**MHIF FEATURED STUDY:**

**Myocardial perfusion and contraction assessed by cardiac MRI in acute and recovery takotsubo syndrome**

**DESCRIPTION:** This study will use the new respiratory motion-corrected automated in-line perfusion mapping stress CMR protocol to quantify regional myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) in TS patients resulting in a “myocardial perfusion map” which can be correlated with a “myocardial contraction map.”

**CONDITION:** Takotsubo syndrome (TS)

**PI:** Retu Saxena, MD

**Co-I:** Scott Sharkey, MD

**RESEARCH CONTACTS:**

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**SPONSOR:** MHIF IIR

**OPEN AND ENROLLING / EPIC message:** Research MHIF Patient Referral

**CRITERIA LIST/ QUALIFICATIONS:**

**Inclusion:**
- Admitted with acute TS without significant coronary artery obstruction as defined on invasive coronary angiogram or CT coronary angiogram
- Typical apical or mid-ventricular ballooning pattern based on initial echocardiogram or left ventriculogram
- Age > 18 years

**Exclusion:**
- Significant acute or chronic renal disease (dialysis or estimated glomerular filtration rate < 30 ml/min/m2)
- Contraindication to adenosine or gadolinium
- Decompensated acute heart failure (need for mechanical ventilation, vasopressor treatment of hypotension, mechanical circulatory support)
- Pregnancy or lactation
- Atrial fibrillation or sustained ventricular tachycardia/ventricular fibrillation
- Asthma requiring hospitalization or oxygen dependent COPD
- Bradycardia or advanced heart block unless pacemaker present
Adult Presentation of Congenital Heart Disease

Christina Thaler, MD PhD

• No conflicts of interest
Definition of Adult Congenital Heart Disease

- Structural heart disease present prior to birth
- Attributed to abnormal fetal development
- Does NOT include heritable diseases
  - Marfan Syndrome
  - Hypertrophic Cardiomyopathy
  - Arrhythmogenic Ventricular Dysplasia


ACHD Classification

CHD Anatomy
- Simple
- Moderate Complexity
- Great Complexity

CHD Physiology
- A: No symptoms / physiologic consequence
- B: NYHA Class II symptoms, mild physiological consequences
- C: NYHA Class III symptoms, moderate physiological consequences
- D: NYHA Class IV symptoms: severe / end stage physiological consequences
Prevalence of CHD in the European Union

- 2000: 0.8 - 1.3 million adults with CHD in the US

ACHD Presenting in Adulthood

• 1% of Korean patients at an academic medical center with an elective echocardiogram performed prior to a physical exam
29 year old pregnant woman with tachycardia

- Referred to cardiology during her second semester of pregnancy due to resting tachycardia with HR 110s and dyspnea on exertion
- BP 104/68, HR 106, RR 20 in clinic
- Noted to have a soft murmur at right upper sternal border
- Echocardiogram obtained

Enlarged RV
Cleft Mitral Valve
Left to Right Shunting Across an Atrial Septal Defect

- Qp:Qs Shunt of 2.3:1
- Preserved LV and RV function
- Enlarged RV
  - EDV 117 ml/m2 (normal 61-98 ml/m2)
- Complex ASD Noted
Complex Atrial Septal Defect

S: Secundum ASD
I: Inferior Sinus Venosus ASD
P: Ostium Primum ASD
C: Coronary Sinus ASD

Types of ASD

- A: Superior sinus venosus ASD
- B: Secundum ASD
- C: Inferior sinus venosus ASD
- D: Ostium primum ASD
- E: Secundum ASD without posterior septal rim
- F: Coronary sinus ASD

Gary Webb, and Michael A. Gatzoulis Circulation. 2006;114:1645-1653
Right Heart Catheterization

- Normal right sided filling pressures
  - RA=6
  - RV=38/9
  - PA=32/11, mean 20
- Normal left sided filling pressures
  - PCWP 8mmHg
- Qp/Qs = 1.8

