CHSS Data Center Fall Work Weekend Report

November 18 – 20, 2016

The Work Weekend was attended by 50 people including 19 CHSS members and 31 guests, including institutional cardiologists, institutional data coordinators, critical care physicians, and research associates; 36 in person and 14 via interactive Webinar. (Appendix 1). The data center staff appreciate the enthusiasm, insight and constructive criticism of the attendees.

A number of topics both work in progress and potential future projects were discussed. These discussions help guide the data center and working groups in developing plans for analysis and importantly, in understanding & interpreting clinical inferences.

The following is a synopsis of the material presented, discussion, plans for future lines of investigation and critiques.

A Modest Proposal: We are overdue for an International Fontan Registry

Brian McCrindle reviewed 3 major Fontan long-term reports (Mayo – Pundi 2015; Australia – Iyengar 2014; NIH – McCrindle 2014). Each relied on traditional risk factor analysis of patient management but late outcomes are affected by non-medical generic non-disease specific issues. He raised the question (& suggested) an International database with 'wide & deep' data. The new approach would recognize complexity and use computational biology. An 'Integrative Database' would contain all of the patients and all of their data. Novel discovery and predictions using pattern recognition and artificial intelligence with high performance computing could be discovered. No doubt there are challenges, including access to the information, legal agreements, IRB/REB approval, standardized protocols, centralized biobanks, linkages, nomenclature, translation and data merging and, of course, major funding to name a few. But this rich dataset could be a first step in personalized medicine to improve health by dealing with non-disease-specific environmental & developmental factors currently unrecognized. It could also be a tremendous resource for nested mechanistic clinical trials. Brian provided a view of what the future of clinical research could become.

Aortic Arch Obstruction in the Critical LVOTO cohort

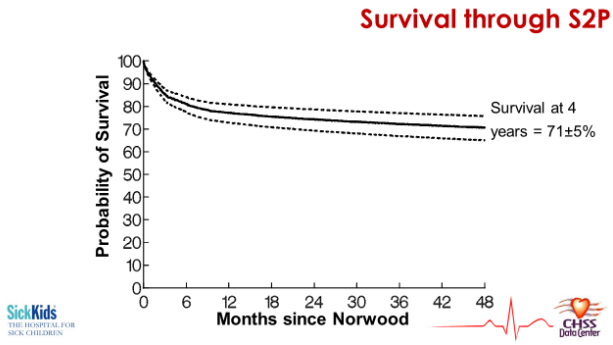
Tara Karamlou proposes a study based upon the critical LVOTO cohort to investigate aortic arch re-intervention post stage I palliation. The proposal has been submitted to the Research Committee (RC) who requested refinements. Tara has reviewed the dataset to discover that among the 579 post Norwood (Classic & Sano, but not Hybrid) there are 99 patients who underwent 128 post Norwood arch procedures (104 cath & 24 operative). One or more subsequent repeat intervention was required in 24%.

In discussion: What are the indications for re-intervention? What is arch obstruction? Is it definable across multi-institutions? Is there a correlation between arch measurements on echo or CT/MRI with re-intervention? The recommendation is to limit the study to defining the outcome post re-intervention in terms of survival and recurrence.

Plan: Tara will complete the data entry & review, and then resubmit a refined proposal to the RC for approval. Goal is to have an approved project for discussion and development at the Spring Work Weekend. We will consider an NIH R21 for this project. Tara may plan a visit to the Data Center this winter.

