Managing the Adult Congenital Heart Disease Patient with Heart Failure

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Disclosure:

• No conflicts of interest to disclose.
Objectives:

• Describe the prevalence of heart failure amongst ACHD patients.
• Identify possible contributors to heart failure.
• Identify factors in diagnosis of heart failure in ACHD.
• Describe treatment of heart failure in ACHD.
Heart failure accounts for 26% of deaths in ACHD patients\textsuperscript{1} (CONCUR Registry Data)

Median age at death 51 years (range 20.3-91.2 years)

20% of ACHD hospitalizations in the US in 2007 had a diagnosis of heart failure\textsuperscript{2} and ACHD patients have only recently exceeded the number of pediatric patients ->a HF tsunami is coming!

\textbf{Heart failure in ACHD is a reflection of the underlying CHD, the surgeries and interventions an individual has had. Therefore there is a need to understand historical operations patients may have had, know the age, era, and conditions under which the individual had surgery.}
Approach to HF in Acquired HD vs. ACHD
McLary J et al. Prog Ped Cardiol. 2014;38:5

A) Heart failure treatment in acquired heart failure

- Neurohormonal modulation
  - RAAS inhibitors / β-adrenergic blockers / Aldosterone antagonists

- EP device therapy
  - ICD / CRT / Ablation

- Invasive hemodynamics to guide treatment

B) Heart failure treatment in ACHD

- Neurohormonal modulation

- EP device therapy
  - ICD / CRT / Ablation

- Structural intervention

- Invasive hemodynamics to guide treatment decisions
Approach to Heart Failure in ACHD

- Understand the physiology of the particular ACHD
- Diagnose heart failure
- Pinpoint contributors
- Is there an interventional or surgical approach to the problem? Heart failure can be the result of residuae of the ACHD lesion or interventional/hybrid/surgical approach.
- Medical therapy
- VAD/Transplantation
Etiologies of Heart Failure in ACHD

• Volume overload (including intra-cardiac shunting)
• Pressure overload
• Systemic right ventricles
• Single ventricle physiology
• Arrhythmias
• Myocardial ischemia (coronary anomalies or surgical injury/poor surgical myocardial protection), surgical fibrosis
• Chronotropic incompetence-surgical/catheter-based injury to the conduction system, drugs such as beta-blockers and Ca blockers
Systemic RV

Blood from body is diverted to the LA->LV->lungs; blood from the pulmonary veins is diverted to the RA->RV->aorta.

Single Ventricle

e.g. extracardiac Fontan-venous blood goes directly to the lungs via passive flow, single ventricle pumps blood to the body and through the lungs.

Mustard & Senning Procedures


Summary of Arrhythmia Etiologies Leading to Heart Failure.

Etiologies of Heart Failure in ACHD

• Ventricular dysynchrony (e.g. RBBB, LBBB)
• Chronic pacing
• Chronic hypoxia (cyanosis)-impairs regulation of mitochondrial function and contributes to dysfunction


• Traditional cardiovascular risk factors as ACHD patients age (weight, sedentary lifestyle, dyslipidemia, smoking, diabetes). Bhatt A et al., Congenital Heart Disease in the Older Adult [www.heart.org](http://www.heart.org). (2015 AHA Guideline)

• Genetic syndromes e.g. Noonan syndrome—about 20% develop a hypertrophic cardiomyopathy
LV Non-compaction can Impair LV Function

• During fetal life the ventricular myocardium is non-compacted and then compacts during development starting at the base of the ventricle and progressing toward the apex, epicardium compacted first and then endocardium.

• In some ventricles, ventricular compaction is arrested before it completes. There are prominent apical trabeculations that communicate with the LV cavity. Non-compaction seen most at the apex of the LV.

• A non-compacted ventricle may not function as efficiently as a compacted ventricle and a cardiomyopathy may result.
Heart Failure in Various Types of ACHD

1Norozi K et al. Am J Cardiol. 2006;97(8):1238-1243.
Heart Failure in Pregnancies of ACHD Patients

• 5% of ACHD pregnancies are complicated by some degree of heart failure\(^1\)
• Markedly increased blood volume (about 40-50%) increases cardiac output by 50% and HR by 17% -> strains ventricles with marginal function.
• Decreased systemic vascular resistance and the resulting drop in blood pressure can cause problems with obstructive lesions.

Patients with moderate to complex ACHD are at risk for development of heart failure, and clinicians should emphasize early referral to an ACHD center to initiate a plan for heart failure prevention or treatment.

Evaluation at an ACHD tertiary care center with a heart failure service and electrophysiological service allows for multidisciplinary care of these complex patients. The ACHD specialist should lead the direction of care, because these patients are not directly comparable to heart failure patients with acquired disease (ischemic and nonischemic).
Diagnosis of Heart Failure in ACHD

• Functional classifications have less utility in ACHD. Need to use objective measures.

• ACHD patients have usually lived with some limitation all their life and HF often occurs slowly so patients are often not a good judge of their functional capacity.

