Update on Clinical Care of the Older Fontan Patient

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Presenter Disclosure Information

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“Update on Clinical Care of the Older Fontan Patient”

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The following relationships exist related to this presentation:

No relevant relationships to disclose
Objectives

• Present the current data on long-term outcomes in the Fontan population

• Discuss current guidelines for management of the adult Fontan patient

• Explore strategies for improving outcomes by partnering with regional congenital cardiac centers and with specialists in other disciplines
Epidemiology

Survival to 18 yrs of Age with Complex CHD

- 1980: 80%
- 1970: 50%
- 1960: 15%
- 1940: 5%

Age at Death for Adults with CHD

Mean Age (yrs)

Tricuspid Atresia  27 ± 5
Univentricular Connection  31 ± 10

n = 2609 patients
199 deaths
Mean age for all dx
37 ± 15 years

Highest mortality
ccTGA  26%
Tri atresia  25%
Univentricular connection  23%

Modes of death
Sudden death  26%
CHF  21%
Perioperative  18%

Fontan Mortality

[Graph showing freedom from death or transplant (%)]

RA-RV connection
Total cavopulmonary connection
RA-PA connection

Logrank p = 0.0230

Fontan Mortality

Freedom from death or transplant (%)

Logrank p = 0.4840

RA-RV connection
Total cavopulmonary connection
RA-PA connection

Time from initial Fontan surgery (years)

Fontan Mortality

- 261 Fontan patients living in New England followed over 12 yrs (median)
- Of 209 perioperative survivors:
  - 11.5% death
  - 2.4% transplant
  - 12.4% conversion or revision

A Multi-organ Disease
A Multi-organ Disease

- **Cardiac**
  - Heart failure
  - Arrhythmia
  - Chronotropic incompetence
  - Valvular disease
- **Hematologic**
  - Thromboembolic risk
- **Vascular**
  - Venous varicosities
  - Endothelial dysfunction
- **Gastrointestinal**
  - Protein-losing enteropathy
  - Congestive hepatopathy
  - Esophageal varices
  - Hepatocellular carcinoma
- **Pulmonary**
  - Plastic bronchitis
- **Renal**
  - Microalbuminuria
  - Hepatorenal syndrome
Congestive Heart Failure

- Systolic dysfunction
  - Pre-Fontan volume loading
  - Limited preload
  - Increased afterload
  - Myocardial fibrosis
  - Systemic right ventricle
  - Valvular regurgitation
  - Ventricular pacing

- Diastolic dysfunction
  - Abnormal relaxation
  - Chronically increased afterload
Congestive Heart Failure

- Few data on use of “adult” heart failure therapies
- **ACE inhibitors (Class Ila recommendation)**
  - Enalapril was not shown to improve exercise parameters or cardiac index in Fontan patients
  - Percent increase in cardiac index from rest to maximum exercise got worse (102% vs. 125%, p<0.02)
- **Beta blockers**
  - Carvedilol failed to show clinical benefit in mixed cohort of young patients with heart failure
  - Trend toward benefit in CHD patients with systemic left ventricle; trend toward harm in CHD patients with systemic right ventricle

Arrhythmia

- IART particularly common in atrio pulmonary Fontan due to atrial scarring and dilation
- >50% likelihood in AP Fontan within 15 years, less in LT/ECC patients
- May be tolerated for short periods, but prolonged can lead to hemodynamic compromise and thrombus formation

Arrhythmia

- Low threshold for DC cardioversion
  - TEE recommended unless symptoms are known to have occurred within 48 hours or documented therapeutic INR for at least 3 weeks

- For recurrent episodes:
  - Antiarrhythmic drugs
  - EP study/ablation
  - Fontan conversion + maze operation
Fontan conversion

- Conversion to total cavopulmonary anastomosis
  - Lowers systemic venous pressures
  - Removes hepatic vein flow reversal during atrial systole
  - With concomitant arrhythmia surgery, good freedom from arrhythmia
  - Improved New York Heart Association functional class

Backer CL. *Cardiol Young*. 2011; 21(Suppl 2): 169-76.
Fontan conversion

Freedom from Death 1994-2010
(n=132)

Years post-conversion*

n=116  n=72  n=31  n=2

Freedom from Arrhythmia Recurrence

Years post-conversion*

n=58  n=43  n=18  n=1

IART
AF

*All performed with arrhythmia surgery

Backer CL. Cardiol Young. 2011; 21(Suppl 2): 169-76.
Arrhythmia

- Involvement of electrophysiologist with expertise in CHD is crucial!
- Anticoagulation recommended once arrhythmia is documented
Thromboembolic Risk