ASD Closure

Younger Age of Closure Has Improved Survival

Worse Survival With Elevated Systolic PA Pressures > 40mmHg

Cardiac Complications Following Surgery

Table 2. Summary of Late Cardiac Events According to Age at Operation.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>≤24 Yrs (N = 62)</th>
<th>&gt;24 Yrs (N = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Implantation of permanent pacemaker</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Valvular heart surgery</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reoperation for atrial septal defect</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>(15%)</td>
<td>(57%)</td>
</tr>
</tbody>
</table>


Arrhythmia by age of ASD Closure

Atrial Fibrillation / Atrial Flutter

- Mayo cohort study 22% of late deaths were secondary to stroke
  - All patients had Atrial flutter / fibrillation
- Danish Registry Study 22% developed atrial fibrillation with closure < 24 years


Surgical Treatment Superior to Medical In Patients Over 40 years

- Primary Endpoint was the first presentation of either: death, pulmonary embolism, major arrhythmic event, embolic cerebrovascular event, recurrent pulmonary infection, functional class deterioration or heart failure

Anticoagulation with Atrial Fibrillation and Congenital Heart Disease

- 2016 and 2020 ESC Guidelines for Anticoagulation
  - Standard atrial fibrillation risk assessment (CHADS2 Vasc Score)
  - Intra-cardiac repair

Hindricks, G. et al. (2020). 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European heart journal. 00: 1-126

Eisenmenger Syndrome

- 54 year old woman with atrial fibrillation and NYHA class III-IV symptoms

- Declined medical treatment other than rate controlling medication and diuretics

- Died 3 years after initial presentation
Survival improved with advanced therapies

- Bosentan: class I indication
- PDE-5 inhibitors: Class Ila indication
- Bosentan and PDE5-inhibitor: Class Ila recommendation
- Oxygen and anticoagulation can be considered
- ASD closure is contraindicated


All Patients with ASD Should Have Life Long Cardiology Follow-up

- Atrial arrhythmias
  - Anticoagulation for atrial fibrillation / flutter if has had prior ASD closure
- Pulmonary hypertension
- Heart Failure
- Change in shunt size

Atrial Septal Defect Summary

- One of the more common ACHD conditions to present in adulthood
- Survival is reduced with late closure
- Percutaneous closure is only for secundum ASDs
- Atrial fibrillation, heart failure and stroke are the most common complications following closure

45 year old woman with longstanding hypertension diagnosed during pregnancy

- Presented to primary care with new onset of dyspnea on exertion and atypical chest pain
Severe Coarctation of The Aorta With Extensive Collaterals

Coarctation of the Aorta on Echocardiogram
Further History

• Symptomatic claudication during walking

• BP 142/71 upper extremity, systolic 98 in lower extremity bilaterally

• Underwent surgical repair with an 18mm interposition graft in the proximal descending aorta

• Subsequently lost to cardiology follow-up

Hypertension in Common And Increases With Age

• Monitoring
  • Resting blood pressure in upper and lower extremities (Class I recommendation)
  • Ambulatory monitoring (Class IIa recommendation)
  • Exercise blood pressure assessment (Class IIb recommendation)

• Often Undertreated
  • UK Cohort Study only 18% appropriately treated

Reduced Long Term Survival

- Reduced long term survival in 834 coarctation of the aorta patient cohort study in the United Kingdom
- Median Age Death 46 years (37-62)
  - Prior VSD or LVOT Obstruction had higher risk of death
- Causes of Death
  - LV failure (10/38)
  - Post-op period for non-coarctation cardiac repairs (5/38)
  - Ruptured descending aorta (2/38)
  - Type A dissection (1/38)
  - Acute Myocardial Infarction (3/38)
  - Sudden Cardiac Death (1/38)
  - Non-cardiac or unknown (14/38)