Dimopoulos K et al. In Shaddy RE (Ed), *Heart Failure in Congenital Heart Disease*. London: Springer-Verlag, 2011; 64.
Cardiopulmonary Exercise Testing in ACHD

• Exercise capacity is often depressed in patients who describe themselves as asymptomatic similar to non-ACHD chronic HF patients.¹

• Cardiopulmonary exercise testing predicts hospitalization and death over the next year.¹


Dimopoulos K et al. In Shaddy RE (Ed), Heart Failure in Congenital Heart Disease. London: Springer-Verlag, 2011; 64.
Six Minute Walk Test (6MWT)

• Useful only in highly symptomatic patients who cannot do a CPET.
Neurohormones: ANP and BNP correlate with disease severity.¹ Neurohormones elevated in all ACHD patients.¹

Neurohormones: Enothelin-1 and Norepinephrine Correlate with Disease Severity

Diagnosis of Heart Failure in ACHD

• There is some degree of neurohormonal activation in asymptomatic patients with ACHD therefore BNP, NT-proANP, and NT-proBNP are all elevated in ACHD patients.

Some Evidence BNP May Predict Survival in ACHD

In tetralogy of Fallot patients
Cyanosis Increases ANP and BNP

• Higher in LV volume overload vs. RV volume or pressure overload
• Higher in LV pressure overload than RV pressure overload
• With volume overload BNP values usually correlate with the magnitude of left to right shunt, PA pressure, PVR, and EDV.
• Useful measure but not a stand-alone test
BNP/NT-proBNP can be used as an adjunctive marker the integrated evaluation and monitoring of patients with known HF to further define severity, response to therapy, and its progression.

BNP/NT-proBNP can be used as an adjunctive marker, not a stand-alone test, to aid in the diagnosis of new HF in symptomatic patients.

Biomarkers such as BNP are Class IA recommendations for diagnosis/prognosis and Class IIB to guide therapy in decompensation in the AHA HF Guidelines
Pulmonary Artery Catheters Rarely Used Due to Anatomy & Shunts That Make Measurements and Calculations Inaccurate

Mustard Procedure
Extracardiac Fontan
VSD
Interventional Therapies for Heart Failure in the ACHD Patient-Primary LV Failure

• Aortic valvar stenosis->valvuloplasty
• Aortic regurgitation->transcatheter/hybrid/surgical valve replacement (if cause is aortic enlargement perform replacement of the ascending aorta).
• Coarctation->angioplasty and stent placement
• Coronary anomalies-surgery to repair anomalous coronaries
• Shunts-> shunt closure (if pulmonary resistance is not too high)-VSD, PDA closure
• Collaterals/fistula-> closure-coils, plugs, particles
Interventional Therapies for Heart Failure in the ACHD Patient-Primary RV Failure

• Pulmonary artery or venous stenosis -> angioplasty +/- stenting
• Pulmonary valve stenosis -> valvuloplasty
• Pulmonary regurgitation -> transcatheter/hybrid/surgical pulmonary valve replacement
• Shunt closure: ASD
• Atrial septostomy - to allow “pop off” shunting when right atrial pressures rise excessively
• Aortopulmonary collaterals -> coil, plug, or particles
Embolization in a Glenn Shunt Patient
Consider Ventricular Interactions

• Tetralogy of Fallot, typically thought of as a right heart problem.
• Right ventricular diastolic dysfunction is prevalent in repaired TOF, due to ventriculotomy scars, VSD patches, RBBB, dysynchrony, ventricular fibrosis.
• RV-LV interaction may cause LV dysfunction due to decreased LV preload

• 20-40% of RV systolic pressure and stroke volume results from LV contraction
• RV pumping can be maintained by LV contraction for long periods of time
## Exercise Training in ACHD Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>ACHD Type</th>
<th>N</th>
<th>Type of Training</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westhoff-Bleck et al (2013)</td>
<td>Atrial switch (TGA)</td>
<td>48 (NYHA Class I/II patients without baffle obstruction or pacemaker)</td>
<td>24 weeks of structured progressive exercise training vs. usual care</td>
<td>Significantly increased VO2, workload, maximum exercise time and NYHA class. Systemic ventricular function and volumes remained unchanged by MRI. No arrhythmias with exercise training.</td>
</tr>
<tr>
<td>Winter et al (2012)</td>
<td>Atrial switch (TGA) or CCTGA</td>
<td>54</td>
<td>10 weeks of 3 sessions per week vs. controls</td>
<td>↑ VO2 and ↓ resting BP. No change in NT-proBNP or QOL. No adverse events</td>
</tr>
<tr>
<td>Study</td>
<td>ACHD Type</td>
<td>N</td>
<td>Type of Training</td>
<td>Outcome</td>
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<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Van der Bom et al. 2014</td>
<td>Atrial switch (TGA) and CCTGA</td>
<td>40</td>
<td>Same as Winter et al (2009)</td>
<td>Short-term benefits of exercise training did not persist over 3 year follow-up period. Sports participation at baseline associated with ↑ exercise capacity, ↓ NT-proBNP levels, ↑ event-free survival</td>
</tr>
<tr>
<td>Duppen et al. 2015</td>
<td>TOF and Fontan</td>
<td>93 (56 exercise group, 37 control)</td>
<td>12 week standardized aerobic training 3x/week vs. usual care</td>
<td>No change in LV, RV, or single ventricle MRI volume, EF, or regurgitant fraction. No significant changes in echocardiogram parameters or neurohormone levels. No adverse remodelling.</td>
</tr>
</tbody>
</table>
Exercise training should be preceded by CPEX testing to determine exercise capacity, assess risk for adverse events, and determine suitability for exercise training (IC)
Limited Evidence for the Efficacy of B-Blockers in Systemic RV and Single Ventricle

