

# CHSS Work Weekend November 17-19, 2017

## Work Weekend Report

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### Goals & Objectives for Work Weekend \*

Critical Left Heart Obstruction	Baseline echos link to triage & outcomes
Critical aortic Stenosis	Develop plan for functional health study
Follow-up conundrum	Ideas to find & contact patient cohorts
Data abstraction	Ideas to facilitate process of chart abstraction
Functional Health analysis	Plan for 2017 Critical left Heart, AVSD & TGA

\* Slides and additional material available until February 28, 2018 @

<https://chssdatacenter.box.com/v/CHSSWWNov2017>

Contact [chss.dc@sickkids.ca](mailto:chss.dc@sickkids.ca) for password

### Fellow Report: The First Four Months

**Paul Devlin, John W. Kirklin/David A. Ashburn Fellow**

A QA report will be sent to all CHSS institutions enrolling patients in the AVSD cohort. Format of the report will be simple to assist institutions in improving consistency.

#### List of Paul's projects:

1. AVSD baseline echo descriptive analysis manuscript - completed
2. Critical Left Heart Obstruction baseline echo submission to JASE as part I
3. Critical Left Heart Obstruction echo cluster analysis submission to JASE as part II (needs Jim Meza's input for resubmission along with Part 1)
4. Arch obstruction post Stage I (PI Tara Karamlou/Piroom Eghtesady)
5. Descriptive analysis of AAOCA ischemia patients, AAOCA ischemia manuscript (PI Anusha Jegatheeswaran/Julie Brothers)
6. Paul's Thesis development & U of T MSc. courses
7. AVSD baseline echo link to triage & outcomes (needs follow-up data)
8. Coarctation follow-up with Nancy Poirier pending REB Approval at Montreal (& then will apply to need REB at SickKids)
9. PC follow-up of late complication/re-intervention

#### Critical AS – FH Outcomes

- 3 previous publications 2001, 2001 & 2010
- Need to define inclusion/exclusion criteria.
- Discussion about **virtual prediction** technique by parametric analysis (what if a patient with UVR went down a BVR pathway?). Interpreting the curves.
- Functional health analysis of AS patients (like Tara's study of FH in AA). What are control values for CHQ & PedsQL? Dr. DeCampli found published comparative references to cite.

- Exercise capacity data: Add control data for peak Vo2 & Max heart rate. Are low values a result of coddling? (i.e. self-fulfilling prophecy?)
- All CHSS DKS patients are on Fontan track; not staging to BVR. Needs to be clarified in manuscript
- This project needs to be submitted to research committee for approval.

### **Arch Obstruction after Norwood: Project Outline**

CHSS data see summary on slides:

Currently of 1116 Stage I patients are enrolled, including 593 Norwood's enrolled from 23 institutions between 2005 & 2016 with median follow-up of 2.8 years. 148 patients have had 220 re-interventions as of last follow-up.

Questions:

1. Do we have the data for obstruction (vs. re-intervention)? (ref Tal Geva paper for various criteria) definition of arch obstruction as > 20 mm Peak-to-Peak echo gradient (vs. many others of 10, 15, 25 etc.)
2. What defines arch obstruction? Do we have that data? Indications for intervention differ among published papers (& among CHSS institutions?). [see extensive (23) references cited].
3. What is the breakdown of arch morphology causing obstruction among the **surgical** patients? Are they all proximal obstructions? Re-review charts for the arch interventions to determine proximal vs. distal.
4. Institutional enrollment (N=23) among the 1116. Is enrollment proportional to the 593 in this study and proportional to their individual institutional 'size'? (i.e. what is the denominator from STS data?)

