Imaging of the Heart Transplant Patient

W. James Parks, MS., MD
Pediatric Cardiologist
Asst Professor of Pediatrics & Radiology
Children’s Healthcare of Atlanta
Sibley Heart Center Cardiology
Emory University School of Medicine
I do not have any relevant financial relationships with any commercial interests.
I will discuss the use of a medical device that is classified by the Food and Drug Administration (FDA) as investigational for the intended use.
Introduction:

The need for myocardial and vascular imaging in patients post Orthotopic Heart Transplantation (OHT) are primarily related to function of the graft. The inherent vasculopathy of rejection remains a constant deterrent. Thus, the need to accurately assess subtle functional changes and coronary obstruction are vital to graft management, therapy and survival.
CMR Assessment of Left and Right Ventricular Systolic Function Pre- and Post-Treatment of Episode of Cardiac Rejection

Pretreatment
LVEF 21%, RVEF 21%

Post-treatment
LVEF 50%, RVEF 44%

Estep et al., J. Am. Coll. Cardiol. Img. 2009;2;1126-1140
Cardiovascular Magnetic Resonance in the Diagnosis of Acute Heart Transplant Rejection: A Review

Organ Rejection: a Critical Component of Care for Patients who have undergone Heart Transplantation

CMR: Can provide an alternative to Biopsy: Vent fxn, morphol, tissue characterization. T2 quantification (spin echo) - criticized for poor reproducibility, but has utility as a screen for rejection.

****T2 quantification can dx rejection w sens & Specif ~ 90%, …correlates w biopsy.

Butler et al., J Cardiovasc Magn Reson 2009 Mar 12;11:7
Prevalence of Different Gadolinium Enhancement Patterns in Patients after Heart Transplantation

Conc: CE-MRI - identifies silent MI in event-free HTX pt and discloses fibrosis in pt w/ absent or mild angiographic Transplant Coronary Artery Disease (TCAD).

Steen et al., J Am Coll Cardiol 2008 Sep 30;52(14):1160-7
Cardiovascular Magnetic Resonance (CMR) using T2 Imaging can visualize Myocardial Edema

Assessment of Myocardial Edema and Myocardial Injury
T2-weighted CMR: Identifies acute vs recent injury of acute coronary syndrome (ACS) vs non-ACS and acute vs chronic infarction.

T2-weighted CMR: Can determine area at risk in reperfused vs non-reperfused infarct. Combined w contrast imaging, the salvaged area and area of revascularization can be quantified.

Utility of Cardiac Magnetic Resonance Imaging for the diagnosis of Heart Transplant Rejection

CMRI with Scheduled Endomyocardial Biopsy to Detect Rejection (necrosis) and Discriminate from Edema and Fibrosis

Result: (m) 51 ± 13 yr. 13 to 3725 d post OHT. *Gado Uptake trend:
Necrosis: 34 ± 21 vs 23 ± 17 for relative uptake, $P < .05$.
Fibrosis: 68 ± 47 vs 102 ± 48 in group w/o fibrosis, $P < .05$.
Edema: 93 ± 55 vs 94 ± 45 absolute uptake.

Conclusion:
(1) CMRI - promising technique for dx of rejection / edema.
(2) Pt with necrosis had increased trend of gado uptake.
(3) Interstitial fibrosis is associated with decreased uptake.

*Gado: Gadolinium

Detection and Prediction of Acute Heart Transplant Rejection with the Myocardial T2 determination provided by a Black-Blood Magnetic Resonance Imaging Sequence

Myocardial T2 Relaxation Time: Black-Blood MRI can predict Acute Heart Transplant Rejection

Black-blood MRI suppresses blood signal when T2 (IR) is calculated by allowing detection of myocardial edema.

Method: 123 MR studies & heart biopsy 8+/-11mo post HTx.