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug(s)</th>
<th>Median Follow-up (mos)</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindenfeld et al. 2013</td>
<td>Carvedilol</td>
<td>1</td>
<td>↑ RVEF</td>
</tr>
<tr>
<td>Giardini et al. 2007</td>
<td>Carvedilol</td>
<td>8</td>
<td>↑ RVEF, ↓ NYHA</td>
</tr>
<tr>
<td>Josephson et al. 2006</td>
<td>Carvedilol or Sotalol or Metoprolol</td>
<td>8</td>
<td>↓ NYHA</td>
</tr>
<tr>
<td>Doughan et al. 2007</td>
<td>Carvedilol or Metoprolol XL</td>
<td>31</td>
<td>↓ NYHA</td>
</tr>
<tr>
<td>Norozi et al. 2007</td>
<td>Bisoprolol</td>
<td>33</td>
<td>No improvement in exercise capacity, neurohormones, RV and LV size or function.</td>
</tr>
<tr>
<td>Shaddy et al. 2007</td>
<td>Carvedilol</td>
<td>161</td>
<td>No clinical improvement</td>
</tr>
</tbody>
</table>
ACE Inhibitors in Repaired Tetralogy of Fallot (TOF)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Median Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norozi et al (2007)</td>
<td>Bisoprolol</td>
<td>33 (RCT)</td>
<td>6 months</td>
<td>No improvement in NYHA, peak oxygen consumption or RVEF</td>
</tr>
<tr>
<td>Babu-Narayan et al (2012)</td>
<td>Ramipril</td>
<td>64 (RCT)</td>
<td>6 months</td>
<td>No improvement in RVEF measured by CMR.</td>
</tr>
</tbody>
</table>

Tetralogy of Fallot is the most common cyanotic congenital heart disease. Has a systemic left ventricle. The pulmonary valve is stenotic and is repaired or replaced and a VSD is closed.
ACEI in Single Ventricle Patients

• Patients after the Fontan procedure (single ventricle repair) are at risk to develop hepatic dysfunction, hepatopulmonary syndrome, and decreased SVR. Therefore ACEI should be used with caution in this patient population. Ryan TD et al. *Curr Treat Options Cardio Med.* 2015;17(5):4-14.
### ACEI in Systemic RV

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Median Follow-up (mos)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecter et al. 2001</td>
<td>Various (no attempt to control)</td>
<td>14</td>
<td>24</td>
<td>No improvement in exercise capacity or RVEF</td>
</tr>
<tr>
<td>Robinson et al. 2002</td>
<td>Enalapril</td>
<td>9</td>
<td>12</td>
<td>No improvement in exercise capacity</td>
</tr>
<tr>
<td>Therrien et al. 2008</td>
<td>Rampiril</td>
<td>17</td>
<td>12</td>
<td>No improvement in exercise capacity or RVEF</td>
</tr>
<tr>
<td>Koutati et al. 1997</td>
<td>Enalapril</td>
<td>18</td>
<td>2.5</td>
<td>No improvement in exercise time, CI, or diastolic function</td>
</tr>
<tr>
<td>Babu-Narayan et al. 2006</td>
<td>Ramipril</td>
<td>64</td>
<td>6</td>
<td>No improvement in RVEF, LVEF, pulmonary regurgitation, neurohormones, or exercise capacity.</td>
</tr>
<tr>
<td>Tutarel et al. 2012</td>
<td>Enalapril</td>
<td>14</td>
<td>13</td>
<td>↓ BNP, no improvement in exercise capacity or echo parameters</td>
</tr>
</tbody>
</table>
Pulmonary Vascular Disease in the Fontan (Single Ventricle) Patient

• Venous hypertension caused by the Fontan procedure (a lack of pulsatile pulmonary blood flow) contributes to pulmonary vascular disease.
• These patients do not meet criteria of a mean PA pressure of 25 mmHg but their pulmonary vascular resistance is high.
• These patients may benefit from pulmonary arterial hypertension therapies.
• So far there is limited evidence on the use of sildenafil and bosentan (no effect) in these patients.

# Sildenafil in Single Ventricle Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giardini et al (2008)</td>
<td>27</td>
<td>1 hour after placebo or sildenafil 0.7 mg/kg (25-50 mg)</td>
<td>↑ peak VO2, ↑ rest and exercise pulmonary blood flow index, ↑ CI, no change in oxygen saturations with sildenafil.</td>
</tr>
<tr>
<td>Goldberg et al (2009)</td>
<td>28</td>
<td>Placebo or sildenafil 20 mg TID x 6 weeks, 6 week washout period, then cross-over x 6 weeks</td>
<td>↑ ventilatory efficiency during peak and submaximal exercise, ↑ oxygen consumption at anaerobic threshold in single LV or mixed ventricular morphology but not RV morphology with sildenafil.</td>
</tr>
<tr>
<td>Morchi et al (2009)</td>
<td>5</td>
<td>Retrospective case series -4 of 5 had f/u catheterization,</td>
<td>↓ PA pressure and PVR, ↑ oxygen saturations with sildenafil.</td>
</tr>
</tbody>
</table>
## ARBs in Systemic RV

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Median Follow-up (mos)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dore et al. 2005</td>
<td>Losartan</td>
<td>29</td>
<td>3.5</td>
<td>No improvement in exercise capacity or NT-proBNP</td>
</tr>
<tr>
<td>Lester et al. 2001</td>
<td>Losartan</td>
<td>7</td>
<td>2</td>
<td>↑ RVEF</td>
</tr>
<tr>
<td>Van der Bom et al. 2013</td>
<td>Valsaratan</td>
<td>88</td>
<td>36</td>
<td>Small decrease in RV volumes and mass. No effect on RVEF, exercise capacity or QOL.</td>
</tr>
</tbody>
</table>

Need larger multi-site studies with homogenous groups of patients with longer follow-up to truly determine the utility of heart failure therapies in ACHD.
ACE inhibitor therapy should not be routinely used for all patients with single ventricle CHD but could be considered in specific cases such as situations of valve regurgitation or ventricular dysfunction.

