected database.

Power Analysis
There are no published data of the correlations between echocardiographic measures and clinical outcome. This study is using retrospective data to explore the relationship among these variables in an exploratory manner. A power analysis was not conducted as there were no data on which to base the calculation. The estimation of proposed sample is based on the number of cases that are anticipated to have the necessary data in their medical record. A general rule of thumb is to have 10 subjects per variable in the multiple regression, thus our sample estimate of 100 – 130 subjects will be appropriate.

Data Analysis
For our statistical analyses, continuous data will be reported as mean ± SD and categorical data will be reported using frequencies. Univariate statistics including Pearson r and Spearman rho will be used to identify significant correlations among variables. Based on these univariate analyses variables will be chosen for a multiple linear regression for continuous outcome variables or logistic regression for binary outcome variables according to each study aim. Statistical significance will be declared when computed p values from two-sided tests are <0.05. Analyses will be performed using IBM SPSS statistics version 20 for Windows (IBM, Inc, Somers, NY).

Data Storage
All information gathered during this study will be kept confidential. Subjects will be assigned case numbers and collected data will only be seen by the research team. The results of this study may be published in scientific journals or be presented at professional meetings, but no individuals will be identified. The collection and handling of data will be in complete accordance with the HIPPA regulations. The research-related records for
13) **Provisions to Monitor the Data to Ensure the Safety of Subjects***

   Not applicable.

14) **Withdrawal of Subjects**

   Not applicable

15) **Risks to Subjects**

   There is no intervention and no additional procedures involved in this study and no risks are anticipated for research subjects. The only potential risk is the loss of confidentiality; see safeguards in Section 26.

16) **Potential Benefits to Subjects***

   There are no direct benefits to the subjects, though there may be benefit to future single ventricle patients.

17) **Vulnerable Populations***

   This research involves children as a vulnerable population (see Attachment A, Checklist HRP-416). This study poses no risk to the health of the children.

18) **Multi-Site Research***

   Not applicable

19) **Community-Based Participatory Research***

   Not applicable

20) **Sharing of Results with Subjects***

   Results of the study will not be shared with subjects or their families.

21) **Setting**

   The research will be conducted in two locations within the Heart Institute for Children. Echocardiogram analysis will be performed in the echocardiogram lab. Chart review will be performed on password protected computers in the Children's Heart Institute offices.

22) **Resources Available**

   The PI has experience in echocardiography and cardiology and is board certified in cardiology. He also has experience with Norwood and post-
Norwood patients and sits on the interstage board at Advocate Children's Hospital. Previous research involved speckle tracking, the same software that will be used in the current study (1).

Use of software and computers will be provided by the echocardiogram lab. Two investigators will be performing the echocardiographic analysis on the lab software from Phillips. Analysis of clips requires only a few minutes per patient. The echocardiogram lab has Phillips software that pulls in images and has the requisite software to perform the analysis.

Biostatistics support will be provided by one of the investigators.

23) **Prior Approvals**

Not applicable

24) **Recruitment Methods**

See protocol section 7.

25) **Local Number of Subjects**

See protocol section 6.

26) **Confidentiality**

All information gathered during this study will be kept confidential. Data collection forms and the database that include the patient name and other PHI will be seen only by the principal investigator and research team. All information and data gathered in this study will be placed in a password protected computer with restricted access by only the investigative team. All data will be destroyed 2 years after results are reported. The results of this study may be published in scientific journals or be presented at professional meetings, but no individuals will be identified. The research-related records for this study may be inspected by a federal regulatory agency and the Institutional Review Board.

27) **Provisions to Protect the Privacy Interests of Subjects**

Study participants data will be collected via the electronic medical record. This data will be stored only on a computer at the Heart Institute for Children and will be password protected. Only the PI and co-investigators will have access to the data.

28) **Compensation for Research-Related Injury**

Not applicable
30) **Consent Process**

We seek exemption from informed consent and HIPPA authorization because there is no greater than minimal risk involved in the research. Based on HRP-416, this waiver is appropriate.

a. This research is not FDA regulated
b. The research does not involve non-viable neonates.
c. The research involves no more than minimal risk to the subjects.
d. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
e. The research could not practicably be carried out without the waiver or alteration.

We request a waiver of HIPPA Authorization and address the following elements from HRP-441.

a. The description of the PHI for which use or access is included in the protocol summary (see section 10) and is necessary for the research.
b. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals.
c. An adequate plan to protect the identifiers from improper use and disclosure (see section 26).
d. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law (see section 26).
e. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.
f. The research could NOT practicably be conducted without the waiver or alteration. These data are already recorded and it would not be feasible to solicit permission from parents.

31) **Process to Document Consent in Writing**

Not applicable.
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32) **Drugs or Devices**

Not applicable.

**References:**


2. [http://www.cdc.gov/ncbddd/heartdefects/hlhs.html](http://www.cdc.gov/ncbddd/heartdefects/hlhs.html)