Lower Survival When Coarctation is Repaired in Adulthood

Indications for Intervention

• Upper extremity/lower extremity resting peak-to-peak gradient >20 mm Hg or mean Doppler systolic gradient >20 mm Hg
• Upper extremity/lower extremity gradient >10 mm Hg or mean Doppler gradient >10 mm Hg plus:
  • Decreased LV systolic function
  • Aortic Regurgitation
  • Collateral flow
• >50 % narrowing with hypertension
  • Only in European Guidelines

Re-intervention in Common

• Surgical patch repair has higher risk for re-intervention (HR 3.69, CI 2.13-6.37)
• Complications at site of coarctation
  • Aneurysm
  • Psuedoaneurysm
  • Re-coarctation
  • Dissection


Stenting has lowest rate of complications at follow-up of 18 months-6 years (median 1.9 years)


Aortic Valve and Ascending Aortic Interventions are Common

• ~50% of patients have bicuspid aortic valve

• All bicuspid valves should have 4 extremity blood pressures

Intracranial Aneurysms

- Occurs in ~10% of Patients
- IIA Recommendation to Screen for Intracranial Aneurysms in 2018 ACHD Guidelines
- Often not seen in young children and teenagers and incidence increased with age
- Often small
- More commonly seen in patients with hypertension
- Unknown if serial screening is indicated


Patients Require Lifelong Close Cardiology Follow-up

<table>
<thead>
<tr>
<th>Frequency of Routine Follow-Up and Testing</th>
<th>Physiological Stage A* (mo)</th>
<th>Physiological Stage B* (mo)</th>
<th>Physiological Stage C* (mo)</th>
<th>Physiological Stage D* (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient ACHD cardiologist</td>
<td>24</td>
<td>24</td>
<td>6-12</td>
<td>3-6</td>
</tr>
<tr>
<td>ECG</td>
<td>24</td>
<td>24</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>TTE</td>
<td>24</td>
<td>24</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>CMR/CCT</td>
<td>36-60</td>
<td>36-60</td>
<td>12-24</td>
<td>12-24</td>
</tr>
<tr>
<td>Exercise test</td>
<td>36</td>
<td>24</td>
<td>24</td>
<td>12</td>
</tr>
</tbody>
</table>

Coarctation of the Aorta Summary

- Hypertension most common symptom
  - Considered as cause of secondary hypertension in patients <30 yr
- Stenting is preferred in adult patients over surgery
- Bicuspid Valve is present in >50% of patients
- All bicuspid valve patients should have 4 extremity blood pressure screening
- Intracranial aneurysms can occur

41 year old asymptomatic man at primary care

- Vitals with heart rate 147 bpm
- EKG with typical atrial flutter
- Started on diltiazem and apixaban
- Referred to cardiology
Echo: Cor Triatrium Sinister

Cor Triatrium Sinister

<table>
<thead>
<tr>
<th>Type of defect</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve regurgitation</td>
<td>42 (24.6)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>28 (18.2)</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Persistent left superior vena cava</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Partial anomalous pulmonary venous connection</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Tetralogy of fallot</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Totally anomalous pulmonary venous connection</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>


Cardiac CT Scan

- Evaluation for associated lesions
  - ASD
  - VSD
  - Anomalous pulmonary venous return

