Research Protocol

Study Title: Optimal Management of Critical Left Ventricular Outflow Tract Obstruction: A Congenital Heart Surgeons' Society Study

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Ultramini Abstract

Development of a multi-institutional inception cohort of babies with critical left ventricular outflow tract obstruction and Atrioventricular (AV) & Ventriculoarterial (VA) concordance undergoing all currently available treatment strategies is proposed. Correlation between morphologic variables and physiology will be sought. Knowledge of post-intervention outcomes in this population will identify incremental risk factors for adverse events and provide the means for selecting optimal care for future patients.

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Background

The Congenital Heart Surgeons' Society (CHSS) is a group of over 170 pediatric heart surgeons who meet annually to discuss problems of mutual interest in patient management. The history of the group dates back to the early days of cardiac surgery, when 16 surgeons met to relate their pioneering operative experiences with complex congenital heart defects.

In 1985 the CHSS established a Data Center with full-time support staff and physician consultants that is now located in The Hospital for Sick Children, Toronto, Ontario, Canada. Twelve multi-institutional cohorts of children with rare congenital anomalies have been studied prospectively over the last 30 years. Careful analysis of these patient cohorts has generated new knowledge that can be directly translated into clinical practice to improve outcomes in congenital heart surgery.

Our previous studies of neonates with aortic valve atresia (AVA) or aortic valve stenosis (AVS), identified useful information, including the elucidation of selection criteria for managing infants with critical AVS with either a bi-ventricular repair or single ventricle palliation. [1,2,3,4] Risk factors for mortality in babies having a Norwood operation were also identified. Data from this study also led to the development of the critical aortic stenosis (AS) calculator.[4,5] This formula has not been validated, but could be in this new study.

Although the survival of infants born with critical left ventricular outflow tract obstruction has steadily improved since Norwood and colleagues [6] first reported a staged reconstructive approach in 1980, early morbidity and mortality continues to be a vexing problem for most centers [1,2,3,7-9] The ideal treatment strategy for these complex patients

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continues to evolve. Most centers advocate the traditional Norwood pathway, and a few recommend primary transplantation or no intervention.[1,2,10] New strategies aimed to improve outcomes of palliation include the Sano modification of right ventricle-pulmonary artery shunt employed with the Norwood procedure, and ductal stenting with concomitant bilateral pulmonary artery banding (hybrid procedure incorporating both surgery and interventional catheterization). [9,11,12,13] In addition, there is a subset of patients with hypoplastic left heart complex (HLHC) as defined by Tchervenkov and associates that share many of these same management controversies[14].

During the present era there has been an increasing prevalence of intrauterine diagnosis and the potential for fetal therapy.[15,16] The introduction of off-pump cavo-pulmonary connection and percutaneous Fontan completion in the catheter laboratory, add further complexity to the therapeutic algorithm for these challenging patients.[13]

This CHSS multi-institutional study will evaluate these emerging therapies for critical left ventricular outflow tract obstruction**.** An echocardiographic assessment of pre-intervention morphology will be correlated with pre-intervention physiology and outcomes of procedures, together with other associated patient and procedural factors.

Specific Aims:

1) **Assemble a multi-institutional inception cohort of infants with critical LVOTO undergoing all currently available and future treatment strategies.**
2) **Determine morphologic correlates of physiology prior to intervention in critical left ventricular outflow tract obstruction.**
3) **Identify risk factors that affect outcomes.**

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4) **Determine the value of emerging management strategies.**

5) **Assess late outcomes including functional health status, quality of life, developmental outcomes, and identification of electrophysiological and other complications.**

Inclusion Criteria:

Any neonate (≤ age 30 days at admission to a CHSS institution), date of admission after December 31, 2004, with AV & VA concordance whose left ventricular outflow tract obstruction precludes an adequate systemic cardiac output through the aortic valve.