Patients with fluid retention associated with ventricular dysfunction should be treated with diuretics to achieve a euvolemic state.

Digoxin may be used to relieve symptoms in children with symptomatic HF and low EF.
• Hydralazine/isosorbide dinitrate is not recommended.

• Direct renin inhibitors cannot be recommended.

• Inotropic therapy may be considered for symptomatic relief in the palliative setting.

• Vasopressin receptor antagonists cannot be recommended for the routine treatment of chronic HF (e.g. tolvaptan)
## Cardiac Resynchronization Therapy (CRT) In ACHD

### CRT in Acquired LV Failure
- LVEF ≤ 35%, QRS duration >150 msec usually with a LBBB pattern, NYHA Class II + on guideline-directed HF therapy\(^1\)
- More ischemia and infarcted tissue that may not be electrically excitable with pacing
- 30% are non-responders to CRT\(^2\)

### CRT in ACHD
- Only 9% of congenital HF presents with LBBB and a QRS duration > 120 msec.\(^1\)
- Higher proportion of RBBB and RV failure in ACHD
- More direct surgical trauma causing conduction delay
- 10.7-29% are non-responders to CRT\(^2\)

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CRT Challenges: Epicardial or Hybrid Systems Often Needed

## CRT in ACHD

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up (months unless otherwise indicated)</th>
<th>Significant Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janousek et al. 2004</td>
<td>8 with systemic RV</td>
<td>17.4 (median)</td>
<td>↑ RVEF</td>
</tr>
<tr>
<td>Strieper et al. 2004</td>
<td>7 (mostly systemic LV with RBBB)</td>
<td>19 (median)</td>
<td>↑ EF</td>
</tr>
<tr>
<td>Dubin et al. 2005</td>
<td>73 with CHD (mostly systemic LV but 17 with systemic RV)</td>
<td>4 (median)</td>
<td>↑ EF</td>
</tr>
<tr>
<td>Moak et al. 2006</td>
<td>6 (100% paced prior to study, 66.7% with normal QRS)</td>
<td>10 (median)</td>
<td>No significant change</td>
</tr>
<tr>
<td>Study</td>
<td>Number of Patients/Description</td>
<td>Follow-up (Mean/Median)</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Khairy et al. 2006</td>
<td>13 (76% with CHB)</td>
<td>16.5 (mean)</td>
<td>↑ EF</td>
</tr>
<tr>
<td>Jauvert et al. 2009</td>
<td>7 with systemic RV</td>
<td>19.4 (mean)</td>
<td>Improved NYHA class</td>
</tr>
<tr>
<td>Cecchin et al. 2009</td>
<td>60 (7 with systemic RV, 13 with single ventricle)</td>
<td>0.7 years (median)</td>
<td>↑ EF, improved NYHA class</td>
</tr>
<tr>
<td>Janousek et al. 2009</td>
<td>109 (33 with systemic RV, 4 with single ventricle)</td>
<td>7.5 (median)</td>
<td>↑ EF, improved NYHA class, 40% of those listed for transplant removed from the list due to improvement</td>
</tr>
<tr>
<td>Perera et al. 2013</td>
<td>67 (75% with CHD)</td>
<td>2.75 years (mean)</td>
<td>↑ EF and significantly reduced systemic ventricular end-diastolic dimensions</td>
</tr>
</tbody>
</table>
CRT in Longer-Term Follow-up Less Clear

Limitations: N=10 Tetralogy of Fallot patients with systolic LV dysfunction

De novo CRT
Upgrades from other pacing devices

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Left ventricle ejection fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24.0 ± 10.5</td>
</tr>
<tr>
<td>Medium term</td>
<td>36.7 ± 13.0</td>
</tr>
<tr>
<td>Long term</td>
<td>26.7 ± 8.8</td>
</tr>
</tbody>
</table>

6 months
53.4 ±29.3 months
CRT in Longer-Term Follow-up Less Clear

Same results with LVESV-effect dropped off with time
CRT in Systemic Right ventricles

• Early results show it improves RV function but it does not reduce systemic atrioventricular valve regurgitation. If this is problem it needs to be surgically dealt with.