• Predisposing factors
  – Venous stasis due to lack of contractile chamber
  – Further venous stasis in setting of dilated right atrium in Fontan pathway
  – Atrial arrhythmias
  – Procoagulant state with deficiencies of hepatic clotting factors (e.g. protein C; protein S; factors II, V, VII, IX, and X)

Thromboembolic Risk

- Prevalence of Fontan thrombus: 12-17%
- Mortality rate: 18%
  - 8% in stable patients vs. 75% in unstable patients (p = 0.01)
- Risk of thromboembolic death: 1.3% at 10 years, 9.2% at 25 years
- Primary predictors for thromboembolic death:
  - Thrombus within Fontan (HR 22.7, p = 0.0002)
  - No aspirin or warfarin (HR 91.6, p = 0.0041)

Inconsistent Medication Therapy Across Pediatric Heart Network Centers

Thromboembolic Risk

- No clear guidelines for when to switch from ASA to warfarin
- No evidence demonstrating superiority of warfarin over aspirin
- Anticoagulation recommended for patients with:
  - Atrial arrhythmias
  - Residual ASD/fenestrations
  - Previous thromboembolic events
  - Poor Fontan hemodynamics
  - Atriopulmonary Fontan
- No data thus far to support use of “next generation” oral anticoagulants in Fontan
Thromboembolic Risk

- Beware of fake-outs due to streaming of SVC/IVC flow and/or sluggish flow through the Fontan pathway

Liver Disease

- Results from chronically elevated central venous pressures in Fontan circulation
- Increasingly recognized as contributor to late Fontan morbidity and mortality

Normal liver

Fontan liver showing fibrosis and dilated sinusoids
Liver Disease

- Of 48 Fontan patients at Children’s Hospital who underwent liver biopsy (ages 5 to 47y)
  - 79% had some degree of portal fibrosis, 33% had severe portal fibrosis
  - 100% had some degree of centrilobular fibrosis, 79% had severe centrilobular fibrosis
  - Patients with severe centrilobular fibrosis had significantly higher alkaline phosphatase and total bilirubin and significantly higher MELD-XI score

Complications of Liver Disease

- Ascites
- Spontaneous bacterial peritonitis
- Hepatic encephalopathy
- Portal hypertension and esophageal varices
- Hepatorenal syndrome
**Complications of Liver Disease**

- **Ascites**
  - First-line treatment of pts with cirrhotic ascites consists of sodium restriction and diuretics (including spironolactone) and abstention from alcohol
  - TIPS is typically NOT an option for Fontan patients because there is rarely a significant hepatic venous pressure gradient to bypass
Complications of Liver Disease

• Spontaneous bacterial peritonitis
  – Risk of SBP in Fontan patients low compared with that in patients with primary liver disease
  – Relatively high opsonic activity of ascites with protein >2.5 g/dL protects against infection
Complications of liver disease

• Hepatic encephalopathy
  – Ammonia-lowering therapies
    • Lactulose to produce 2-4 bowel movements per day
      – Degrades to lactic acid which promotes passage of NH3 from tissues into lumen
      – Acidification inhibits ammoniagenic coliform bacteria
      – Acts as cathartic, reducing colonic bacterial load
    – In patients refractory to lactulose, antibiotics may be added
      • Reduce colonic concentration of ammoniagenic bacteria
      • Rifaximin better tolerated than neomycin but cost and potential of resistance are concerns
Complications of liver disease

- Portal hypertension and esophageal varices
  - Due to generalized venous hypertension
  - Varices develop at portal vein pressures of ~10 mmHg and are at higher risk of bleeding at ~12 mmHg
  - Propranolol used in patients with portal hypertension but may not yield same benefit in Fontan patients
  - Measures for decreasing venous pressures can result in rapid improvement of varices and bleeding
Congestive Hepatopathy and HCC

- Cirrhosis is associated with an increased risk of hepatocellular carcinoma.
- In cases related to hepatitis B or C, hemochromatosis or EtOH, annual risk of HCC is 2-4%.
- Congestive hepatopathy or “cardiac cirrhosis” not typically considered to be associated with high risk of HCC.
Congestive Hepatopathy and HCC

Congestive Hepatopathy and HCC

• Chronicity of hepatic congestion in Fontan physiology is unique

• Screening for HCC suggested in the presence of advanced (3-4/4) centrilobular OR portal fibrosis

• Sensitivity of ultrasound in combination with AFP for detecting early mass lesions ~60% (vs. 80% for CT or MRI)

• After surgical resection, recurrence rate in cirrhosis is high; for Fontan patients, heart-liver transplant may be treatment of choice
Vascular Disease

• Lower extremity venous disease

  – Results in pain, reduced physical function and mobility, depression and social isolation
  – Prevalence of chronic venous insufficiency
    ~60% with 1/3 of those classified as severe
  – Independent risk factors include higher number of prior catheterizations and history of DVT
Graduated Compression Stockings