RESULT: T2 (>/= 56ms) detected rejection seen at biopsy (>/= ‘Internat Soc Heart & Lung Transplant’ - gr2): sens 89% & specif 70% (p < 0.0001). T2 increased w gr2 (n=11) c/w gr0 (n=49, p<0.05), gr1A (n=34, p<0.05) & gr1B (n=21, p<0.05); T2 addn’l increase w gr3 (n=8) c/w gr2 (p<0.05). Pt w/o rejection =/> gr2 (baseline), T2 > nl (>/= 56ms) correl/w occurrence of =/> gr2 within next 3mo: sens 63% (12/19), spec 78% (64/82) (p=0.001).

Conc: T2 weighted - Black-Blood imaging can identify most moderate acute rejections seen w biopsy and is a predictor of occurrence.

Marie et al., J Am Coll Cardiol 2001 Mar 1;37(3):825-31
Concentric Left Ventricular Hypertrophy Assessed by Cardiac Magnetic Resonance Imaging

Risk of Death in Cardiac Transplant Recipients

Study (median) 6.0 yr post HTx. Top quartile: Indexed LV mass and concentricity (mass/volume) =/>35.8 g/m^2.7 and =/>1.5 g/ml. Hx of rejection (odds ratio [OR] 5.9; 95% [CI], 2.1–16.4; p < 0.01 and post-txplt yr of MRI (OR, 1.2; 95% CI, 1.1–1.4; p < 0.01) were associated with the top quartile of LV mass in multivariable models.

Conc:

LV mass and LV concentricity: Independently associated with cardiovascular death [HR], 1.11 per g/m^2.7, 10.1 per g/ml, p ≤ 0.01).

LV concentricity - Independently associated with all mortality [HR] 4.4 per g/ml, p < 0.01).

Reduced Myocardial Perfusion Reserve and Transmural Perfusion Gradient in Heart Transplant Arteriopathy Assessed by MRI

Detection of Transplant Arteriopathy by reduced Myocardial Perfusion Reserve (MPR) and Resting Endo/Epimyocardial Perfusion Ratio

3 grps & 15 volunteers eval post Gado infusion (rest and w adenosine).
Grp A (#10) - no LVH/rejection. Nl angio w CFR >/= 2.5
Grp B (#10) - either LVH or episode of rejection. Nl angio CFR >/= 2.5
Grp C (#7) – HTx arteriop dx by angio. CFR < 2.5

Result: Grp C: MPR & Endo/Epi ratio reduced c/w cntrl (p< 0.0001).
Grp A (p <0.0001). Grp B (p <0.01 & p <0.04). HTx arteriop excluded by MPR >2.3 w sens & specif of 100% & 85%. LVH & rejection excluded, arteriop excluded by Endo/Epi ratio >1.3 w 100% & 80%.

Conc: MR perfusion detects arteriop by decreased MPR. If no LV H or prior rejection - resting Endo/Epi ratio may be sufficient for diagnosis.

**** CFR = Coronary Flow Reserve

Muehling et al., J Am Coll Cardiol, 2003; 42:1054-1060
Gated Blood Pool Imaging (GBPI): Can CMR replace GBPI to assess annual LV ejection fraction post-HTx?

Methods: 49 pt at annual review - LV fxn by GBPI and CMR.
Ejection Fraction and limits of agreement determined.

Result: (mean) EF (+/- 2SD) GBPI 58.3 +/- 18%. CMR 57.6 +/- 18%.

Conc: LVEF by CMR was comparable to GBPI in post-HTx pt.
CMR allows quantitative volumetric analysis, assessment of wall motion and valvular function.

CMR - should be considered the "gold standard" for post-transplant volumetric and functional evaluation. It can offer additional information over ... other traditional imaging modalities.

Sturgnell et al., Heart Lunc Circ, 2010 Jul;19(7):400-5. Epub 2010 Mar 30
Myocardial Perfusion Imaging Role in Heart Transplantation

CHOA, Sibley Heart Center Cardiology 2007
Analysis of Cardiac Dimensions, Mass and Function in Heart Transplant Recipients Using 64-slice Multi-detector Computed Tomography (MDCT)

Twenty (20) pts: **MDCT and Echocardiography.**

Observers (2): semi- and automated software for analysis.

Challenges: high resting heart rates and body mass indices.

**Results:** Ejection fraction (MDCT) slightly lower (mn diff: $-2 \pm 9\%$, $p = 0.29$) than echo and correlation - moderate ($R = 0.49$ to $0.54$).