Participation in the study will be contingent upon approval by the participating institution's Institutional Review Board (IRB)/Research Ethics Board (REB) and must be in accordance with all applicable laws and regulations. The CHSS website will include a detailed Data Transfer Agreement template that may be utilized (with substitution or modification) for this purpose.

Morphologic Criteria:

1) **Patients with aortic valve atresia and AV & VA concordance**

2) **Patients with AV & VA concordance and critical left ventricular tract obstruction due to either:**

   a. **Aortic valve stenosis**

   OR

   b. **Anatomically normal but hypoplastic left heart**

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3) **Patients with a VSD will be included**

Exclusion Criteria:

First intervention at a non-CHSS institution

AV or VA discordance

Atrioventricular Septal Defect

Definitions

Aortic valve atresia: the absence of blood flow across the aortic valve, as determined by Doppler echocardiography.

Critical: neonates with ductal-dependent systemic circulation, those with at least moderate left ventricular dysfunction, or those requiring intervention within the first month of life. Neonates listed for transplantation within 1 month after birth qualify even though their transplant may be after age 1 month.

Hypoplastic left heart syndrome: a spectrum of cardiac malformations with normally aligned great arteries, characterized by underdevelopment of the left heart including atresia, stenosis or hypoplasia of the aortic or mitral valve (or both valves), and a variable degree of hypoplasia of the left ventricle. [1] (see footnote)

Hypoplastic left heart complex: A subset of babies at the milder end of the spectrum of hypoplastic left heart syndrome characterized by mild to moderate hypoplasia of the structures of the left heart, consisting of aortic and mitral valve hypoplasia without valve stenosis or atresia, hypoplasia of the left ventricle, left ventricular outflow tract,

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ascending aorta, and transverse arch, with or without aortic isthmus coarctation[1] (see footnote)

Study Population

1) **Bi-Ventricular Cohort:** Babies undergoing trans-catheter balloon or surgical valvotomy, or primary aortic valve replacement (including the Ross or Ross-Konno operation), or the Yasui procedure (aortopulmonary anastomosis with Rastelli connection). A transplant will be considered a distinct endpoint.

2) **Uni-Ventricular Cohort:** Babies undergoing the Norwood procedure and its modifications (a standard systemic-PA shunt or RV-PA conduit), and those undergoing ductal stenting with bilateral PA banding. These babies may undergo subsequent cavo-pulmonary anastomosis or Hemi-Fontan, followed by percutaneous Fontan completion in the cath lab or subsequent surgical Fontan completion.

[1] Reworded from Hypoplastic left heart syndrome: Nomenclature, definition, and classification. Tchervenkov CI, Jacobs JP, Weinberg PM et al., November 2004

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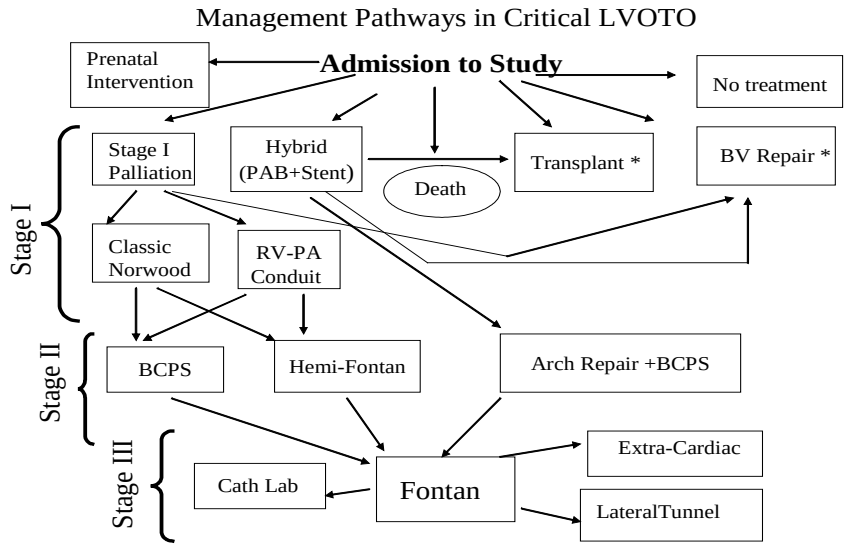
Figure 1: Management Pathways:



Legend. Figure 1: *Admission into the study will be admission at age ≤ 30 days to one of the CHSS institutions. There are 6 possible initial therapeutic interventions after admission into the study. Death may occur before or after any of these six initial interventions, or following any of the subsequent staged interventions. * Transplant may occur primarily or anytime thereafter, and similarly biventricular repair* may be elected after initial palliation. LVOTO, left ventricular outflow tract obstruction; Ao, aorta; RV-PA, right ventricle-pulmonary artery; BV, biventricular repair; BCPS, bidirectional cavopulmonary shunt; PAB, pulmonary artery banding*

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Materials and Methods

Study Design

The study is prospective and observational, requiring collection of existing data from the medical record. Management decisions will be made by the treating physician and will not be influenced, altered, or directed in any way by the patients' participation in this study. Based on preliminary data from the CHSS[1,2], the 1 year survival following traditional Norwood operation was 60%, and the 5 year survival was 54%. From preliminary data the expected reduction in adverse events (including mortality) from use of the modified RV - PA shunt is approximately 13%. Enrollment for this cohort will be at a rate of approximately 75 subjects per year. Recruitment of this number of subjects should be readily attainable, as in our previous experience, the CHSS enrolled 710 neonates within six years of inception[2]. With the intent to compare the survival and outcomes for patients treated with different treatment pathways, including patients treated by Norwood procedures, the Hybrid procedure, primary and secondary transplantation, as well as non-surgical cardiac intervention procedures (i.e., cardiac catheterization), for each subsequent study analysis to be performed, the CHSS Data Center will compute sample size/power to ensure statistically meaningful results.

Patient Recruitment and Informed Consent

Prospective patients will be identified upon admission to the hospital by daily review of diagnostic codes. Parents/guardians of patients, who agree to learning more about the study, will then be approached by specially trained research study staff. Informed consent (and authorization, as applicable) will be obtained prior to patient

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involvement in the study, and approval gained by each participating institution's IRB/REB prior to enrollment. Neonates will be stratified into a treatment group based upon initial management as applied by the member institution. Yearly follow-up will be obtained as described below to track clinical events and outcomes. Life-long annual follow-up will be conducted on this cohort, as longitudinal functional and quality of life assessments are essential elements of the study.

Data Collection

Following receipt of informed consent (and authorization, as applicable) at the participating sites, each subject is assigned a unique screening number, and the study Patient Enrollment Form is completed to enroll new subjects. The CHSS Data Center Registration Form for the study will be used to register new subjects and a unique study number will be assigned. The CHSS Data Center will not register any living patient until a copy of the signed consent form (and authorization, as applicable) is received. Inclusion in this study is requested for patients identified prospectively at the participating CHSS member institutions, but who die before written informed consent is obtained, and will be conducted in compliance with all applicable laws and regulations, including approval for waiver/alteration of the consent process (as applicable). Families of these patients will not be contacted for research purposes. Only the information already in the medical record will be used and only aggregated data will be reported in publications, precluding families from identifying themselves in any publication. When a participating CHSS institution sends information on a deceased patient, the CHSS Data Center will follow the same procedures to include them in the study that are used for those enrolled while living

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patient participants.