- Pulmonary vein stenosis can occur prior to or following surgery

Clinical Presentation in Adults

<table>
<thead>
<tr>
<th>Symptoms/clinical findings</th>
<th>All patients (N=171), n (%)</th>
<th>Obstructive membrane (N=70), n (%)</th>
<th>Non-obstructive membrane (N=99), n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>46 (26.9)</td>
<td>31 (44.3)</td>
<td>15 (15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>25 (14.6)</td>
<td>19 (27.1)</td>
<td>6 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombotic/ischemic events</td>
<td>27 (15.8)</td>
<td>8 (11.4)</td>
<td>19 (19.2)</td>
<td>0.175</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>56 (32.8)</td>
<td>25 (35.7)</td>
<td>31 (31.3)</td>
<td>0.549</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (3.5)</td>
<td>2 (2.9)</td>
<td>4 (4.0)</td>
<td>0.999</td>
</tr>
<tr>
<td>Pre-syncope</td>
<td>4 (2.3)</td>
<td>1 (1.4)</td>
<td>3 (3.0)</td>
<td>0.643</td>
</tr>
<tr>
<td>Chest pain</td>
<td>13 (7.6)</td>
<td>2 (2.9)</td>
<td>11 (11.1)</td>
<td>0.047</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>6 (3.5)</td>
<td>6 (8.6)</td>
<td>0 (0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Infections</td>
<td>7 (4.1)</td>
<td>6 (8.6)</td>
<td>1 (1.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>55 (32.2)</td>
<td>6 (8.6)</td>
<td>49 (49.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>65 (38.0)</td>
<td>37 (52.9)</td>
<td>28 (28.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Treatment

• Atrial flutter ablation

• Surgery
  • Resection of atrial membrane
  • Warden procedure with baffling RPV to the LA via ASD

Follow-up

• Re-obstruction is rare

• Pulmonary vein stenosis can occur prior to or following surgery
Cor Triatrium Sinister Summary

- Membrane creating obstruction in the left atrium
- Associated with other congenital heart defects
- Re-obstruction rare after surgery
- Most common complications
  - Heart failure
  - Pulmonary hypertension
  - Thrombotic / ischemic events
  - Atrial fibrillation

32 year old at primary care for pre-operative clearance for an orbital tumor

- Murmur heart on exam
- Noted to have worsening exercise tolerance
- Surgery was delayed for cardiac evaluation
Echo – Diagnosed with Pulmonary Hypertension

Right Heart Catheterization

- Elevated RV pressures but normal pulmonary artery pressures
  - Mean RA 5 mmHg
  - RV 83/0 mmHg
  - PA 29/7 mmHg; mean 16 mm Hg
  - PCWP 8 mmHg
Branch Pulmonary Artery Stenosis

- Decision to intervene based upon
  - RV hypertension
  - Progressive RV enlargement / decreasing function
  - Distribution of pulmonary blood flow

- Restenosis is common
  - 46% in a series of 26 patients at mean follow-up of 41 months


Cancer and Congenital Heart Disease

- Swedish cohort study 21,982 patients with CHD up to age 41 years
- Hazard ration of 2.24 (95% CI 2.01-2.48) for developing any type of malignancy
- Similar results found in cohort studies in Taiwan, Canada, and California


Branch Pulmonary Artery Stenosis Stenting Summary

• Rare cause of RV hypertension

• Intervention is based on symptoms and RV function / dilation

• Restenosis is common following intervention

• All patients need lifelong follow-up

36 year old woman with chest pain during exercise

• 15 years: Syncope, no significant evaluation

• 28 years: Murmur and told she likely had mitral valve prolapse

• 20s: Active, but felt she had poor exercise endurance

• 36 years: Chest tightness while training for a triathlon
  • Exercise EKG stress test, peak HR 156 bpm, peak BP 124/60
  • Consistent with an “MI”
  • Recommended outpatient echo
Echocardiogram

- Congenitally corrected transposition of the great arteries
- Systemic right ventricle
  - Moderately reduced EF
- Epstein like tricuspid valve
Congenitally Corrected Transposition of the Great Arteries

- Abnormal L looping of the primitive heart tube

Coronary Arteries are a Mirror Image of Normal Anatomy
Heart Failure is Common During Adulthood

Any Heart Failure

Moderate to Severe RV Dysfunction

Group I: Patients with associated cardiac abnormalities
Group II: Isolated ccTGA


Medical Treatment for Heart Failure is Controversial

• Systematic review failed to show benefit with conventional HF therapy
  • Underpowered (total of 187 patients)
  • Included both D and L Transposition of the Great Arteries
  • Up to 50% drop out rates
  • Inclusion criteria included near normal RV EF
  • Follow-up times as short as 4 months