LV mass was signifi lower by MDCT (mn diff: $-87 \pm 44$ g, $p < 0.001$).

***Inter-observer agreement for MDCT of LV fxn ($R = 0.90$) and mass ($R = 0.83$) were excellent.***

Cardiac Allograft Vasculopathy: Coronary Computed Tomography and Virtual Histology Assessment

Cardiac Allograft Vasculopathy - The Leading Cause of Late Morbidity and Mortality in Heart Transplantation (HTx)

Correlation:  Histology and Coronary CT post Cardiac Txplt. Coronary angiography, Intravascular ultrasound and Coronary CT.

Results: 10 pt - w intimal thickening/plaque >0.5 mm
2 grps w plaque:
(1) w necrotic core > 30% and Ca+
(2) combined core < 30% and Ca+

Conc: Inflammatory plaque in graft vessel disease can be detected by (noninvasive) CT.

Ballesteros et al., Transplant Proc, 2010 Oct;42(8):3175-7
Prevalence of Different Gadolinium Enhancement Patterns Patients after Heart Transplantation

Contrast-Enhanced Imaging (CE-MRI) detects chronic Txplt Coronary artery disease (TCAD)-related Myocardial Infarction even in patients with angio classified mild TCAD

53 pt w infarct-typical CE-MRI areas classified: I=/<25%, II=25% to 50%, III=50% to 75% and IV=/>75%. Infarct-atypical: diffuse, spotted, intramural & infero-septal. Pt w infarct-atypical CE-MRI assoc w better LV Fxn c/w infarct-typical CE-MRI or combined

LVEF = 66 +/- 6% v 45 +/- 16% v 60 +/- 13%
LVEDV=139 +/- 32ml v 148 +/- 27ml v 164 +/- 43ml
LVESV = 47+/-15ml v 81+/-27ml v 69+/-38ml, p < or = 0.05

Steen et al., J Am Coll Cardiol 2008 Sep 30;52(14):1160-7
Allograft Rejection and Vasculopathy are the Main Factors Limiting Long-Term Survival after Heart Transplantation

Ten survivors post OHT (8 m, m age 52.1±12yr, 73±11mos post OHT) Coronary angiography, multi-slice CT, ventricular biopsy and CMRI. Allograft vasculopathy & atherosclerosis were detected by multi-slice CT & angio w positive correlation (r = 1).

Result: Late contrast enchancement (DE - MRI) correlated positively (r=0.92, r²=0.85, p<0.05) w histological dx of rejection by biopsy.

Conc: Combined non-invasive approach using multi-slice CT & MRI can assess CAV & rejection post OHT before invasive methods.

TurboFlash

Usta et al., J Cardiothorac Surg. 2009; 4: 43
Quantitative Myocardial Blush Grade (MBG): Cardiac Allograft Vasculopathy (CAV) related to microvascular perfusion (MVP) and function post Heart Transplantation.

72pt/cath. MBG: time-grey-level contrast intensity rise. G(max)/T(max) = (G/T). 72pt&18vol(s)-CMR diastolic strain rate (DSR) & MVP w pharmacol hyperemia.

Result: G/T of MVP & mean DSR (r(2)=0.68 & r(2)=0.58, P<.001, both). Visual & quant MBG w G/T=2.7/s higher accuracy c/w stenosis severity / angio for microvasc integrity / CAV (AUC=0.78, SE=0.06, 95%CI =0.66-0.87 of lumen narrowing vs AUC=0.91, SE=0.03, 95%CI = 0.84-0.97 for G/T; P<.01). **MBG predicted survival (chi(2)=14.0, P<.001), c/w blush (chi(2)=5.4, P=.02) and coron narrowing (chi(2)=4.8, P=.04).**

Conc: Quant MBG aided identity of CAV in pt with impaired perfusion reserve but w/o angio evident atherosclerosis.

