

PROTOCOL

Congenital Heart Surgeons' Society Studies in Congenital Heart Disease

Background Information

Dr. John Kirklin and Dr. Eugene Blackstone established the CHSS Data Center at the University of Alabama, Birmingham in 1985. The Data Center's role is to coordinate the CHSS cooperative studies.

The first study began in 1985, with infants with Transposition of the Great Arteries entering participating institutions within 14 days of birth. Enrollment continued until 1989, by this time 890 infants were entered. In subsequent years, the following studies, which are now closed to enrollment, were initiated (accrual dates as indicated):

- 1985-1989: Transposition of the Great Arteries (TGA)
- 1987-1997: Interrupted Aortic Arch (IAA)
- 1987-1997: Pulmonary Atresia with Intact Ventricular Septum (PAIVS)
- 1987-1997: Pulmonary Stenosis with Intact Ventricular Septum (PSIVS)
- 1990-1993: Coarctation of the Aorta (CoA)
- 1994-2000: Aortic Valve Atresia (AVA)
- 1994-2000: Aortic Valve Stenosis (or hypoplasia of the LV inflow/outflow without complete atresia) (AVS)
- 2002-2014: Pulmonary Conduit (PC)

Studies in other cohorts, which are open to enrollment, have also been initiated. These are addressed in separate protocols.

Follow up for all studies initiated prior to the end of 1997 were put on hold as the CHSS Data Center was relocated at The Hospital for Sick Children in Toronto, Ontario, Canada.

How many centers participate in the studies?

At present there are over 70 centers that participate in the CHSS studies in North America, as well as representation from Argentina and Brazil.

What is the role of the CHSS Data Center?

The Data Center regularly contacts each participating institution regarding new patients being enrolled in studies. The Data Center also facilitates the follow-up of patients enrolled in studies, including obtaining written informed consent from parents/guardians and from subjects who are eligible to provide consent, in cases where the subjects are no longer followed by the institutions where they were originally enrolled into the study in or before the year 2000. Study duration will be for a subject's lifetime, from study initiation, or until the subject withdraws or is withdrawn or discontinued from the study. If a subject withdraws or is withdrawn or discontinued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.

Throughout the course of each cohort study, the subject's clinical and surgical cardiac-related reports will be obtained as well. Typically this information will be sent to the 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 (parent/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.

Confidentiality is respected and no information that discloses patient identity will be released without consent unless required by law. Each subject is assigned a unique study number at the CHSS Data Center that is used for all data entry and analysis purposes. All data analysis, review, and published results will be performed in a de-identified manner. The master list (key) and the study data will all be securely stored (using a double lock system) at the Data Center, and kept separate from each other. All data and records generated for each cohort study will be kept confidential in accordance with applicable institutional policies, laws and regulations. Each study will be conducted in compliance with each participating CHSS member institutions' research policies and procedures and all applicable laws and regulations. There is minimal risk with each of the cohort studies, mainly from the potential for breach of privacy and loss of confidentiality. The investigators and site personnel and the CHSS Data Center personnel will ensure that confidential information, including personal health information/identifying personal information, will be secured and will not be revealed to unauthorized parties. The investigators and site personnel and the CHSS Data Center will use the study data and records only for the intended study purposes. The information collected as part of each cohort 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.

The Data Center website (www.chssdc.org) will be used to disseminate information to member institutions and patients.

What is the role of the participating center?

Each center has an identified contact person who is responsible for securely sending patient information to the CHSS Data Center according to identified criteria for a specific study and signed consent forms/assent forms (and authorizations, as applicable) for study participation.

Each center also participates in the regularly scheduled follow-up of patients who have been enrolled in specific studies. This would include securely providing information about the patient since the last follow-up, for example: demographic and contact information, operative notes, catheterization and echocardiogram reports.

Follow-Up Form/Questionnaires Data Collection

The CHSS Data Center conducts annual follow-up for each of the studies. Study participants and/or their parents/guardians, as appropriate, are contacted on an annual basis and requested to complete the annual follow-up form (e.g., providing any updates in contact information and medical/surgical updates, as applicable), and also to complete the questionnaires for the study. The questionnaire data collection will be done using non-standardized CHSS Data Center questionnaires, and standardized questionnaires including the PedsQL™ quality of life and cardiac modules (1-8). The 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 or electronically).