Criticism about Current analysis abstract submitted to AATS:

- Why the Competing Risk graph? (It doesn't make any sense! Delete it.)
- Instead, simply do K-M or repeated events, etc.
- What of the 69 patients with arch intervention beyond stage II? (about 1/3 of total events)

Solutions:

- Present an overview of ALL re-interventions post Norwood as an introduction & perspective to the specific study presented.
- Do analysis of all re-intervention for all events (i.e. post Stage I AND beyond Stage II) as a baseline & introduction to compare to the data for 'up to & including stage II' i.e. show the overview of arch intervention to justify talking about the cut-off at stage II [The clear message is to replace the CR with this overview as the introduction to the analysis of arch obstruction and pressure gradient data]
- Modulated renewal analysis for all interventions shows no difference in protection for each successive intervention. Interesting data! Are these curves different for cath compared to surgery?
- Freedom from arch intervention slide: correct the horizontal axis title: change it to 'time since last intervention'.
- Add death after intervention to the analysis, utilizing arch intervention as a time-varying covariable.
- Consider type of Stage I as a variable for arch intervention (i.e. BT shunt vs Sano)
- Add death after intervention to the analysis
- Next step: revise analysis & develop manuscript

# Coarctation of the Aorta: A Long-term Follow-up Study

Ismail Bouhout/Nancy Poirier

Review of RedCap questionnaire: suggestions:

- **NB. Put vital questions first**
- Focus on hypertension and re-intervention as first questions
- Simplify & Shorten. (e.g. just ask for current MD name & address)

Follow-up Ideas:

1. **A Google search?** A List of CHSS Institutions/Date of birth range/state/gender/parent names/address in 1990s. Contact Google for help!
2. Link to admin data?

But how do we get the patients to respond?

IRB decision pending @ Montreal but the project passed MHI scientific committee review (health benefit) the group felt we could not learn more by analyzing the entire cohort (initial paper only 325 of 985 patients?), given change in practice since 1989-92.

## Critical Left Heart Obstruction: Linking Baseline Echo to Surgical Triage and Outcomes

Discussion about continuing failure to derive useful information from STS database about the denominator of CHSS cohorts. Can the failure to link to STS link be corrected?

Problems identified:

- Duke Algorithm needs corrections
- CHSS coordinators may not enter CHSS eligibility in STS
- Many coordinators neither enter STS data nor have access to reports
- Member institutions (surgeons) do not send reports to CHSS data center. Can the STS-CHSS link be resuscitated? Who could do it from the STS side?
- JK: Could the data center collect long-term data on all CHSS patients as Quality Assurance (QA)?

## Remote Data Abstraction: What We Learned

Tara Karamlou

**Background:**

- 4 institutional coordinators voluntarily extracted data on their institution's patients who had Arch re-intervention
- They extracted 50% of the total data entered on re-intervention (a considerable accomplishment). Credit should be given to these coordinators (authorship/acknowledgement/other/working group)
- Coordinator phone conferences without surgeons were helpful & rewarding
- Regular calls for support & education are essential
- QA checks needed and IF the data is simply not recorded in the charts then revision of data collection form is needed in real time OR modify yes/no to specific values, such as pre-term age rather than premy Yes/No

Other lessons learned:

- data verification
- deadline can't be tight
- don't change data collection (except to delete fields as outline above)
- special IRB approval may be needed
- Include coordinators in creating the data collection forms.
- Use a secure data entry system such as RedCap to avoid headaches that can occur with row shifting in Excel.
- The DC still need to collect hospital reports to check data on occasion

## **AVSD: What Predicts a Successful 2V Repair? Echo Progress Report and Analysis Discussion**

**Operational issues:**

- Discussion about data extraction during a WW: Consider extracting op reports in the critical left heart obstruction cohort at the Spring Work Weekend
- Is WW data extraction worthwhile? It needs careful planning, pulling of records and recording, perhaps on RedCap?
- Simplify echo reading to collect only 'significant' variables (aim for 1/10<sup>th</sup> of current > 100 echo variables). Otherwise estimated time to 'catch up on missing echos is 1 ½ to 2 years!
- Other option is VPN or Cloud access for remote reading (need to have > 1 reader access at the same time). Caveat: *REB may see VPN as 'data leaving the DC'? Needs solution!*
- Are follow-up echos in pts requiring re-op post BVR sufficient? Group thought yes.