The following data will be obtained from the medical record:

Demographic/Anatomy/Physiology

- Admission form demographics or equivalent
- All pre and post-procedure cardiac catheter reports
- MRI (if performed)
- Echocardiography reports
- A copy of the initial and subsequent echo images on CD/DVD or by secure data transfer (pre & post cardiac procedures) for independent, blinded review and qualitative analysis
- Admission history and physical (to include height, weight, oxygen saturation, signs and symptoms, and any relevant clinical impressions)
- Operative record, including perfusions sheet & anesthetic flow sheet
- All cath lab interventional procedure reports & anesthetic flow sheets
- ICU flow sheet for 24 hours pre-op & 24 hours post-op to determine pre and post intervention condition.
- All subsequent hospital admissions: admit history and physical, diagnostic reports, interventional/surgery reports, changes in treatment plan (e.g., new medications), discharge summary
- Autopsy/Death report (if applicable)

Follow-up:

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Upon consent (and authorization, as applicable) at the site, and registration at the CHSS Data Center, Data Center staff will contact the parent/guardian of the subject to welcome them into the study and remind them of the annual contacts throughout their study participation. Similarly, when the subject is eligible to and provides consent (and authorization, as applicable) to participate in the study him/herself, and the CHSS Data Center is provided with this information, the CHSS Data Center staff will contact the subject to welcome him/her into the study (study continuation) and remind him/her of the annual contacts through his/her study participation. A cross-sectional annual follow-up will be conducted by the CHSS Data Center. A Follow-Up Form and Questionnaires will be sent to the subjects or parents/guardians of the subjects, as appropriate, to determine the subject's clinical status and obtain information regarding functional status and any updates in contact information. The follow-up form, non-standardized questionnaires and also age specific and parent version of standardized quality of life questionnaires (PedsQL™) will be completed, as applicable, on an annual basis. [17-24]

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Specific follow-up data therefore include:

Outcomes/Follow-up:

- Clinic letters
- Echo reports
- Catheter reports (diagnostic and interventional)
- Death reports
- Operative, anesthetic, perfusion records of further operations.
- Exercise testing (if performed)

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Typically this information will be securely transferred to the CHSS Data Center from the participating sites. In cases where the subject is followed at a non-CHSS institution or a non-participating CHSS institution, with the permission of the subject (parents/guardians, as applicable), the CHSS Data Center may send the subject (parents/guardians, as applicable) a Consent for Release of Medical Information form, which the subject (parents/guardians, as applicable) can then sign and take to their health care provider requesting that the specified information be released to the CHSS Data Center. Alternatively, the subject (parents/guardians, as applicable) may themselves request through the institution that holds the information, that the information be forwarded to the CHSS Data Center.

Subjects may withdraw (or be withdrawn by their parents/guardians, as applicable) from the study at any time without any impact on their care. Subjects may also be discontinued from the study at the discretion of the principal investigator at the participating CHSS institution if there is an inability to re-contact the subject/subject's parents/guardians and verify outcome, in which case the subject would be considered as 'lost to follow up'. The investigator may also withdraw subjects to protect the subject for reasons of safety or for administrative reasons. If a subject withdraws or is withdrawn or discontinued from the study at any stage, no further information about him/her will be collected for use in the analysis. However information already collected will continue to be used as needed to maintain the integrity of the research.

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Confidentiality and Security

Appropriate patient identity protection safeguards will be observed by the participating CHSS member institutions, as well as the CHSS Data Center, for the transmission of the patient information (e.g., baseline and follow-up patient care charts or compact discs (CDs) or echo tapes, updates in contact information) and signed consent forms/assent forms (and authorizations, as applicable) and the Patient Enrollment Form. Secure file transfer or secure courier service will be used as appropriate. The annual Follow-up Form and Questionnaires will be securely provided to the subjects or parents/guardians (as applicable), and returned to the Data Center by the subjects (or parents/guardians), in a secure manner acceptable to the subjects (parents/guardians, as applicable) (e.g., mail, fax, electronically). Data are abstracted from the copies of the confidential medical records and forms submitted to the CHSS Data Center. Trained dedicated personnel will perform all data extraction and entry into a secure computerized database in a de-identified manner. A master list (key) will be kept separate from the study data. Only appointed personnel at the Data Center will be able to connect the individual subject to the data. Records are kept in a locked, secure location with restricted access. The study participant's unique study number is used for all further analysis, and specific variables will be entered into a secure, password protected computer at the Data Center. These data files are restricted to the study investigators and the CHSS study team. Each member institution utilizes a Data Transfer Agreement with the CHSS Data Center to maintain the highest level of confidentiality for all participants. The Data Center will be responsible for maintaining a log of IRB/REB approvals and checking to ensure that