Functional Health Status Data Collection

As the participants in the prospective observational cohorts grow up from childhood to adolescence and adulthood, the Data Center may also undertake systematic data collection on their functional health status during this transition. These data collection can be specific to one or more cohorts, depending upon the patients' age in the cohort. This data collection will be done using standardized data collection instruments such as:

1. Transition Readiness Assessment Questionnaire (TRAQ) (9)
2. The MyHeart Scale

Mechanism by which studies are conducted

The CHSS members meet annually to review the progress of each study, decide on which lesion will be studied, determine inclusion and exclusion criteria, data sources, parts of the medical record and mechanism for follow-up. In the past, the data collection was not hypothesis driven. This has been instituted when the Data Center relocated to The Hospital for Sick Children in 1997.

Please refer to the attached appendices for further information regarding each of the aforementioned cohorts in follow-up phase only (i.e., currently closed to enrollment), including study objectives, enrollment and publications.

References

- (1) Varni JW, et al. The PedsQL™: Measurement Model for the Pediatric Quality of Life Inventory. *Medical Care* 1999; 37(2): 126-139.
- (2) Varni JW, et al. The PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. *Medical Care* 2001; 39(8): 800-812.
- (3) Varni JW, et al. The PedsQL™ 4.0 Generic Core Scales: Sensitivity, responsiveness, and impact on clinical decision-making. *Journal of Behavioral Medicine* 2002; 25: 175-193.
- (4) Varni JW, et al. The PedsQL™ 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. *Ambulatory Pediatrics* 2003; 3: 329-341.
- (5) Varni JW & Limbers CA. The PedsQL™ 4.0 Generic Core Scales Young Adult Version: Feasibility, reliability and validity in a university student population. *Journal of Health Psychology* 2009; 14: 611-622.
- (6) Varni JW, Limbers CA, Neighbors K, Schulz K, Lieu JEC, Heffer RW, Tuzinkiewicz K, Mangione-Smith R, Zimmerman JJ & Alonso EM. The PedsQL™ Infant Scales: Feasibility, internal consistency reliability and validity in healthy and ill infants. *Quality of Life Research* 2011; 20: 45-55.
- (7) Uzark K, Jones K, Burwinkle TM & Varni JW. The Pediatric Quality of Life Inventory™ in children with heart disease. *Progress in Pediatric Cardiology* 2003; 18: 141-148
- (8) Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM & Varni JW. Quality of life in children with heart disease as perceived by children and parents. *Pediatrics* 2008; 121: e1060-e1067
- (9) Sawicki GS, Lukens-Bull K, Yin X, Demars N, Huang I-C, Livingood W, Reiss J, and Wood D. Measuring the Transition Readiness of Youth with Special Healthcare Needs: Validation of the TRAQ—Transition Readiness Assessment Questionnaire. *J. Pediatr. Psychol.* 2011; 36(2): 160-171

Appendix I: Transposition of the Great Arteries (TGA) Study

Objectives:

- To assemble a multi-institutional inception cohort of neonates with Transposition of the Great Arteries.
- To compare survival outcomes of neonates age 2 weeks presenting with various forms of TGA.

From 1985 to 1989, 890 neonates with TGA were enrolled from 24 institutions.

Publications:

Williams WG, McCrindle BW, Ashburn DA, Jonas RA, Mavroudis C, Blackstone EH and members of the Congenital Heart Surgeon's Society. Outcomes of 829 neonates with complete transposition of the great arteries 12 – 17 years after repair. [European Journal of Cardio-Thoracic Surgery 24\(2003\) 1-10.](#)

Culbert EA, Ashburn DA, Cullen-Dean G, Joseph JJ, Williams WG, Blackstone EH, McCrindle BW, and the Congenital Heart Surgeons Society. Quality of Life of Children After Repair of Transposition of the Great Arteries. [Circulation. 2003;108:857-862.](#)

Castaneda AR, Trusler GA, Paul MH, Blackstone EH, Kirklin JW, and the Congenital Heart Surgeons Society. The early results of treatment of simple transposition in the current era. [Journal of Thoracic and Cardiovascular Surgery 1988: 95: pp 14-27.](#)

Kirklin JW, Blackstone EH, Tchervenkov CI, Castaneda AR. Clinical outcomes after the arterial switch operation for transposition. Patient, support, procedural, and institutional risk factors. Congenital Heart Surgeons Society. [Circulation 1992: 86\(5\): pp 1501-1515.](#)

Norwood WI, Dobell AR, Freed MD, Kirklin JW, Blackstone EH, and the Congenital Heart Surgeons Society. Intermediate results of the arterial switch repair. A 20-institution study. [Journal of Thoracic and Cardiovascular Surgery 1988: 96: pp 854-862.](#)

Turley K, Verrier ED. Intermediate results from the period of the Congenital Heart Surgeons Transposition Study: 1985 to 1989. Congenital Heart Surgeons Society Database. [Annals of Thoracic Surgery 1995: 60\(3\): pp 505-510.](#)