**Research Questions:** (see updated slides available at [www.chssdc.org](http://www.chssdc.org))

- There is substantial mortality among BVR. Is that fruitful for analysis?
- Study of 1<sup>st</sup> echo to be published (descriptive analysis only)
- Next analysis will use baseline & follow-up echos to assess patient triage & outcomes but should also include pre-discharge & 1-year echos and clinical outcomes (i.e. follow-up needed)
- What is the median age of definitive operation after PAB?
- Re: RV/LV inflow gradient: sort out the difference in end-diastole measurement technique vs. early diastole readings of previous review. Is there a correction factor for the earlier reading? ICL will review 10 to 20 echos from previous core lab review to compare readings at end-diastole

## **Grant Writing for CHSS Projects**

**Eugene Blackstone**

**Mini Discussion: analysis of long-term outcome:**

- Kaplan-Meier is a non-parametric statistic (*product limit estimator*) used to estimate the survival function from lifetime data
- Edward Kaplan (transatlantic GE engineer interested in engine failure) studied the lifetime of vacuum tubes at Bell Labs. Paul Meir (cancer research) worked with survival of cancer patients.
- Each separately submitted similar manuscripts to J Am Statistical Assoc. The editor insisted they combine their manuscripts as they were addressing the same problem from different direction.
- Nelson–Aalen estimator is a non-parametric estimator of the cumulative hazard rate function in case of censored data or incomplete data. It is used in survival theory, reliability engineering and life insurance to estimate the cumulative number of expected events.
- Reference: (<http://www.medicine.mcgill.ca/epidemiology/hanley/c609/Material/NelsonAalenEstimator.pdf>)

## Other important References:

- Discussion of Cox proportional hazard vs. parametric analysis of long-term survival
- Appendix p 2008 in Cardiology in the Young 2008;18 (suppl.2):208
- Nelson's repeated events & modulated renewal (*Recurrent Events Data Analysis for Product Repairs, Disease Recurrences, and other applications. Nelson, Wayne B. Technology & Engineering 2003*)
- Am Statistical white paper on p value & me & p values (*THE AMERICAN STATISTICIAN. Editorial 2016;70:129-33*)
- Blackstone (JTCVS 2017 "Can we live without p values?")
- Machine Learning (ref: Lee, J-G. Deep learning in medical imaging. Korean J Radiology 2017;18:570-84)

## CHSS & Research

Gene's theme is based upon Daniel Burnham, the architect of Chicago (among other cities) famous quote:

**"Make no little plans. They have no magic to stir men's blood..."**

- We discussed Gene's question: **What can (or could) CHSS do that cannot be done (or isn't being done) by competitive individual institutions or currently funded groups?**
- CHSS founding principle is birth (*or its closet surrogate admission to a CHSS institution*) to death follow-up. However, money, participation & analytic time, whether simple or advanced statistical analyses are limited. What could the CHSS accomplish with, for example \$8,000,000/year? (The **'No little plans'** theme)
- CHSS strengths are:
  - Long-term follow-up, (life-long)
  - Quality and quantity of the data
  - Art & science statistical analyses.
  - CHSS birth to death long-term follow-up is beyond the 3 to 5 years limits of granting agencies.
- Our limitation is the small % of cases enrolled & relatively small institutional participation rate by the 81 CHSS institutions. Currently we are (seen as) insular.

## Options:

1. Consider public health issues based on prevalence, severity & impact across a lifetime (see Oster, ME. et al. Public Health Science Agenda for CHD: Report form CDC. J Am Heart Assoc 2013;2:e000256
2. Could CHSS expand to Nationwide registry & do follow-up of 'all' CHD patients? i.e. CHSS as a clinical coordinating center for CHD research?
3. Registries for Kawasaki & Fontan. These were proposed by PHN, are good projects but not funded by NIH because they are long-term studies.
4. CHSS Randomized controlled studies? A new venture. e.g. anticoagulation strategies in Fontan. steroids vs. gamma globulin in Kawasaki?
5. NIH funding from DoD (Dep't of Defense – e.g. AAOCA study?) check who gets funded by DOD.
6. Could every CHSS institution enter ALL of their cases, (maybe start with 5 specific lesions), as QA AND as a requirement of CHSS membership? CHSS would monitor long-term outcomes as QA

These and other ideas for future direction of CHSS research & QA need further consideration.