- Lower extremity elevation and mechanical compression are mainstays of therapy
- Start with 20-30 mmHg pressure
- Do not use TEDS (pressure <10 mmHg)
- Higher pressure at the foot helps push fluid up the leg
- **Knee highs** are better tolerated than thigh highs
Protein-Losing Enteropathy

- Fontan Physiology – Chronically Low Cardiac Output
- Inflammation
- Inflammatory Mediator Release
- Abnormal Mesenteric Vascular Resistance
- Venous Congestion
- Abnormal Enterocyte Function
- Altered Glycosaminoglycans
- ? Congenital Lymphatic Malformations
- +/− ? Genetic Predisposition
- Protein-Losing Enteropathy

Protein-Losing Enteropathy

Survival analysis of patients with PLE

Protein-Losing Enteropathy

- Proposed treatments
  - Dietary modification (low-fat, high MCT diet)
  - Medications
    - Diuretics
    - Spironolactone
    - Unfractionated heparin
    - Steroids (e.g. budesonide)
    - Sildenafil
    - Octreotide
    - Infliximab

- Procedures
  - Pacemaker
  - Fontan fenestration
  - Fontan revision
  - Transplant
Plastic bronchitis

- Higher mortality rate for plastic bronchitis associated with CHD (29%) than non-CHD-related (8%); an additional 12% of CHD patients with plastic bronchitis experience life-threatening events

- Treatments
  - N-acetylcysteine
  - Systemic/inhaled steroids
  - DNase
  - Inhaled urokinase/tPa
  - Sildenafil
  - Bosentan
  - Chest physiotherapy
  - Bronchoscopic removal
  - Fontan fenestration
  - Transplant

Taking the Plunge: Referring for Transplant
Transplantation for ACHD

ADULT HEART TRANSPLANTATION

All pair-wise comparisons with Cardiomyopathy are significant at p < 0.05; Coronary Artery Disease vs. ReTX: p < 0.0001

ISHLT

Issues Complicating Transplant

- Sensitization (h/o multiple transfusions)
- Debilitated/poor substrate/other organ dysfunction
- Elevated PVR
- Increased risk of postoperative infection
- Multiple prior surgeries
- Anatomic complexities
  - Alterations in donor harvest (longer segments of pulmonary artery, aorta, pericardium)
  - Increased risk of bleeding/trauma at transplant
  - Necessity of extracardiac repair
  - Prolonged pump & ischemic times
Exercise Testing Identifies Patients at Increased Risk for Morbidity and Mortality (Fontan)

HR (95% CI): 7.5 (2.6-21.6)

VO₂ ≥ 16.6 ml/kg/min

VO₂ < 16.6 ml/kg/min

Exercise Testing Identifies Patients at Increased Risk for Morbidity and Mortality

Predicting Fontan Failure

MELD-XI Score Predicts Fontan Patients At Risk For Failure

Log rank p = 0.006

MELD-XI score = 11.76($\log_e$ creatinine) + 5.112($\log_e$ bilirubin) + 9.44

Assenza GE et al. ACC Scientific Sessions 2011.
Typical follow-up

• Follow-up every 6 to 12 months
• Echo or MR/CT imaging once a year
• Cardiopulmonary stress testing every 1 to 2 years
• Holter/event monitoring based on symptoms
• Laboratory studies
  • Liver function tests including INR
  • Basic metabolic panel
  • Complete blood count
  • Hepatitis C screening if surgery before 1992
  • Alpha fetoprotein every 6 months if advanced fibrosis
• Abdominal imaging (U/S or MRI) every 6 months if advanced fibrosis, otherwise based on labs
• Role for routine liver biopsy?
Indications for Cardiac Catheterization

- Development of volume retention
- Protein-losing enteropathy
- Plastic bronchitis
- Decreasing functional capacity
- Increasing arrhythmias
- Increasing cyanosis
- Hemoptysis
Topics for Routine Counseling

- Weight and exercise
- Smoking
- Alcohol
- Drugs, including caffeine
- Contraception
- Pregnancy
- Oral health/SBE prophylaxis
Exercise

- Physical activity levels for children and adolescents after Fontan are markedly reduced.
- As adults, nearly half of all Fontan patients are either overweight (37%) or obese (5%).
- Bethesda guidelines for competitive sports in Fontan patients are fairly restrictive.
- In adults, we generally few restrictions other than those related to warfarin (contact sports) plus heavy isometric exercises.