Trusler GA, Castaneda AR, Rosenthal A, Blackstone EH, Kirklin JW, and the Congenital Heart Surgeons Society. Current result of management in transposition of the great

arteries, with special emphasis on patients with associated ventricular septal defect. [Journal of the American College of Cardiology 1987; 10: pp 1061-1071.](#)

Wells WJ, Blackstone EH, and the Congenital Heart Surgeons Society. Intermediate outcome after Mustard and Senning procedures: A Study by the Congenital Heart Surgeons Society. [Pediatric Cardiac Surgery Annual of the Seminars in Thoracic and Cardiovascular Surgery, Vol 3, 2000,pp 186-197.](#)

Williams WG, Quaegebeur JM, Kirklin JW, Blackstone EH, and the Congenital Heart Surgeons Society. Outflow obstruction after the arterial switch operation: A multiinstitutional study. [Journal of Thoracic and Cardiovascular Surgery. 1997; 114:975-90.](#)

Appendix II: Interrupted Aortic Arch (IAA) Study

Objectives:

- To determine outcomes for neonates with interruption of the aortic arch (IAA).
- To determine what patient management variables improve outcomes.

From 1987 to 1997, 470 neonates with IAA were enrolled prospectively from 33 institutions.

Publications:

Jegatheeswaran A, McCrindle BW, Blackstone EH, Jacobs ML, Lofland GK, Austin EH 3rd, Yeh T, Morell V, Jacobs JP, Jonas RA, Cai S, Rajeswaran J, Ricci M, Williams WG, Caldarone CA, DeCampi WM. Persistent risk of subsequent procedures and mortality in patients after interrupted aortic arch repair: a Congenital Heart Surgeons' Society study. [Journal of Thoracic and Cardiovascular Surgery. 2010 Nov;140\(5\):1059-75.e2.](#)

Konstantinov IE, Karamlou T, Blackstone EH, Mosca RS, Lofland GK, Caldarone CA, Williams WG, Mackie AS, McCrindle BW for the members of the Congenital Heart Surgeons Society. Truncus Arteriosus Associated with Interrupted Aortic Arch in 50 Neonates: A Congenital Heart Surgeons' Society Study. [The Annals of Thoracic Surgery 2006; 81:214-23.](#)

Konstantinov IE, Karamlou T, Williams WG, Quaegebeur JM, delNido PJ, Spray TL, Caldarone CA, Blackstone EH, McCrindle BW, and the members of Congenital Heart Surgeons Society; Surgical Management of Aorto-Pulmonary Window Associated with Interrupted Aortic Arch: A Congenital Heart Surgeon's Society Study. [Journal of Thoracic and Cardiovascular Surgery. 2006; 131:1136-41.](#)

McCrindle BW, Tchervenkov CI, Konstantinov IE, Williams WG, Neirotti RA, Jacobs ML, Blackstone EH, For the members of the Congenital Heart Surgeons' Society. Risk Factors Associated With Mortality and Reinterventions in 472 Neonates with Interruption of the Aortic Arch: A Congenital Heart Surgeons Society Study. [Journal of Thoracic and Cardiovascular Surgery. 2005; 129\(2\): 343-350.](#)

Jonas RA, Quaegebeur JM, Kirklin JW, Blackstone EH, Daicoff G. Outcomes in patients with interrupted aortic arch and ventricular septal defect. A multiinstitutional study. Congenital Heart Surgeons Society. [Journal of Thoracic and Cardiovascular Surgery. 1994; 107\(4\): 1099-1113.](#)

Chin AJ, Jacobs ML. Morphology of the ventricular septal defect in two types of interrupted aortic arch. [Journal of the American Society of Echocardiography 1996; 9\(2\): pp 199-201.](#)

Appendix III: Pulmonary Atresia with Intact Ventricular Septum (PAIVS) Study Pulmonary Stenosis with Intact Ventricular Septum (PSIVS) Study

PAIVS Objectives:

- To determine the proportion of neonates reaching defined end-states (i.e. Bi-ventricular Repair, Fontan, Heart Transplant, One-and-a-half ventricle repair or death).
- To identify risk factors associated with end-state, including Bi-ventricular Repair Fontan, Heart Transplant, One-and-a-half ventricle repair or death).

From January 1987 to April 1997, 408 neonates with PAIVS admitted to a CHSS institution within 30 days after birth were prospectively enrolled in a multi-institutional study. PAIVS was defined as no communication between the right ventricle (RV) and pulmonary trunk and absence of ventricular septal defect (VSD) as determined by echocardiographic, catheterization, or surgical findings.