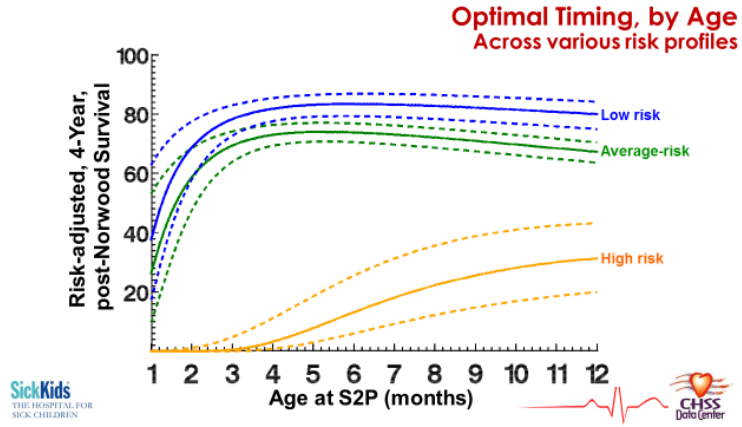
LVOTO: Optimal Timing of Stage II

Jim Meza presented an extensive amount (but only a portion) of his analyses investigating the optimal timing for Stage II that would decrease the interval of high post stage I mortality rate while maximizing post Stage II survival.



In essence, the question is: Can the above survival curve be improved by optimal timing of Stage II?

Much of the discussion focused on the following graph.



With average and low risk patients (to be defined carefully) there does appear to be an optimal time at about 3 months with a wider optimal range for low risk patients. However it does not make clinical sense to delay Stage II for 12 months in high risk patients. How to interpret these data?

Update from NHLBI: Gail Pearson MD, ScD

The NIH proportions 10% of its $33B budget to congenital heart disease. Gail Pearson, Director of Clinical Research, has a background in pediatric cardiology. She presented by Webinar an excellent overview of NHLBI and the research funding opportunities it offers. Among the critical challenges they are promoting: 1) integration of registry & research data to facilitate molecular genomic & pathobiology; 2) 'smart devices' to monitor physiology that would automate intervention when appropriate; and 3) novel methods to generate hypotheses that expedite bedside to basic 'reverse' translation. She suggests browsing the website www.nhlbi.nih.gov/research for ideas about funding sources. Grants of particular interest are R01, R21 (secondary analyses of existing databases) and R13 (conferences specific to the mission of NHLBI) as well as 'people support' such as K08 & K23 (Mentored Career development awards) and mentored and career awards K99-R00 (pathway to independent research) and K24 (mid-career patient-oriented research award). A further Website recommendation for details is https://researchtraining.nih.gov/programs/career-development. There are opportunities for CHSS collaboration with NIH, such as the genomics PCGC database. CHSS applications should stress the uniqueness and that most of the data is US-based. Some opportunities are limited to US citizens & US institutions which makes our mission to outsource data more important.

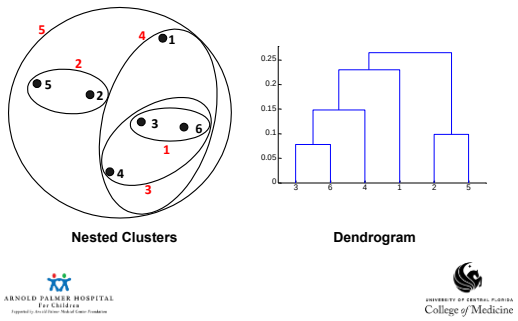
AVSD: Descriptive Analysis of Baseline Echos

Cheryl Fackoury has read 194 baseline echos noting 111 morphologic & functional variables. Jim Meza presented a summary of these data. Dominance is right 22%, balanced 53%, left 5% and unable to determine 21%. Median AVVI is

0.47 (0.2 to 0.7); LV inflow index 0.5 (0.3 – 1.2). Correlations have been done for ventricular geometry vs. inflow physiology; RV/LV inflow angle; and LVII. An abstract has been submitted to AATS.