Korosoglu et al., Am Heart J, 2010 Apr;159(4):643-651.e2
Cardiac CT of the Transplanted Heart: Indications, Techniques, Appearance and Complications of Anastomosis Sites

Improved Anti-Rejection Therapy and Infection Control have Improved Survival post Heart Transplant (HTx)
Coronary Allograft Vasculopathy (CAV) remains a limiting factor

HTx pt undergo annual coronary angiography for vasculopathy
Angiography allows indirect detection of CAV but not wall thickening / intimal hyperplasia; and is assoc w 1%-2% risk of complication. ECG gated multi-detector CT can provide comprehensive / noninvasive eval of pt in a single study.
CT enables eval of coronary lumen & wall, thus screening, dx, grading, & f/u of CAV, detect post-HTx complications; malignancy, infection, cardiac, vascular anastomoses and function.

Cardiac CT of the Transplanted Heart:
Indications, Techniques, Appearance and Complications

Anastamosis Sites

Computerized Tomography of Two Hearts Beating in One Chest

Gated Cardiac CT
Important in evaluating the complex anatomy and anastomoses of the donor and recipient heart: Postop follow-up - hearts, vessels and lungs contributing to the prolonged survival of heterotopic HTx pts.

Lai et al., AJR:191, December 2008 Vol.91 no6 1711-1716
Cardiac Allograft Vasculopathy - cause of mortality in Htx pts:

Prognostic value of stress (myocard) perfusion

166 pts-54 ± 10 yr (140m) limited bike exercise or dobutamine (+/- 40 μg/kg/min) imaging 7.4 ± 2.5 yr p HTx. IV - 370 MBq of technetium-99m tetrofosmin (t99) – injected @ peak stress & 24 hr p test. Abnl: reversible or fixed defect: 55 pts (33%), median f/u 2.5 yr, 54 deaths (33%, 16/cardiac. Abnl = higher in pts w cardiac death (CD) than pt w/o (69% vs 29%, P = 0.01).

Peak rate-pressure product - only predictor (risk 0.84, 95% CI 0.73 to 0.97, chi-2, 7.7, P = 0.006). Abnl perfusion – indepen predictor CD (risk ratio 3.5, 95% CI 1.6 to 11.7, chi-2, 4.7, incremental clinical and stress test variables, P = 0.01).

Conc: stress perfusion w t99 CT provides incremental data for the prediction of Cardiac Death p OHT.

Elhendy et al., Am J Cardiol, 2002 Apr 15;89(8):964-8
Non-invasive Diagnostic of Cardiac Allograft Vasculopathy by 31P MR Chemical Shift Imaging

31P MR Chemical Shift Imaging can Diagnose Coronary Vasculopathy by Variations in Cardiac high-energy phosphates in Adult HTx Recipients

Method/Result: CAV-defined by angio – irregular / concentric narrowing of coronary artery. 8pt w CAV(grp A) & 18pt w/o(grp B) compared w 9 volunt (grp C). 31P 3D chemical shift MR imaging ratio of phosphocreatine (PCr) and ATP. Ratio-lower in grp A than grps B & C (p = 0.003) & (p = 0.001). A PCr/ATP value of 1.59 was optimal value to predict CAV - specif & sens 100% & 72%.

Conc: 31P Chemical shift MR imaging is a promising, non-invasive method to detect modifications of high-energy phosphates related to CAV or as indicator for screening coronary angiography.

Caus et al., Eur J Cardiothorac Surg 2006;29:45-49
Quantification of Absolute Myocardial Blood Flow by Magnetic Resonance Perfusion Imaging

Serial Imaging of the Myocardium during Gadolinium Transit

MR Perfusion showed reduced Regional Myocardial Blood Flow & Hemodynamically Significant Coronary Artery Disease

Lee et al., J Am Coll Cardiol Img 2009;2:761–770
Cardiac Allograft Vasculopathy and Late Graft Failure - main limiting factors of long-term success of heart transplantation:

Graft Function in Long-Term Survivors

Method: 22pt enrolled w mn age @ OHT 46±13.5yr, mn donor age 28.5±10.1yr, mn graft ischemic time 189±58 min, mn f/u 18.5±2.4yr (range 15–22). All w CMRI and DSCT.