• An increased incidence of VT was noted with CRT (10% before CRT vs. 25% after CRT, \( p=0.02 \))

• Does CRT cause a proarrhythmia effect in ACHD or is it just a progression of the underlying ACHD substrate?...further study required

• At this time there are no recommendations in ACHD to implant a CRT-D (the guidelines talk only about ICD) unless someone needing a defibrillator for prior sustained VT or sudden arrest also meets CRT guidelines unlike in acquired LV failure

• Only case reports of CRT-D in ACHD in the literature
Pros vs. Cons of using CRT-D in ACHD Patients

**PRO**

- Some forms of ACHD have a high incidence of sudden death (e.g. transposition of the great arteries (TGA) after atrial switch procedures, congenitally-corrected TGA) associated with decline in systemic RV function or in tetralogy of Fallot with reduced LV and RV function
- Number of years of life at risk higher in ACHD than acquired heart failure

**CON**

- Difficult implants due to anatomy in many ACHD patients
- High lead complications especially in younger more active patients
- More inappropriate shocks in CHD patients (41% in Yap et al, 2007) vs. LV acquired heart failure patients (10% in SCD-HeFT trial).
- Younger patients experience greater adverse psychological functioning and worse quality of life with ICD than older patients.
2014 HRS ACHD ICD Recommendations

• ICD therapy is indicated in adults with CHD and a \textit{systemic left ventricular ejection fraction} less than or equal to 35%, biventricular physiology, and New York Heart Association (NYHA) class II or III symptoms.

• ICD therapy is reasonable in selected adults with \textit{tetralogy of Fallot} and multiple risk factors such as left ventricular systolic or diastolic dysfunction, non-sustained ventricular tachycardia, QRS duration $\geq 180$ ms, extensive right ventricular scarring, or inducible sustained ventricular tachycardia at electrophysiological study.
• ICD therapy may be reasonable in adults with a *single or systemic right ventricular ejection fraction* <35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration ≥140 ms, or severe systemic AV valve regurgitation.

• ICD therapy may be considered in adults with CHD and a *systemic ventricular ejection fraction* <35% in the absence of overt symptoms (NYHA class I) or other known risk factors.
• Adults with CHD and advanced pulmonary vascular disease (Eisenmenger’s syndrome) are generally not considered candidates for ICD therapy.

• Endocardial leads are generally avoided in adults with CHD and intracardiac shunts. Risk assessment regarding hemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized.
• Permanent pacemaker implantation is recommended for advanced second- or third-degree AV block associated with ventricular dysfunction.

• LV apical pacing can be useful in epicardial ventricular pacing systems.

• CRT can be useful with a systemic LV with an EF < 35%, complete LBBB, QRS duration > upper limit of normal for age, NYHA Class II-IV on guideline directed medical therapy.
• CRT may be considered with a systemic RV with an EF < 35%, complete RBBB, QRS duration > upper limit of normal for age, NYHA Class II-IV on guideline directed medical therapy.

• CRT may be considered for single ventricle patients with an EF < 35%, complete BBB, QRS duration > upper limit of normal for age, NYHA Class II-IV on guideline-directed medical therapy.
• ICD implantation can be useful in the patient with unexplained syncope and at least moderate LV dysfunction and DCM

• ICD therapy may be considered with DCM who have an LVEF < 35% and who are in NYHA Class II or III

• Ablation therapy is recommended in the patient with tachycardia-induced cardiomyopathy when medical therapy fails
• CRT is indicated with a systemic LVEF ≤ 35%, SR, complete LBBB with a QRS ≥ 150 msec (spontaneous or paced) and NYHA class II to IV (ambulatory symptoms). (Similar ISHLT 2014 Pediatric HF Guideline recommendation but it is Class IIa Level of evidence B)

• CRT can be useful with systemic LVEF ≤ 35%, SR, complete LBBB with a QRS 120-149 msec (spontaneous or paced) and NYHA class II to IV (ambulatory symptoms).

• CRT can be useful with systemic LVEF ≤ 35%, an intrinsically narrow QRS and NYHA class I to IV (ambulatory) symptoms who are undergoing new or replacement device implantation with anticipated requirement for significant (>40%) ventricular pacing. Single site pacing from the systemic ventricular apex/mid-lateral wall may be considered alternatively.
CRT indications in adults with congenital heart disease

**Systemic RV**
- RVEF ≤35%
- NYHA II-IV
- BBB
- QRS ≥120 ms
- Class III, Level B
- *NYHA IV
- Delay transplant/mechanical support 
  Class III, Level C

**Systemic IV**
- LVEF ≥55%
- NYHA I-II
- *Sinus rhythm*
- QRS ≥120 ms
- Class III, Level B

**Single ventricle**
- RV dilation
- NYHA I-II
- RBBB
- QRS ≥120 ms
- Class III, Level C
- *NYHA IV
- Delay transplant/mechanical support 
  Class III, Level C

- Severe subaortic-ventricular obstruction/function
- NYHA I-II
- RBBB
- QRS ≥110 ms
- Class IIIa, Level C

- Cardiac surgery
- QRS ≥110 ms
- *Progressive ventricular dilatation/dysfunction 
  Class IIIb, Level B

- Ventricular dilation
- NYHA I-II
- QRS ≥110 ms
- *Progressive ventricular dilatation/dysfunction 
  Class IIIa, Level C

- RV dilatation
- NYHA I-II
- RBBB
- QRS ≥110 ms
- Class IIIa, Level C

- TV surgery
- NYHA I-II
- RBBB
- QRS ≥110 ms
- Class IIIb, Level B

**HRS 2014 ACHD Guidelines**

**GUERIN FAMILY CONGENITAL HEART PROGRAM**
• CRT can be useful with a single ventricle EF ≤ 35%, ventricular dilatation, NYHA II-IV (ambulatory) symptoms, and a QRS ≥ 150 msec that produces a complete RBBB or LBBB morphology (spontaneous or paced). (ISHLT Pediatric HF Guidelines 2014 consider this a IIB Level of evidence C recommendation).