## AAOCA Ischemic Descriptive Analysis

Anusha Jegatheeswaran & Paul Devlin

### Background:

- Anusha presented 49 patients who presented with ischemia (defined as one or more of sudden event, +ve. ischemia test or specified symptoms) among the 1<sup>st</sup> 560 enrolled AAOCA patients.
- Among the 49 ischemia patients (28 are anomalous left, 21 are right) there are 18 sudden events (12 have anomalous left, 6 are right)

- Among the 560, 236 tested –<sup>ve</sup>. for ischemia & and 275 (49%) were not tested (and therefore are not classified based on their ischemic status).

**Discussion:**

1. Reorganize tables to reflect clinical practice (in spite of recent phone conference that suggested the present format) e.g. if ischemic & left, then what are the odds of ischemia with (or without) an intramural, an inter-arterial, etc. EHB: a common problem of “Column % vs. row %”.
2. Add completion date by responsible surgeon to atomization form
3. Discussion re: presentation of ischemia: Why are only 42% tested for ischemia? Julie suggests that ischemia testing favours patients with anomalous right because the lefts will have surgery anyways; right will only go to surgery if ischemia test is +<sup>ve</sup>.
4. Investigate tested vs. not tested patients for similarities & differences.

Overall, 28 lefts with ischemia are among 46 tested and the 20 rights, among 184 tested.

AAOCA	Ischemia	Tested –ve.	Ischemia/Tested
Left	28	26	61%
Right	20	184	11%
Other	1	6	17%
Total	49	236	21%

Among the 49 ischemia patients, anomalous left and right are about equal (57% vs. 41%)

5. Raj. Need standardization of imaging. CHSS should adopt his CT & MRI protocol?
6. Re: Surgery. 40 of 49 ischemia pts had surgery; mostly unroofing (all but one) But 9 had no surgery (5 left 4 right) among whom 4 died 2 refused surgery, 1 is missing follow-up & 2 referred for surgery but we have no op. record. Data Center needs follow-up for these 2.
7. Re: presentation. JK - present left vs. right AND **give an overview of all surgery**, left vs. right; and symptoms vs no symptoms; etc. 317 of 560 had surgery including 40 of the 49 ischemia patients. **Use this overview of 317 surgical procedures as an introduction & justification for your analysis of the 49.**
8. WMD re: Why exercise testing in only 42% of patients? N/A until > age 6 or 7: what test & what indication? Compare tested and non-tested patient groups. If initial test, what is protocol for re-testing? Annually if competitive sports, otherwise when?
9. Perhaps Mike Jiang (a graduate engineer & 1st year medical student interested in CC series of AAOCA) could use CHSS measurement data from CT & MRI to construct a fluid dynamic model of AAOCA to demonstrate potential morphologic variations that cause ischemia?

## Artificial Intelligence in AAOCA

Jai Nahar

*Associate professor of pediatrics, George Washington University School of Medicine and Health Sciences, cardiologist, Children’s National Medical Center*

- Jai presented a compelling overview of the potential for using AI in the analysis of AAOCA risk stratification and outcomes by phenotype variation & to discover the unknown mechanism of sudden death.
- He gave a comprehensive summary of potential mechanisms of death including mechanical coronary squeeze, subclinical ischemia causing fibrosis & VT, cardiomyopathy, channelopathy, genetic factors, etc. & importantly, unknown factors
- We have an opportunity to combine CHSS data & AI (ref Anthony Chang. Big data in medicine: The upcoming artificial intelligence. Progress in Ped Cardiol;2016;43:91-4)

- AI involves physician/machine interface. He discussed machine learning types; supervised, unsupervised and reinforcement.
- Cognitive computing are systems that mimic human cognition via artificial neural networks (ref. Lee, J-G et al.; Korean J Radiology 2017;18:570-84)
- Machine learning in medicine (ref Deo, RC et al Circ 2015;132:1920-30) see Table 4. Variables vs. Patients vs. outcomes to produce clusters and predicted result (survival) AI as 'Augmented Intelligence'

#### Discussion & questions:

- How to account for unnatural history? (e.g. A patient in whom surgery is indicated but is an operative death?)
- Raj: Is AAOCA suitable for AI approach?
  - Outcome events are rare
  - Are there biomarkers?
  - Can phenotypic classification (Phenomapping) clustering of patients and variables produce clusters associated with outcomes?
  - How do we identify what the hidden variables are?
  - Can we identify patients who 'should' be ischemic?