Result: LV volume index - nml range: LVEDV/BSA 61±16 ml m⁻², LVESV/BSA 22±15ml m⁻², LVSV/BSA 38±6ml m⁻², LV mass/BSA: 72±18gm⁻², LVEF 0.59±0.08. 2pt(9%) global hypokinesia and 2 pt(9%) akinesia (1) segment.

DSCT: 41% pt - nml coronary angio. 41% w wall thickening. 18% w one =/+ >60% stenosis.

Conc: nml graft function & morphology @>15 yr post OHT. Significant number w allograft vasculopathy and initial stages of disease.

Transplant Coronary Artery Disease

Intravascular Ultrasound of a Coronary Artery in a Heart Transplant Patient... Intimal Hyperplasia at 1 year

B. CT of Coronary Vasculopathy, Bogot et al., RadioGraphics, 27, 1297-1309.
Electron-Beam Computed Tomography in the Assessment of Coronary Artery Disease After Heart Transplantation

**EBCT detects Allograft Coronary Calcification**

112 HTx pt (25 f; 17-69 yr; m52) 1-153mo (m46). EBCT & coronary angio in all pt & ICUS of LAD in 100pt. Calcif in 84pt (75%).

Angio: 16 pt >50% stenosis, all w calcif: 1a score of <55 ($P<0.0001$).

*EBCT sens 94%, specifi 79%, a +pred value 43%, and -pred value 99% for detecting stenosis.* ICUS showed calcif plaque in all pt. w LAD score >9. EBCT total ca+ score assoc w degree of intimal proliferation in that pt w/o ICUS +allograft vasculopathy had a med score of 0 (25th %’le, 0; 75th %’le, 0), pt w Stanford class IV had med score of 41 (9 to 98, $P<0.0001$).

**Conc:** EBCT allows noninvasive detection of coronary vasculopathy in transplant recipients.

Knollman et al., *Circulation.* 2000;101:2078-2082
Multislice CT in Graft Vascular Disease
A Pilot Study

**Graft Vessel Disease (GVD):**

*A Long-term Complication in Heart Transplant Patients (HTx)*

Multislice CT: visualization of coronary anatomy, lumen & wall thickness. 16 slice detector in GVD c/w angio and intravascular ultrasound (IVUS).

**Methods:** 32 pt w mean f/u - 2016d had CT 24 hr prior to angio assoc w IVUS, if angio was nl. Sens, specif & pred-value of the CT c/w other methods.

**Results:** Angio/CT not done on 2pt/8pt for serum creat >1.5 mg/dL. CT c/w angio: sens 50%, specif 81%. -pred value 81%, +pred value 50%, precision 72%.

**Conc:** CT high –pred value for GVD. 64-detector CT will improve temporal and spatial resolution.

Tissue Doppler Imaging Detects Severely Abnormal Myocardial Velocities that identify Children with Pre-terminal Cardiac Graft Failure after Heart Transplantation

Children w OHT may die / require re-transplant. Chronic Graft Failure due to severe Coronary Allograft Vasculopathy (CAV)

Detection of OHT failure by Tissue Doppler (TDI) ultrasound: contraction and relaxation velocities. 53 pt (0.5-20.1 yr m10.21), HTx (0.2-18 yr (m5.7).

Result: LVEF diverged 3-6mos prior to endpoint (p<0.001). Tricuspid S veloc: 2.0cm/sec, p<0.002- 2.9cm/sec 3mo, p<0.001. Tricuspid E veloc: 3-6 mo 1.9cm/sec, p<0.02- 3.7cm/sec 0-3 mos prior to endpoint, p< 0.001. Mitral S veloc 1.5cm/sec 0-3mo before terminal endpoint, (p = 0.002).

Mortality Prediction: LVEF, tricuspid annulus syst & diast veloc, tricuspid regurg severity were significant in predicting mortality. Coron angio performed in 5/26pt had severe coron artery disease - all were pre-terminal.

Fyfe et al., J Heart and Lung Transplant 2006 May;25(5):510-7
Pulse Doppler Tissue Imaging

Sa

Ea

Aa
Noninvasive Detection of Elevated Left Ventricular Filling Pressure in Cardiac Transplant Recipients Using Doppler Echocardiography

(A) Pulsed Doppler - mitral flow and annular velocity tissue Doppler at time of right-sided cardiac cath.