• CRT may be considered with a systemic EF > 35%, an intrinsically narrow QRS, and NYHA Class I-IV (ambulatory), who are undergoing new or replacement device implantation with anticipated requirement for significant (> 40%) ventricular pacing. Single site pacing from the systemic ventricular apex/mid-lateral wall may be considered as an alternative.
HRS 2014 ACHD Recommendations re CRT

• CRT may be considered if undergoing cardiac surgery with an intrinsic or paced QRS duration ≥ 150 msec, complete BBB morphology ipsilateral to the systemic ventricular, NYHA Class I-IV (ambulatory) symptoms, and progressive systolic systemic ventricular dysfunction and/or dilatation or expectation of such development regardless of the EF, especially if epicardial access is required to implement CRT.

• CRT may be considered with a systemic RV undergoing surgery for tricuspid valve regurgitation with an intrinsic or paced QRS duration ≥ 150 msec, complete RBBB, NYHA Class I-IV (ambulatory symptoms, regardless of the degree of RV systolic dysfunction. (Similar ISHLT 2014 Pediatric HF Guideline recommendation (Class IIB level of evidence C))
HRS 2014 ACHD Recommendations re CRT

• CRT may be considered with severe subpulmonary RV dilatation and dysfunction (e.g. tetralogy of Fallot) with complete RBBB with QRS ≥ 150 msec, NYHA class II-IV (ambulatory) symptoms.
• CRT may be considered in selected patients with NYHA Class IV symptoms, severe systemic ventricular dysfunction in an attempt to delay or avert transplantation or mechanical support.
• CRT is not indicated with a narrow QRS complex (< 120 msec).
• CRT not indicated with comorbidities and/or frailty that limit survival with good functional capacity to < 1 year.
Heart Transplantation

• Fewer redo congenital patients get heart transplants due to high panel of reactive antibodies (PRAs) from multiple transfusions during surgery and allograft use (elevated Class I and II anti-HLA antibodies), complex anatomy, need for longer donor vessels, and multi-system involvement (e.g. liver cirrhosis).

• May be difficult to bridge with a VAD (systemic collateral sources of pulmonary circulation may make unloading difficult).

• Some patients have high PVR and require heart-lung transplant.

• Some need multi-organ transplantation (e.g. heart-liver) due to cardiac-induced liver failure for example.
• High output heart failure can occur after transplant if there are significant aortopulmonary collaterals (e.g. Glenn shunt, Fontan procedure). These should be ligated intraop if they are accessible. If not they can be embolized (coils, particles) postop if needed with improved outcomes.
Aortopulmonary Collaterals in ACHD Transplant
Heart Transplant Survival ACHD vs. Non-ACHD

$P < .0001$ at each time point
Conditional Survival ACHD vs. non-ACHD (survivors beyond 1 year)

$P < .0001$ at each time point
## Heart Transplant Survival in ACHD


<table>
<thead>
<tr>
<th>Investigators (year)</th>
<th>Era</th>
<th>Source</th>
<th>n</th>
<th>30-day survival</th>
<th>1-year survival</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izquierdo <em>et al</em> (2007)</td>
<td>1991-2006</td>
<td>SC</td>
<td>8</td>
<td>75%</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Greutmann <em>et al</em> (2009)</td>
<td>1985-2006</td>
<td>SC</td>
<td>13</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>Patel <em>et al</em> (2009)</td>
<td>1987-2006</td>
<td>UNOS</td>
<td>689</td>
<td>80%</td>
<td>69%</td>
<td>57%</td>
</tr>
<tr>
<td>Lamour <em>et al</em> (2009)</td>
<td>1990-2002</td>
<td>CTRD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>488</td>
<td></td>
<td>80%</td>
<td>70%</td>
</tr>
<tr>
<td>Irving <em>et al</em> (2010)</td>
<td>1988-2009</td>
<td>SC</td>
<td>37</td>
<td>70%</td>
<td>68%</td>
<td>58%</td>
</tr>
<tr>
<td>Karamlou <em>et al</em> (2010)</td>
<td>1990-2008</td>
<td>UNOS</td>
<td>575</td>
<td></td>
<td>76%</td>
<td>63%</td>
</tr>
<tr>
<td>Davies <em>et al</em> (2011)</td>
<td>1995-2009</td>
<td>UNOS</td>
<td>1,053</td>
<td>~80%</td>
<td>~79%</td>
<td>~60%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cardiac Transplant Registry Database + Pediatric Heart Transplant Study.

SC, single center; UNOS, United Network of Organ Sharing.