LVOTO: Cluster Analysis of Baseline Echocardiographic Data

W. DeCampli gave a brief presentation on the fundamentals and theory of cluster analysis. Cluster analysis is a broadly applicable technique in which "similar" objects are grouped together, the goals being to simply define taxonomy, or, more specifically, to determine broad categories associated with "outcome variables". "Similarity" must be defined in terms of a set of variables. The optimal grouping of objects then relies on a definition of how the variables are combined to determine the degree of similarity between two objects. For less than or equal to three independent variables, clustering can be visualized graphically, with each variable corresponding to an orthogonal axis of the space, and with each object being a point corresponding to the three values of that object's variables. Then, the "distance" between the points is just given by the usual geometrical distance, and that defines how "close" one object is to another. In >3 dimensions (for example, the study we have been working on is 136-dimensional!) is harder to visualize, but mathematically the distance between objects is analogously defined. There are many algorithms for clustering, and Jim Meza has used "agglomerative hierarchical Ward's method clustering". The optimization problem consists of sequentially finding pairs of clusters (each beginning with one object) that are closest to each other (as measured by the "distance" definition), then redefining that as a new, single cluster that is at the next hierarchical level. The process is then repeated until you end up with a single cluster. In the figure, for the six objects in two-dimensional space, there are four hierarchical levels, as shown in the dendrogram. The sensitivity and specificity of cluster solutions, like all statistical methods, is affected by the number of objects (patients, cases) and by outliers. There are several validation tests for clustering.



Martijn Slieker, an echo research fellow with Luc Mertens, worked or a year in the CHSS ICL reviewing 650 baseline echos. Jim Meza presented a cluster analysis of the 136 functional and morphologic echo variables collected for each neonate. The analysis created 3 distinct clusters determined by measurable variables. Group 1 neonates have multiple levels of left-sided obstruction, group 2 is true HLHS, and group 3 is equivalent to critical AS. While these categories are not new, they are supported by clinical data. A preliminary analysis also shows they correlate with patient management and long-term outcome. The two most important variables driving the primary clustering are LV size, and presence of aortic atresia (and mitral valve size to some extent).

W. DeCampli suggested that the analysis include validation and sensitivity tests. Several validation schemes exist: the entropy test, F-measure, and "overall similarity" test. Gene suggested bootstrapping, also. The CCF group does cluster work with statisticians at University of Miami, so this group is a potential resource for our further work.

Plan: Dr. Meza will confirm the validity of the clusters and pursue other cluster methods when he visits Cleveland. At a breakout session, the working group reviewed the draft manuscript to contribute editorial advice.

AAOCA: Advanced Imaging

Dr. Raj Krishnamurthy presented advanced CT imaging of AAOCA. He stressed the need for a checklist to standardize diagnostic criteria. He is also interested in combining CT/MRI data with the clinical outcomes data in CHSS to turn technologic advancement into clinical relevance.

CT is superior to echo in defining ostial location and morphology and the intramural and inter-arterial course. Virtual angioscopy can almost duplicate the photos taken intra-operatively. It also offers new functional assessment of

flow dynamics that could help in quantifying patient risk. Post-op abnormalities are not rare and are of concern as to predictability.

Raj stressed the need to standardize diagnostic imaging and correlate findings with clinical parameters and outcomes. He suggests, "**Focus on clinical value (of CT/MRI) not just diagnostic innovation**".

Breakout Sessions:

A. LVOTO Cluster Analysis

The LVOTO cluster analysis breakout session continued the discussion from the main forum. The primary question was of interpretation and of next steps in the analysis. The focus of the paper has evolved into an emphasis on the use of novel methodology within the analysis of congenital heart disease from an anatomic perspective, but using "big data" analytic techniques, i.e. cluster analysis. The paper will be titled and themed along the lines of "Bringing Precision Medicine to Congenital Heart Disease." Further steps include investigation of verification methods and of other applications of cluster analysis in fields such as genetics and psychometrics.

B. AAOCA: Predictors of Ischemia

AAOCA enrollment has now exceeded 540 patients. Mean age at enrolment is 10 years, 2/3rds are male and 300 (55%) underwent surgical repair. Among the first 450 enrolled, 201 had tests for ischemia; 29 were positive (n=17) or had an episode of sudden death (n=12)

An expert echo review of the 29 ischemic patients with 29 age-matched 'controls' was done in the ICL as a preliminary to analysis of the entire cohort. In addition, the 12 sudden cardiac arrest patients were compared to 17 ischemic-positive patients without sudden death. The only variable of interest may be the length of the intramural segment (see table below). However, the intramural segment of all 29 ischemic patients was not different than the 29 age-matched controls. Additionally, we must hypothesize that ostial shape & stenosis is an important factor, although this was not evaluated in the present analysis (see table below) and echo images are not technically ideal for measurement of intramural length or for detecting orifice anomalies.