Follow-up

- 37 years: Started on Ace-I for EF 45%, follow-up systemic RV EF 53%
- 39-43 years: Developed arrhythmias: Asymptomatic NSVT, atrial flutter, and Mobitz type II AV block
- 43 years: Complete AV block, received dual chamber pacemaker

Rhythm Abnormalities Common

- Pacemakers common
  - 45% patients with ccTGA and associated abnormalities
  - 27% patients with isolated ccTGA
- Arrhythmias
  - 47% patients with ccTGA and associated abnormalities
  - 29% patients with isolated ccTGA
- Sudden Cardiac Death
  - 5 of 39 patient had sudden cardiac death in a single center series
    - All had normal to mildly reduced RV function
    - NYHA Class I-II symptoms
Follow-up

• 44 years: Moderate to severe TV valve regurgitation and moderate systemic RV dysfunction (EF mid 40s)
  • Received 27mm Mosaic porcine bioprosthetic systemic AV valve
  • Early endocarditis at 6 days post-operatively

• 45 years: 6 months post TV valve replacement, developed increased resting gradient 16-20mmHg with thickened leaflets that resolved with warfarin

Tricuspid Regurgitation is Common

Table 4. Demographic and Clinical Variables by Patient Group

<table>
<thead>
<tr>
<th></th>
<th>Group I (Associated Lesions)</th>
<th>Group II (No Associated Lesions)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr, mean ± SD)</td>
<td>32 ± 12</td>
<td>34 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>37% female</td>
<td>52% female</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>51%</td>
<td>34%</td>
<td>NS</td>
</tr>
<tr>
<td>RV Dysfunction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>70%</td>
<td>55%</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>39%</td>
<td>32%</td>
<td>NS</td>
</tr>
<tr>
<td>TR:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>82%</td>
<td>85%</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>57%</td>
<td>40%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Survival is poor following surgery after systemic RV EF <40%


Survival Poor if Sub-Pulmonary Pressure >50mmHg

Tricuspid Valve Replacement is Favored Over Repair

- High rates of TV regurgitation following repair compared to replacement
  - Series was small (16 patients)
- Tricuspid valve typically dysplastic or Epstein like


ccTGA Patients Require Close Long Term Follow-up

- Monitor for
  - Heart Failure
  - Arrhythmias
  - Systemic Tricuspid Regurgitation

<table>
<thead>
<tr>
<th>TABLE 31</th>
<th>CCTGA: Routine Follow-Up and Testing Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of Routine Follow-Up and Testing</strong></td>
<td><strong>Physiological Stage A</strong> (m/s)</td>
</tr>
<tr>
<td>Outpatient ACHD cardiologist</td>
<td>12</td>
</tr>
<tr>
<td>ECG</td>
<td>12</td>
</tr>
<tr>
<td>TTE</td>
<td>12-24</td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td>As needed</td>
</tr>
<tr>
<td>Holter monitor</td>
<td>12-60</td>
</tr>
<tr>
<td>CMR/CT</td>
<td>36-60</td>
</tr>
<tr>
<td>Exercise test</td>
<td>36-60</td>
</tr>
</tbody>
</table>
Congenitally Corrected Transposition of the Great Arteries

- Most common complex CHD to present in adulthood
- Heart failure is almost universal in adulthood
- Arrhythmias are common
- Tricuspid valve regurgitation extremely common
  - Correction recommended prior to LV EF <40%

Conclusion

- Congenital Heart Disease Can Present in Adulthood
  - Often diagnosed by echocardiogram
  - First presentation in adulthood is often either atrial arrhythmias or heart failure in a young patient
CHD Patients Have Increased Mortality Compared to the General Population

Recurrence of CHD in Offspring

- Prenatal screening with fetal echocardiography can be offered to women to screen for CHD if either parent has a history of CHD.

- Same lesions do not always occur.

Newberger. Trends in CHD, the next decade. Circulation 2016

Improved Outcomes When Cared For At a Comprehensive Adult Congenital Program


CHD: A Life Long Condition