Pearson D et al. 2008; 5th National Conference of the ACHA.
Pregnancy in Fontan Patients

- UCLA, multicenter
  - 33 pregnancies, 15 live births (45%)
  - CV complications in 2
  - Atrial flutter, CHF, valvular regurgitation

- CONCOR investigators 1986-2003
  - 10 pregnancies, 4 live births (40%)
  - CV complications in 3 (heart failure, atrial flutter)
  - Obstetrical/fetal complications in 3 (pregnancy induced HTN, premature delivery, small for gestational age)
  - High incidence of menstrual disorders, infertility

- Potential issues: arrhythmia, heart failure, thrombotic events, premature delivery, restricted fetal growth

Potential new therapy?

- Vasodilator therapy
  - PDE5 inhibitors and non-selective ER blockers shown to improve pulmonary vascular resistance
  - Case reports of improved plastic bronchitis, PLE
  - Various small studies showing improved echo indices of myocardial performance, NYHA class, ventilatory efficiency, peak VO$_2$, and non-invasive measures of cardiac index and pulmonary blood flow
Proceed with caution!

- In September, FDA issued a warning about using sildenafil for PAH in patients age 1 to 17 years based on the STARTS-1 trial.
  - Secondary analysis found higher mortality rate in children taking high doses of sildenafil vs. those taking low doses (HR=3.5; p=0.015).
  - Most common causes of death were PAH and heart failure.
  - For now, starting sildenafil in this age group for reasons other than PAH is not recommended.

Fontan Mortality

Logrank p = 0.4840

Current Fontan-Related Studies

- Inspiratory Muscle Training to Improve Functional Capacity in Fontan patients
- Characterization of Renal Function in Adult Fontan Patients
- Transient Elastography of the Liver in Patients with Fontan Circulation
- Multicenter Cross-Sectional Assessment of Liver Health in Adults with Fontan Circulation
- STORCC: Standardized Outcomes in Reproductive Cardiovascular Care
- Cardiopulmonary Rehabilitation for Adolescents and Adults with Congenital Heart Disease
- ACHD Biorepository
Key Points

• Fontan patients are at risk for dysfunction of multiple organ systems

• More data is needed to improve our ability to provide evidence-based care to the ACHD population

• Collaboration with NECCA is crucial to clinical studies aimed at improving Fontan outcomes

• A multidisciplinary approach is necessary to provide optimal care to our patient base
Building an “Adult Fontan Clinic”

- Cardiologists/ACHD specialist
- Hepatologist
- Nephrologist
- Pulmonologist
- Surgeons
- Psychiatrist/Social Worker
- OB/Gyn
Thank you!

- **BACH Physicians**
  - Mike Landzberg
  - Michelle Gurvitz
  - Mary Mullen
  - Sasha Opotowsky
  - Michael Singh
  - Larry Sloss
  - Anne Marie Valente
  - Fred Wu

- **Physician Assistants**
  - Disty Pearson
  - Nancy Barker
  - Caitlyn Joyce

- **Nurse**
  - William Kerr

- **BACH Fellows**
  - Yonathan Buber
  - Sara Partington
  - Keri Shafer
  - Shailendra Upadhyay

- **Administrative Assistants**
  - Samantha Buechner
  - Lauren Serge

- **Research Team**
  - Amy Harmon
  - Alice Huang
  - Lilamarie Moko
  - Jenna Schreier
A Case

- 16yo man with DILV, malposed great vessels, subaortic stenosis and aortic arch hypoplasia.
  - Damus-Kaye-Stansel with aortic reconstruction, R BT shunt in Boston at 3 days of age.
  - At 6 months, bidirectional Glenn, BT takedown, balloon aortoplasty for recurrent coarctation in Portland, ME.
  - Had post-op SVT on procainamide and amiodarone.
  - At 2 years, fenestrated Fontan in Portland, ME.
  - Fenestration closed in 2008.
A Case

- 16yo man with DILV, malposed great vessels, subaortic stenosis and aortic arch hypoplasia.
  - Currently, no shunts, open venous connections, normal BP, no LVOT or desc Ao gradient, mild MVR, mild neo AoVR, SV EF roughly 60-65%.
  - Exercise testing shows single APCs & VPCs, no couplets, no exacerbation with exercise. O2 sat 97% down to 92% during exercise. Able to reach 84% of PMHR, exercise capacity at 10%ile for age.
  - Holter: some VPCs < 10, APCs < 100 per 24 hrs. No recent arrhythmias.
A Case

- 16yo man with DILV, malposed great vessels, subaortic stenosis and aortic arch hypoplasia.
  - He (and his dad) have questions about 16-year-olds with SV physiology:
    - Does sex present a problem for the heart?
    - What illicit drug use poses a cardiac risk?
    - Can he participate in wrestling with the high school team, as the coach wishes?
    - Can he become police officer or security guard as he wishes?
    - What about antibiotic prophylaxis in Fontan patients? Are they palliated cyanotic heart disease with a conduit (yes) or repaired cyanotic heart disease 6 months after patch (no)?