The following table illustrates the essence of the echo data comparison of ischemic patients

AAOCA Data of 29 Ischemia Patients Among 201 tested for Ischemia

Summary of 26 tables:

Variable		**Ischemic test only N=14**		**Sudden death n=12**	
Which coronary is anomalous?					
Right		8		4	
Left		4		6	
Unable to determine		2		2	
Where does it arise?					
Right sinus		4		6	
Left		8		4	
Other		1		0	
Abnormal V function		**1/13**		**2/11**	
Mitral insufficiency		**1/13**		**6/13**	
Colour Doppler	Done	9/10		8/9	
Angle of origin		11/12		8/11	
High ostial origin	Yes	0/12		2/12	note: 14 unsure
Round orifice or slit-like origin		----	no data	---	
Inter-arterial	Yes	12/13		10/11	
Intramural	Yes	11/12		7/12	

Length intramural	**Mean**	**5.5 (+-3.5)**	**8.4 (+-2.7)**
	Median	**4.0**	**8.7**

Plan:

1. Review 25 CT and 9 MRI images of these 2 patient groups
2. Correlate and corroborate anatomic details with the echo reviewed groups.
3. The background evidence from these 2 reviews will be used to design a research plan to incorporate the entire echo, CT & MRI data.
4. Julie Brothers will write a draft manuscript describing the clinical characteristics of all ischemia patients updated as of December 31, 2016
5. The data center staff will enter remaining patients in time for December 31 deadline of #4
6. ICL group will consider a manuscript of the echo, CT & MRI data of ischemia patients
7. Investigate http://asecho.org/what-we-do/research-resources/academic-imaging-core-labs/ to consider imaging registry options.
8. Dr. Brothers suggested a third paper looking at the entire cohort, addressing the issues developed in the two preceding papers (described above).

C. Coarctation of the Aorta

Nancy Poirier, with Amine Mezine's help, presented an overview of the dormant coarctation cohort. Patient enrolment was between 1990 and 1994 (n = 975). Follow-up of these patients ended in 1997. The only CHSS publication was in 1994 by Quaegebeur (JTCVS) wherein the patients with isolated CoAo or CoAo and VSD were reported (n=326). This subset of patients is now 703. The other patients (n=272) have major associated lesions, many of which are now separate study cohorts and therefore not of interest to the outcome of coarctation per se.

In discussion the group felt it necessary to update the follow-up. Further they suggested this be done only with a patient-based questionnaire. The cohort is unique (all neonatal repairs) and follow-up could be of patient benefit, & certainly of no risk.

Plan:

1. Given the time gap since enrollment/last contact, estimate the proportion of participants that we are likely to be able to locate/contact (i.e., that would be at the same address or same phone number since enrollment/last contact).
2. Meet with REB to discuss a plan to contact these patients, stressing it will be an interaction between patient and health care, not the biology of the disease.
3. Dr. Poirier will write a draft RC proposal outlining the research question and detailing what is needed such as a draft questionnaire (functional health, medical events, employment status), and budget.

D. LVOTO Enrollment Process

The issue is to determine a reasonable interval to enroll patients. The majority of the cohort (70%) was enrolled within the first 6 months of life. However a few were enrolled post Fontan and appear to be retrospective rather than prospective. Extenuating circumstances may be that these late enrolments were done by an institution that just joined a study late and did a retrospective review of all their patients since CHSS inception date. In addition, in the early stages, it took institutions time to sort out how best to proceed, given HIPAA requirements.

In discussion, the group proposed that a maximum of 12 months for enrollment be enacted going forward. For the patients already sent late, we should review each to determine any that were clearly retrospective.

Linda Lambert mentioned that she had IRB approval to contact patients she was unable to meet with in the hospital via a mail-out and follow-up phone call. Consideration should be given to incorporating this additional method of contact in the protocol.