**Bottom line: There are opportunities for CHSS to use the AAOCA dataset to collaborate with machine learning experts and generate novel information using these emerging AI techniques.**

## TGA cohort 32 years post enrollment

Paul Devlin & Bill Williams

#### Background:

- Among the initial cohort of 891 TGA neonates enrolled between 1985 & 89, 801 underwent a definitive repair (516 ASO, Mustard 110, Senning 175 & Rastelli 29). During the 2017 follow-up, 246 patients were contacted (21% have been lost to follow-up), and 96 completed a functional health questionnaire.
- There are 4 potential research questions to consider with the current 2017 update
  1. Why does the late hazard for atrial repairs differ? (Late hazard for Mustard is rising rapidly whereas Senning and ASO remain flat)
  2. What can be learned from the Rastelli experience?
  3. What factors affect late functional health outcomes?
  4. What are late re-interventions after the ASO?
- Questions 1 & 4 require additional clinical reports of recent (> 2010) follow-up events. Obtaining these additional reports is challenging due to regulatory issues. 4 of the 24 enrolling institutions no longer have a surgeon member & most of the patients will have 'graduated' from pediatric institutions.

#### TGA discussion

- The alarming rise in late hazard for death may be a compelling argument with IRBs to allow patient contact given their potential health benefit.
- We do have sufficient data to address questions 1 & 3. (i.e. need medical records)
- Functional health among the TGA patients has been assessed in 2000, 2010 & 2017 using 3 different age-matched instruments. Discussion focused on analysis techniques to 'normalize' these tests over time among the entire dataset of 629 tests and among the 51 patients who answered > 1 questionnaire. Is the data analyzable?
- Are there published comparisons of Peds QL with S36? There are physical function questions 36 in SF36 vs 4 on PedsQL i.e. there is some correlation but not necessarily concordance (even parent child questionnaires differ)

- Re-op post ASO/Late hazard in atrial switch/Rastelli report: Stephanie Fuller suggests we could liaise with ACHD clinics for follow-up data. We will follow-up with Craig Broberg, call scheduled in January.
- Anusha will be circulating a draft manuscript on Functional Health based on the 2010 follow up, after completion of the IAA FHS manuscript that is being edited at present.

## **AAOCA Future directions: Imaging Project Proposal**

### **Craig Fleishman, Rajesh Krishnamurthy & Anusha Jegatheeswaran**

- AAOCA atomization data is a compilation of information compiled from surgeons (335), echo (404), CT (218), MRI (96), Cath (13) & autopsy (5).
- But what we need now is a core lab review of all CT/MRI imaging for all patients. (What is the research question for this review?) MRI is mostly for function whereas CT is preferred for morphology. CT may be more consistent among institutions.
  - What is AAOCA age distribution?
  - Why only 1/3<sup>rd</sup> of patients have a CT?

With respect to the core lab...

1. Can images be reviewed by remote access? For critical measurements needed Software cost is \$200K
2. Vitria company has offered software to do advanced 3D imaging; best option
3. Am College Radiology visualization software & DB image transfer system. Grant application in progress by Raj
4. CHSS needs to support/write/encourage/etc. submission. Deadline is RFP resource-based grant within 2 months but it is annual. Need letter of support/intent
5. IRB advice re: Cloud storage/reading/DB

Craig: CHSS need in-service education (send protocol for echo and CT or MRI based on best methodology to data coordinators) and Webinar for CT/MRI standard format.

- We'll likely need to engage a cardiologist with a focus on imaging for this cohort.
- Follow-up data is held up by IRB issues. But we need follow-up questionnaire (Anusha to draft)
- Also collect clinical reports +/- follow-up images for post-op AAOCA patients
- 3 months post-op; stress testing post-op [when? check enrollment text for detail.]