PSIVS Objectives:

- To determine outcomes and associated patient and management factors for neonates with pulmonary stenosis with intact ventricular septum.
- To observe the transition from surgical to percutaneous management.

From 1987 to 1997, 448 neonates with PAIVS or PSIVS were enrolled prospectively from 33 institutions.

Publications:

Karamlou T, Poynter JA, Walters HL 3rd, Rhodes J, Bondarenko I, Pasquali SK, Fuller SM, Lambert LM, Blackstone EH, Jacobs ML, Duncan K, Caldarone CA, Williams WG, McCrindle BW. Long-term functional health status and exercise test variables for patients with pulmonary atresia with intact ventricular septum: A Congenital Heart Surgeons Society study. [J Thorac Cardiovasc Surg. 2013 Apr;145\(4\):1018-1027.e3.](#)

Karamlou T, Poynter JA, Walters HL, Rhodes J, Bondarenko I, Pasquali SK, Fuller SM, Lambert L, Blackstone EH, Jacobs ML, Duncan K, Caldarone CA, Williams WG, McCrindle BW. Long-term Functional Health Status and Exercise Test Variables for Patients with Pulmonary Atresia with Intact Ventricular Septum: A Congenital Heart Surgeons' Society Study. [AATS Annual Meeting April 30, 2012.](#)

Ashburn DA, Blackstone EH, Wells WJ, Jonas RA, Pigula FA, Lofland GK, Manning PB, Williams WG, McCrindle BW, and the Congenital Heart Surgeons Society. Determinants of Mortality and Type of Repair in Neonates with Pulmonary Atresia – Intact Ventricular Septum. [Journal of Thoracic and Cardiovascular Surgery, 2004; 127\(4\):1000-1008.](#)

Hanley FL, Sade RM, Blackstone EH, Kirklin JW, Freedom RM, Nanda NC, and the Congenital Heart Surgeons Society. Outcomes in neonatal Pulmonary Atresia with intact ventricular septum. A multiinstitutional study. [Journal of Thoracic Cardiovascular Surgery 1993; 105:406-423.](#)

Hanley FL, Sade RM, Freedom RM, Blackstone EH, Kirklin JW, and the Congenital Heart Surgeons Society: Outcomes in critically ill neonates with pulmonary stenosis and intact ventricular septum: A multiinstitutional study. [Journal of the American College of Cardiology 1993; 22\(1\):183-192.](#)

Appendix IV: Coarctation of the Aorta (CoA) Study

Objectives:

- To determine outcomes for neonates with coarctation of the aorta.
- To analyze the importance of different treatment strategies.

From 1990 to 1993, 893 neonates with CoA were enrolled prospectively from 32 institutions.

Note: There is no follow-up phase being conducted for this cohort.

Publications:

Quaegebeur JM, Jonas RA, Weinberg AD, Blackstone EH, Kirklin JW, and the congenital Heart Surgeons Society. Outcomes in seriously ill neonates with coarctation of the aorta: A multiinstitutional study. [Journal of Thoracic and Cardiovascular Surgery 1994; 108: pp 841-54.](#)

Appendix V: Aortic Valve Atresia (AVA) Study Aortic Valve Stenosis (AVS) Study

Inclusion Criteria:

Neonates younger than 30 days at the time of admission
First procedure at a CHSS member institution
Concordant atrioventricular and ventriculoarterial connections and either Aortic Valve Atresia (AVA) or critical Aortic Valve Stenosis (AVS).
AVA is defined as the absence of blood flow across the aortic valve, as determined by color Doppler echocardiography.
AVS is critically important left ventricular outflow tract obstruction or hypoplasia, with demonstrated patency of the aortic valve and either moderately or severely reduced left ventricular function at admission or presence of duct-dependent systemic perfusion.

Exclusion Criteria:

First procedure at a non-CHSS institution
Age >30 days at the time of admission
Atrioventricular or ventriculoarterial discordance
Any AVA or AVS that does not meet the morphologic criteria

From 1994 to 2000, 566 neonates with AVA were enrolled prospectively from 26 institutions, and 421 neonates with AVS were enrolled prospectively from 28 institutions.