The Data Center should categorize which institutions have IRB/REB approval to enroll patients identified prospectively who have died before being consented. We need to know of all institutions that are enrolling only living patients.

CT images should be added to the protocol, and to the data collection forms.

A Manual of Operations for this and all our cohorts would be beneficial.

We also discussed the inadvertent error in naming the cohort LVOTO. Some patients with mitral atresia do not have LVOTO per se. It would have been better to label this cohort 'critical left heart obstruction' but a name change would require a more extensive amendment in every institutional IRB/REB and the coordinators understand the diagnostic criteria. It was suggested we list examples, including mitral atresia, to clarify the criteria.

Ebstein Anomaly

Kim Holst presented an update on progress towards activating this cohort. The study has received SickKids REB approval. But before rolling this out to other CHSS institutions (so they may submit for IRB/REB review and approval), further updates are required, including: revisions to data collection forms, creation of echo and MRI data collection forms and protocol revisions, which will require an amendment submission to and approval from SickKids REB.

Enrollment will be both prospective beginning in2017 and retrospective to 2010/01/01. Research questions focus on classification, timing at various ages, early and late morbidity and mortality.

Plan:

1. Echo, MRI, clinical protocols/manuals & imaging data forms to be developed in next 4 weeks. Craig Fleishman, Luc Mertens, Raj Krishnamurthy, possibly Lars Gross-Wortmann, and Mayo Clinic faculty member (to be identified by Kim) will be recruited to create MRI forms. The data center will submit for SickKids REB approval, as appropriate.
2. Identify principal contacts in Echo & surgery at each CHSS institution
3. Exercise testing was discussed at length. The approved protocol allows for collecting exercise reports but exercise testing will be at variable times, per standard of care. Cost of planned exercise testing would be an issue and previous analysis shows benefit only in patients whose r-l shunts were occluded. Joe Dearani will solicit a cardiologist to write a suggested ET protocol/manual, however, so that the "clinically driven" ETs may at least be somewhat standardized, where feasible.
4. We should develop a **Manual of Operations** for this cohort to explain the details of the study to institutional data coordinators, cardiologists and surgeons. Linda volunteered to help write a manual based on NIH experience.
5. Core lab in-service of participating centers
6. Data base build
7. **IRB approval may be greatly simplified by using a Single Institutional Review Board (for US sites/institutions).** As an example, a new NIH policy taking effect May 25, 2017 mandates (with exceptions) Single Institutional Review Board approval for US sites/institutions participating in multi-center studies. Details are available at http://osp.od.nih.gov/sites/default/files/sIRB_FAQs_Final_UPDATED2016.pdf
8. In the meantime, the Data Center (WMD) will work with CHSS surgeons and IDCs to recruit an institutional cardiologist registry. These cardiologists will become the principal link between enrollable patients in both Ebstein's and AAOCA and institutional IDCs. A subset of this registry will comprise ICL "core groups" for reading images. They will also be invited to participate more broadly in studies, where relevant.
9. Lastly, it was suggested that the Ebstein's (and possibly other cohort) protocols be published, perhaps in the WJPCHS. Joe D will talk to Marshall Jacobs about this possibility.

Why CHSS is uniquely positioned for answering important questions in congenital heart disease: Insight into some of its methodology

Gene Blackstone gave an outstanding presentation on the above topic. He covered a discussion of nomograms, prediction, repeated events and time-varying covariates. He explained the advantages of **Parametric** (a parameter is a constant that influences behavior of mathematical object) analysis to identify risk factors (variables that vary from individual to individual) that affect outcomes and can be used to make statistical predictions. Binary events (alive or dead) are easily managed and easily portrayed graphically. However every event that occurs over time (recurring events) are more difficult to analyze. Wayne Nelson's technique of quantifying cost of GE refrigerator repairs vs. replacement cost using cumulative risk segmented into time-related intervals is a solution. Further, there are techniques for quantifying (weighted) events (not all strokes are the same!). The outcomes are then measured as 'good as new refrigerator', 'better then new' or 'less than new'. Examples of the probability of re-admission subsequent to each re-admission were presented. Finally, introducing time-varying covariables has allowed Jim Meza to investigate optimal timing of Stage II intervention or to generate a risk score for patients on a transplant waiting list. (*Authors' note: No claim is made that this short abstract reflects the considerable & valuable content presented.)*