<table>
<thead>
<tr>
<th></th>
<th>ACHD Transplant</th>
<th>All Other Transplant</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Undergoing re-transplantation*</td>
<td>6.9</td>
<td>2.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median interval between transplant and re-transplant (years)*</td>
<td>6.3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

ACHD is a risk factor for poor late outcomes after re-transplantation (HR 2.75, 95% CI 1.13-6.68, \( p = 0.026 \))
Desensitization Improves Outcomes for CHD Patients Undergoing Heart Transplant

- Plasmapheresis and IVIG
- Drugs to decrease sensitization such as monoclonal antibodies and proteasome inhibitors
- Intravenous immunoglobulin (IVIG)
• Transplant evaluation, when considered, should include in the risk-benefit assessment not only the mortality or morbidity of transplantation but also the presence of antibodies secondary to multiple prior surgeries in some patients and the coexistence of multisystem dysfunction (i.e., renal, hepatic, pulmonary hypertension).
Desensitization Improves Survival in High PRA CHD Transplant

• 14 patients pediatric CHD patients with high pre-transplant PRA (>10%) treated with desensitization (plasmapheresis, IVIG, pulse cyclophosphamide, and rituximab) vs. 56 with low (≤10% PRA).
No difference in survival between high PRA patients with desensitization and low PRA CHD patients

• Fresh whole blood used at some centers to decrease bleeding in neonatal cardiac surgery has been shown to increase anti-HLA sensitization (WBCs are not removed from the blood).

• Also have to assess whether the continued use of homografts outweighs the disadvantages of sensitization. Can use bovine pericardium or CorMatrix or treatment of the allograft with glutaraldehyde before use.

• Avoid or limit transfusion of blood products during congenital heart surgery.
There may be a stronger immune response in young adults...would a different immunosuppression strategy in young adult ACHD patients make a difference?
• It has been shown that ACHD heart transplant recipients are less likely to receive induction therapy and steroid maintenance vs. other transplant patients. There is a survival advantage for pediatric CHD patients receiving induction and steroid maintenance. Would increasing induction therapy and steroid maintenance would improve ACHD outcomes?
Mechanical Assist Devices

• Berlin EXCOR most frequently used
• Increasing numbers of Heartware and HeartMate II devices being used as well as the SynCardia Total Artificial Heart (new 50 mL ventricle for BSA greater than 1.2 m²).
• Challenges of unusual anatomy and heart locations require considerable preoperative planning.

Heartmate II flipped backwards
• It is reasonable to treat systemic ventricle dysfunction with ACE inhibitors and diuretics.

• It is reasonable to consider atrial septostomy in an effort to augment cardiac output in patients with a chronically failing Fontan physiology.

• Heart transplantation may be beneficial for severe systemic ventricle dysfunction or protein-losing enteropathy.
European ACHD Guideline HF Recommendations

• No specific drug recommendations other than diuretics and digoxin due to lack of evidence.
• Case reports and animal studies only with no convincing evidence of improvement for right ventricular failure or hypoplastic left heart syndrome

• A number of clinical trials are underway with single ventricle pediatric patients at present. Atrial tissue obtained at first cardiac operation and cardiac progenitor cells (CPC) isolated and cultured to multiple them. CPCs then instilled via transcoronary infusion.

• CPCs from neonates have shown stronger regenerative ability vs. adult-derived CDCs.

• Much more investigation needed
The Future of HF in ACHD

• Leadless pacemakers are in clinical trials (only a single chamber pacemaker at present) -> when these are available as CRT devices this will make it a lot easier to use this therapy in ACHD.

• Subcutaneous defibrillators-only defibrillate and do not pace at present and very large. When these do more than just defibrillate this will facilitate treating ACHD patients for primary prevention.

• Increasing understanding of genomics in HF and ACHD may make it possible to have personalized medicine for ACHD HF causes that target the pathway inducing HF.
Case Study #1

- 28 year old male born with transposition of the great arteries diagnosed as a neonate
- Underwent a Senning (atrial switch procedure) at 6 months of age.
- Did well until 2012 when he had a left posterior cerebral artery stroke. Investigation with TEE demonstrated a dilated aortic root with no aortic valve regurgitation. No source for the stroke was identified. No arrhythmias on a Zio patch. No other comorbidities.
Case Study #1 Symptoms/Family History/Social History/Meds

- No dyspnea on exertion, walks 10 flights of stairs per day
- No chest pain, no palpitations, no presyncope, never had a syncopal event
- No orthopnea, no PND, no ankle edema
- No family history of CHD, sudden death, early coronary artery disease or arrhythmias.
- Nonsmoker. Drinks alcohol 1-2 times per month.
- Meds: Plavix 75 mg daily.
Case Study #1 Exam

• No JVD
• S1, S2, no S3, Grade II/VI systolic murmur
• Air entry audible throughout with no crackles
• No ankle edema
• No ascites, no hepatomegaly
• Good peripheral pulses
Case Study #

Short PR interval with unusual p wave axis (atrial ectopic rhythm from suture damage to the SA node during the Senning procedure), right ventricular hypertrophy with right axis deviation.
Case Study #1: Echo

• Mild to moderate systemic tricuspid valve regurgitation
• Small left ventricle with hyperdynamic systolic function
• Dilated and hypertrophied systemic right ventricle with mild to moderately depressed systolic function.
• Mild pulmonary valve regurgitation.
• Mild aortic root dilatation. Aortic annulus 3.27 cm (z=6.09)
MRI 2012 continued

- Aortopulmonary collateral from the transverse arch feeding the right lower lobe of the lung.
- Enlarged right phrenic artery which also supplies the right lower lobe.
- Duplication of the right renal artery.
- No intracardiac thrombus
• No baffle obstruction or leaks, Qp:Qs 1:1
• CI  4.64 L/min/m2
• LVEF 71.4%, LVEDVI 76 mL/m2 (z score -0.4)
• RVEF 50.2%, RVEDVI 136.8 mL/m2 (z score 3.6). RV hypertrophied and dilated.
• No systemic ventricle wall motion abnormalities.
• Aortic root 32 x 33 mm, ascending aorta 28 x 29 mm
• TV annulus 51 mm, MV annulus 21 mm, mild systemic TR (20-25% regurgitant fraction)
Factors to Consider:

• Systemic RV
• Up to moderate systemic TV regurgitation
• Moderately depressed systemic RV function
• Atrial ectopic rhythm
Treatment Plan

• Zio patch annually as patients after atrial switch generally develop sinus node dysfunction and many eventually need a pacemaker (based on AHA ACHD recommendation).