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participating sites are not submitting records or data without the appropriate IRB/REB approval documentation on file.

All data and records generated for this study will be kept confidential in accordance with applicable institutional policies, laws and regulations. The investigators and site personnel and the coordinating site will use the study data and records only for these study purposes. The information collected as part of this study will be securely retained for 7 years after all study publications are completed. The research information will be securely destroyed according to the applicable institutional policy effective at that time.

Risk Assessment

The main risk in this study is the potential breach of privacy and loss of confidentiality. There is a minimal risk of likelihood of harm. All reasonable safeguards to secure the confidentiality of information will be taken by the investigators and their research personnel and the CHSS Data Center personnel. Every effort will be made to keep personal health information (PHI) from unauthorized disclosure. Any breach will be reported. We believe this study overall is minimal risk.

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Statistical Analysis

Two expert statistical consultants (Drs. E Blackstone and B McCrindle) will supervise all aspects of data analysis and summation.

The CHSS Data Center has a history of incorporating advanced statistical methodologies for generating important new knowledge relating to congenital heart surgery, and continues to incorporate novel techniques with the help of the Quantitative

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Health Sciences Department Heart and Vascular Institute at the Cleveland Clinic Foundation.

Descriptive statistics will be compiled, with data described as frequencies, medians with ranges, or means with standard deviations as appropriate. In addition to traditional inferential statistics to compare groups and determine associations, advanced techniques will include multiphase parametric modeling of time-related events in the hazard domain, competing risk methodology (for competing and mutually exclusive end-states), analysis of repeated events (modulated renewal), and incorporation of time-varying covariates (usually interim procedures). These will be utilized to identify risk factors for various outcomes including survival, conversion to various end-states, and functional outcomes. Demographic, morphologic, physiologic, institutional, and procedural risk factors associated with each hazard phase of mortality, morbidity, adverse late functional or neurological outcome, or re-intervention will be sought by multivariable analysis, including hazard analysis as originally described by Blackstone and colleagues[25]. The bootstrap method will be utilized to guide final variable selection for multivariable models.

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Echocardiogram variables will be analyzed to determine echocardiogram predictors of outcome after procedures. As previously utilized in our research, late survival and right ventricular performance in the Norwood Blalock-Taussig (BT) group compared to the Norwood with Sano Modification was examined. All post-Norwood echocardiogram reports were used to capture reported grade of RV dysfunction and tricuspid regurgitation (TR). Time related prevalence of ≥ moderate RV dysfunction and TR were characterized using nonlinear mixed-model regression decomposed into

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multiphase-parametric models. Echocardiographic data will be use both as predictors for outcomes, and also as outcomes itself.

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Publications

The results of this study will be presented at national meetings and/or published in academic journals. No subject PHI or identifying personal information will be disclosed in any presentation or publication about the study.

Conclusion

The spectrum of critical left ventricular outflow tract obstruction is a challenging management problem in congenital heart surgery, with substantial morbidity and mortality despite the dramatic improvements in management of other congenital defects. Emerging therapeutic protocols may improve outcomes, but careful evaluation of the impact of these innovations is needed before embracing one as the ideal therapy for this broad morphologic spectrum. This study will provide important insight into the factors that impact upon and predict outcomes for these babies and will assist us in selecting the most efficacious therapy for successful management. We will also identify modifiable risk factors that may lead to specific interventions to improve outcomes.

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