(B) Pulsed Doppler of mitral inflow and tissue Doppler velocity at time of repeat right heart cath (4 wk later). Mean measured pulm cap wedge pressure (PCWP) decreased (24/11 mmHg). The E/Ea ratio decreased (15/5), predicting decrease in wedge pressure (24/9 mmHg) PCWP 2.6 +/-1.46.

Estep et al., J. Am. Coll. Cardiol. Img. 2009;2;1126-1140
The Role of Multimodality Cardiac Imaging in the Transplanted Heart

Global Radial Strain Derived From the Speckle-Tracking Technique

(A) Global radial strain (38%), peak 47%, obtained from the parasternal short-ax view in pt 1 wk post-HTx (biopsy grade 2R performed on the same day).

(B) Improvement in the global radial strain (58%), peak 68%, 2 wk after enhancement in immunosuppression (biopsy grade 1R) acute cellular rejection.

Estep et al., J. Am. Coll. Cardiol. Img. 2009;2;1126-1140
Doppler Tissue Imaging Validation Studies

Ea decreases w/ impaired diastolic fxn
E/Ea ratio correlates with PCWP
Ea, Aa pattern does not pseudonormalize
Ea is relatively preload independent
Ea correlates with Tau
  - *** Sohn et al, J Am Coll Cardiol 1997 30(2): 474-80
E/Ea ratio can estimate LAP
Longitudinal Myocardial Motion/Velocities

Abraham et al., *Circulation* 2007 116(22):2597-2609
Strain Rate Determination from Phase Contrast MR Velocity Data

PC-MRI of the Left Ventricle (basal and mid-short axis)
Radial Strain and Strain Rate Algorithm
10 volunteers: Tissue Velocity & SSFP Data

*** 3D Myocardial Motion using PC - MRI

Delfino et al., JMRI 2008 : 27, 522-528

*** Hanekom et al., Ultrasound in Med & Biol 2004 (30)11, 1451-1460
Myocardial Tissue Velocity Measured by MR Phase Velocity Mapping (MR PVM) and Tissue Doppler Imaging (TDI)

**Correlation Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Normals (N=10)</th>
<th>Patients (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal Wall</td>
<td>0.88</td>
<td>0.78</td>
</tr>
<tr>
<td>Lateral Wall</td>
<td>0.88</td>
<td>0.72</td>
</tr>
<tr>
<td>Both Walls</td>
<td>0.88</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Velocities measured under normal conditions and in a dysynchronous patient, showing the correlation coefficient $R$ for both methods.

Delfino, Oshinski et al., ISMRM 2007
### Determination of Transmural, Endocardial and Epicardial Radial Strain / Strain Rate from Phase Contrast MR Velocity Data

<table>
<thead>
<tr>
<th></th>
<th>Basal slice</th>
<th>Mid slice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocard peak (sec(^{-1}))</td>
<td>4.5 +/- 2.3</td>
<td>3.6 +/- 1.6</td>
</tr>
<tr>
<td>Epi-card peak (sec(^{-1}))</td>
<td>3.4 +/- 1.8</td>
<td>2.9 +/- 1.3</td>
</tr>
<tr>
<td>pValue</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Diastole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocard</td>
<td>-4.9 +/- 2.3</td>
<td>-4.4 +/- 2.8</td>
</tr>
<tr>
<td>Epi-card</td>
<td>4.4 +/- 2.3</td>
<td>4.0 +/- 1.4</td>
</tr>
<tr>
<td>pValue</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Contour agreement for peak strain rates / PCMR & Cine SSFP

Delfino, Oshinski et al., JMRI 2008; 27:522-528
Conclusion:

1. Current imaging techniques provide varied options for assessing cardiac structure and function needed to monitor graft status and illuminate concerns.

2. Computerized tomography and magnetic resonance imaging techniques are adaptable and constantly undergoing modifications that will allow improved detailed imaging assessments of implanted grafts needed to monitor and review progress made in graft survival.