• Lisinopril 5 mg daily to start and later up-titrate as long as BP tolerates for systemic right ventricular function and to try to prophylax against further systemic TV regurgitation and aortic root dilatation. (based on AHA ACHD recommendation)

• Cardiac MRI/MRA in the next year to reassess effect of lisinopril, aortic root size. If flow changed through the aortopulmonary collateral and significantly flooded the right lower lobe at any point this could be coil embolized. (based on AHA ACHD recommendation)
Case study #2

- 30 year old female born with tricuspid atresia, pulmonary atresia and transposition of the great arteries, large VSD, small muscular VSDs.
Case Study #2 History continued

• Underwent a right Blalock-Taussig shunt (R subclavian to R pulmonary artery) via a right thoracotomy within the first few weeks of life.
Case Study #2 continued

• Glenn shunt (SVC->PA)-date unknown (sends upper body blood directly to lungs and reduces single ventricle workload)
• At 8 years of age she underwent an aortopulmonary Fontan procedure
• Had not seen a congenital cardiologist from age 18 until age 29 years

Hepatology. 2012.56(3):1160-1169, DOI: 10.1002/hep.25692
http://onlinelibrary.wiley.com/doi/10.1002/hep.25692/full#fig1
Aortopulmonary Fontan (RA->PA connection)

All of the blood from the body goes directly to the lungs; blood coming from the lungs and the coronary sinus goes into the heart

Case Study #2

• Developed atrial fibrillation in 2009->started on sotalol but no anticoagulation.
• February 2010->repeated atrial fibrillation and was cardioverted x 1. Five ED visits for arrhythmias that year. Started on warfarin.
• 2012-fatigue possibly from sotalol->changed to digoxin an metoprolol
• Found to have significant pulmonary artery stenoses bilaterally->5/2014 had left PA stent which migrated distally and a second stent was inserted, right PA angioplasties.
Case Study #2

- Aortopulmonary collaterals too small to coil.
- Paracentesis for 6 L of fluid.
- Liver biopsy to evaluate function for possible transplant vs. Fontan revision with MAZE-liver damage not reversible per hepatology
- Fecal alpha-1 antitrypsin negative therefore no protein-losing enteropathy. Esophageal varices found on MRI.
- RA thrombus seen adherent to the lateral/inferior RA 7 x 4 x 7 cm.
- Decision to proceed with heart/liver transplant listing
Case Study #2

• Then found to be sexually active with no birth control -> Nexplanon -> menorrhagia -> required transfusion.
Case Study #2: Symptoms

- Intermittent dyspnea on exertion but able to walk 3 miles
- Ascites, no ankle edema, no orthopnea, no PND
- No palpitations, no chest pain, no presyncope
Case Study #2: Physical Examination

• Single S1, normal S2, no S3, no murmur
• No JVD.
• Liver 2-3 cm below the right costal margin
• Lungs clear to auscultation
• Sats 98%.
• No ankle edema
• No gross ascites
• Functional class II, Stage D
Case Study #2: Medications

- Digoxin 0.25 mg daily.
- Ferrous sulfate 325 mg daily. (for recent anemia secondary to menorrhagia).
- Furosemide 20 mg daily.
- Metoprolol XL 25 mg daily.
- Spinolactone 25 mg daily.
- Warfarin 4 mg daily to keep INR 2-3. HRS I/B recommendation
Case Study #2: Labs/Cardiac MRI/MRA

• AST 21, ALT 18, ALP 86, albumin 3.9, total protein 6.1, total bili 0.9
• Normal electrolytes
• Creatinine 0.7

Cardiac MRI/MRA-combined ER about 47% (likely underestimated due to irregular HR. Septal hypokinesis. Fontan flow 2.1 L/min/m2
Case Study #2: EKG Rate Controlled AF, early R wave progression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vent rate</td>
<td>59 BPM</td>
</tr>
<tr>
<td>PR interval</td>
<td>40 ms</td>
</tr>
<tr>
<td>QRS duration</td>
<td>100 ms</td>
</tr>
<tr>
<td>QTc</td>
<td>430 ms</td>
</tr>
<tr>
<td>P-R axis</td>
<td>+9 171</td>
</tr>
</tbody>
</table>

Technician: STEPHANIE VASQUEZ
Test no:

Referred by: GARY GOULIN
Confirmed by: XUNZHIANG WANG MD
Case Study #2: GUERIN FAMILY CONGENITAL HEART PROGRAM

Cardiomegaly with severe RA enlargement
Treatment Plan

• No cardioversion due to large RA thrombus
• Rate control
• Dental clearance for heart-liver transplant listing
• Endoscopy +/- varices banding
• Remove Nexplanon due to bleeding and need for transfusion that can increase sensitization
Thank you for your attention

• Comments/Questions?