## **Critical Left Heart Obstruction: Linking baseline echo data to surgical triage & outcomes**

- Do we need to do this before the annual follow-up?
- Analysis using Virtual survival & 'life-months' gained.
- Requires getting rid of non-overlapping options (e.g. severe HLHS in whom a BVR is not ever an option – maybe a 5% probability of ineligibility) Paul will need to go to Cleveland for machine learning.
- EHB suggests we include the older cohort data, especially the AS cohort that mostly eligible for either BVR or UVR. Virtual survival is better analysis than propensity matching/scores as it is patient-specific vs. average based. It is done in 'R'!
- Suggestion: Repeat the calculator formula and use the new additional patients to confirm/deny.
- Is there value in analyzing the cross-overs?
  - 26 Hybrid went on to Norwood
  - 16 went from BVR to UVR (14 BAV & 2 surgical valvotomies)
  - 23 crossed from UVR to BVR
- Question re: pre-op data: Can we obtain data from an STS data export to be sent in e-format for input

## Sunday Wrap-up Discussion

### Single (Central) IRB

- Dr. DeCampli has set up some preliminary discussions with the IRB at the University of Central Florida (UCF). UCF is willing to host the cIRB for CHSS studies, and Dr. Stephenson has mentioned that SickKids could potentially host a cREB for Canadian sites.
- This would potentially decrease the need for amendments and work by coordinators at each site. This can be onerous when a simple change needs to be implemented. It would also help decrease the burden of CHSS related activities that each site would have to do on their own.
- There is also a potential to create one IRB for all cohorts. This would be even more general in nature, but again help facilitate a decrease in coordinator workload.

### Follow-Up

Dr. Kirklin suggested that follow-up should be decentralized, with the onus on each institution to follow their own subjects. Historically, decentralized follow-up has led to more subjects lost to follow-up. However, continuing with the theme of transforming CHSS studies into Quality Assurance studies, follow-up could be made a requirement for each site, and may lead to greater compliance in returning follow-up questionnaires.

### STS Data

To facilitate data extraction at the Data Centre, it was suggested that the Data Centre could request some of the data that is already been compiled for the STS. More information is needed to determine which STS data fields are relevant to the CHSS studies, and whether we may be able to amalgamate some fields.

### Surgeon Engagement

There was a short discussion on ways to increase surgeon engagement, including adding extra points in the US News & World Report for institutions which are active participants in CHSS studies (through involvement in Working Groups and/or through high enrollment in studies).

### Dues

There was a short discussion on potential strategies to increase the funding for the CHSS. While the number of patients increases each year, increasing the workload at the CHSS, dues do not increase.

Potential strategies discussed included:

1. Increasing dues for all sites
2. Increasing dues for sites that do not enroll
3. Basing dues on proportion of eligible patients enrolled

### Data Extraction

Due to wording in current consent forms and Data Transfer Agreements, it is not possible for data to leave the Data Centre. One solution is to set up VPN access for collaborators so that data could be read remotely. However, Dr. DeCampli mentioned that remote reading by VPN could be interpreted as transmission of data outside the Data Centre. Brenda will check on this with the SickKids REB and Legal departments. As an alternative, Brenda suggested that each institution could perform data extraction.

## Appendix 1: Participants

### In Person Attendees

Eugene Blackstone  
Igor Bondarenko  
Ismail Bouhout  
Sally Cai  
Brenda Chow  
William DeCampi  
Paul Devlin  
Cheryl Fackoury  
Christoph Haller  
Osami Honjo  
Anusha Jegatheeswaran  
Michael Jiang  
Tara Karamlou  
Rick Kim  
James Kirklin  
Kristina Kovach  
Julia Lo  
Louis Clauden  
Amine Mazine  
Brian McCrindle  
David Meyer  
Michael-Alice Moga  
Conall Morgan  
Jai Nahar  
Kate Pearson  
Kamal Pourmoghadam  
Toshiharu Shinoka  
Arti Singh  
Christo Tchervenkov  
Bill Williams

### Webinar Attendees

Carl Backer  
David Blitzler  
Julie Brothers  
Ali Dodge-Khatami  
Craig Fleishman  
Stephanie Fuller  
Marshall Jacobs  
Minoo Kavarana  
Rajesh Krishnamurthy  
James Meza  
David Overman  
Nancy Poirier  
Shubhika Srivastava