Wrap-up Session

LVOTO Presentation at STS

Given the audience of the plenary session of STS consists of mostly non-pediatric surgeons, a broad overview introduction is needed. Then to introduce the statistical methods, examples of its utility in adult cardiac and general thoracic surgery would catch the audience's attention. The essence of the presentation is to define the optimal timing of stage II that would decrease the risk following stage I without increasing the risk following Stage II. The explanation (although not available from these data) is that intervention before the pulmonary vasculature resistance falls will compromise survival post Stage II. Using the parametric survival analysis of all 534 Stage I neonates, how much and in whom can the survival curve be improved by optimizing timing of stage II?

Dr. Blackstone also reiterated the concept of looking at individual patient trajectories. Jim Kirklin suggested four inferences to summarize in the STS talk: 1. High risk patients can be found that are better off with transplant, (2) in lower risk patients, don't advise BDG at age < 3 mos., (3) discuss methodology (as above), and that it can be more broadly applied in studies such as this.

Data Outsourcing

The CHSS executive has mandated the DC to investigate ways and means of outsourcing data sets for analysis to interested members. The intent is to increase academic output and member participation in research. The DC will meet with our REB & legal department for further advice of how best to proceed. The Research committee will canvass the membership to measure the level of interest.

Membership List

Surgeons and member institutions are a moving target. PRRI tries to keep the list current and the DC contributes where possible. Dr. DeCampli has asked the CHSS membership for updated surgeon location and institutional status.

STS-CHSS Link

New STS reports that link STS and CHSS institutional activity are imminent. The DC will cross-reference data from the institutional STS reports we receive to see if the accuracy of total eligible vs. total enrolled has improved.

New Proposals

TGA

Ram Subramanyan is developing a research proposal to examine late outcomes of these patients, now 28 to 32 years post repair. The proposal is timely as follow-up of this cohort will be initiated early in 2017. The DC will assist Ram in developing the proposal.

LVOTO cohort and the Fontan Phase

New follow-up of this cohort is needed before the next step of an analysis to investigate transition to Fontan state.

Data link CHSS to AAOCA CT/MRI database

Raj Krishnamurthy raised the question of whether his CT/MRI data could be linked to clinical data that the CHSS has. To be investigated further.

Hotel Accommodation

The Chelsea hotel, while convenient, is too busy and perhaps dated. We should investigate an arrangement with the Marriott on Bay St (2 blocks south of the Tower) or other hotels in the area.

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Version 2016/12/13

W. D. DeCampli, W.G. Williams, Brenda Chow & Data Center Staff

Appendix I
CHSS Fall Work Weekend 2016 Attendees

Annette Flynn
Anusha Jegatheeswaran
Bill DeCampli
Bill Williams
Brenda Chow
Brian McCrindle
Chasity Wellnitz
Cheryl Fackoury
Christian Pizarro
Christo Tchervenkov
Christopher Caldarone
Craig Fleishman
David Kalfa
David Overman
Diane Hershey
Eugene Blackstone
Gail Pearson
Gerhard Ziemer
Igor Bondarenko
Ilina Ristevska
James Kirklin
James Meza
Jeffrey Jacobs
Joseph Dearani
Julie Brothers
Kamal Pourmoghadam
Kathryn Coulter
Kimberly Holst
Kristina Kovach
Linda Lambert
Lucia Mirea
Marshall Jacobs
Meena Nathan
Nancy Poirier
Nitin Madan
Paul Devlin
Pirooz Eghtesady
Plato Alexander
Rajesh Krishnamurthy
Ram Kumar Subramanyan
Rene Herlong
Richard Kim
Robert Dabal
Ruchika Karnik
Sally Cai
Santosh Uppu
Shubhika Srivastava
Susan McIntyre
Tara Karamlou
William Douglas