AVA Publications:

Ashburn DA, McCrindle BW, Tchervenkov CI, Jacobs ML, Lofland GK, Bove EL, Spray TL, Williams WG, Blackstone EH for the Congenital Heart Surgeons Society. Outcomes after the Norwood operation in neonates with critical aortic stenosis or aortic valve atresia. [Journal of Thoracic and Cardiovascular Surgery, May 2003, 1070-1082.](#)

Jacobs ML, Blackstone EH, Bailey LL and the Congenital Heart Surgeons Society. Intermediate survival in neonates with aortic atresia: a multi-institutional study. [Journal of Thoracic and Cardiovascular Surgery 1998;116:pp 417-31.](#)

AVS Publications:

Hickey EJ, Caldarone CA, Blackstone EH, Williams WG, Yeh T Jr, Pizarro C, Lofland G,
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Tchervenkov CI, Pigula F, McCrindle BW; Congenital Heart Surgeons' Society. Biventricular strategies for neonatal critical aortic stenosis: high mortality associated with early reintervention. [J Thorac Cardiovasc Surg. 2012 Aug;144\(2\):409-17, 417.e1](#)

Lofland G, McCrindle BW, Williams WW, Blackstone EH, Tchervenkov C, Sittiwangkul R, Jonas R, and the Congenital Heart Surgeons' Society. Critical Aortic Stenosis in the neonate: a Multi-institutional study of management, outcomes and risk factors. [Journal of Thoracic and Cardiovascular Surgery, 2001;121:pp10-27](#)

McCrindle BW, Blackstone EH, Williams WG, Sittiwangkul R, Spray TL, Azakie A, Jonas RA, and the members Congenital Heart Surgeons' Society. Are Outcomes of Surgical Versus Transcatheter Balloon Valvotomy Equivalent in Neonatal Critical Aortic Stenosis? [Circulation 2001 104\[Suppl I\]:I-152 -I-158.](#)

Appendix VI: Pulmonary Conduit (PC) Study

Objectives:

- To assemble a multi-institutional inception cohort of infants less than 2 years of age having pulmonary ventricle-pulmonary artery conduit placement
- To determine the best conduit for infants and young children
- To determine optimal conduit for replacement of previous conduits

Inclusion Criteria:

Valved Conduit implant at age <2years at member institution. Date of first implant AFTER January 1, 2002

Note: Patients who have 1.5 ventricle repair (e.g. CCTGA) are included Survival to hospital discharge after conduit insertion

First pulmonary ventricle-pulmonary artery conduit placement

Informed consent from parents/guardian

Exclusion Criteria:

Single Ventricle RV-PA conduit, e.g. Norwood RV-PA conduit

Non-Valved Conduit

VSD Fenestrated or not closed

From 2002 to 2014, 632 neonates with PC were enrolled prospectively from 29 institutions.

Publications:

Poynter JA, Eghtesady P, McCrindle BW, Walters HL 3rd, Kirshbom PM, Blackstone EH, Husain SA, Overman DM, Austin EH, Karamlou T, Lodge AJ, St Louis JD, Gruber PJ, Ziemer G, Davies RR, Jacobs JP, Brown JW, Williams WG, Tchervenkov CI, Jacobs ML, Caldarone CA; Congenital Heart Surgeons' Society. Association of Pulmonary Conduit Type and Size With Durability in Infants and Young Children. [Ann Thorac Surg. 2013 Aug 22.](#)

Poynter JA, Eghtesady P, McCrindle BW, Walters III HL, Kirshbom P, Blackstone EH, Husain SA, Overman DM, Austin EH, Karamlou T, Lodge A, St. Louis J, Gruber P, Ziemer G, Davies RR, Brown J, Williams WG, Jacobs JP, Tchervenkov C, Jacobs ML, Caldarone CA. Effect of Conduit Type and Size on Right Ventricle-Pulmonary Artery Conduit Durability in Infants Less Than Two Years of Age: A Congenital Heart Surgeons' Society Study. [Society of Thoracic Surgeons 49th Annual Meeting, Los Angeles, January 2013.](#)

Hickey EJ, McCrindle BW, Blackstone EH, Yeh T, Pigula F, Clarke D, Tchervenkov CI, Hawkins J and the CHSS Pulmonary Conduit Working Group. Jugular venous valved conduit (Contegra®) matches allograft performance in infant truncus arteriosus repair. [European Journal of Cardiothoracic Surgery. 2008; 33\(5\): 890-898.](#)

Karamlou T, Blackstone EH, Hawkins JW, Jacobs ML, Kanter KR, Brown JW, Mavroudis C, Caldarone CA, Williams WG, McCrindle BW, and the Pulmonary Conduit Working Group for the members of the Congenital Heart Surgeons Society. Can Pulmonary Conduit Dysfunction and Failure be Reduced in Infants and Children Less Than Age Two Years at Initial Implantation? [Journal of Thoracic and Cardiovascular Surgery, October 2006, 132\(4\), pp 829-838.](#)