Assessing Cardiovascular Risk in Renal Transplantation

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Case Presentation

• **HPI:** 61 yo man with a history of HTN, DM, ESRD 2/2 DM nephropathy s/p DDRT in 10/11 who presented to Renal Transplant clinic for routine follow-up appointment one month post-transplant. He described 3 days of SOB, palpitations, and chest pain with activity. Reported the symptoms resolved with rest. He had an unlimited ET prior, and had never had these symptoms in the past.

• **PMH:**
  - HTN
  - DM, for >20 years
  - ESRD, presumed 2/2 DM; h/o CKD since 2003, listed for tx in 2/07
  - S/p DDRTx in 10/11; on HD via L-AVF for 7 years; post-transplant course c/b slow graft function (no dialysis, Cr nadir 0.9); received standard immunosuppression with Simulect induction, Tacrolimus, Cellcept, steroids
• **All**: seasonal; no known medication allergies

• **Medications:**
  - Tacrolimus 2mg qam, 1mg qpm
  - Cellcept 1000mg q12
  - Prednisone 10mg qam and 5mg qpm
  - Clonidine 0.2 mg BID
  - Lantus 28 units qhs
  - Humalog insulin SS
  - Septra 1 tab daily
  - Valycte 450mg daily
  - Prilosec 40mg daily
  - Simvastatin 10mg daily

• **SH**: Originally from Guyana. Lives in Brooklyn with his wife. +History of tobacco use (3-4 cigarettes/week, quit 3 yrs ago), occasional ETOH use, no illicit drug use.

• **FH**: Mother died at age 67 from complications of DM. Father died at age 75, also from complications of DM.
• **Physical Exam:**
  - VS – Afeb, HR 98, BP 147/63, RR 16, O2 sat 100% RA
  - Gen: NAD, A+Ox3
  - HEENT: MMM, no lesions
  - Neck: supple, no JVD
  - CV: RRR, nl s1s2, systolic murmur loudest at the base
  - Chest: CTAB
  - Abd: soft, nt/nd, RLQ with well-healed scar, no ttp over graft site
  - Ext: WWP, no LE edema, L-AVF with +bruit/thrill

• **Labs:**
  - BMP: Na 137, K 5.1, Cl 105, Co2 22, BUN 28, Cr 0.8, Gluc 217
  - CBC: WBC 7.5, Hgb 11.6, Plt 270
  - Tn-I: 0.027 -> 0.046 -> 0.246
• **EKG**: NSR, 1mm STE in III, aVF, with ST depressions with TWI in I, aVL

• **Hospital Course**: The patient underwent emergent cardiac catheterization, which revealed moderate lesions in mid-RCA and mid-LAD, as well as severe lesions in OM1 and OM2. S/p balloon angioplasty to OM1/OM2 without stenting. He was discharged home on Plavix BID in addition to ASA. Follow-up stress test in 1/12 with normal LVEF and without evidence of ischemia.
Pre-transplant Cardiac Testing

- 8/2006 - **Stress Electrocardiography with Adenosine**: Negative for chest pain, EKG negative for ischemia
- 8/2006 – **TTE**: Normal LV function, LVEF 73%; mild MR.
- 12/2009 – **TTE**: LVEF normal, LVEF 65%; abnormal LV relaxation (grade I diastolic dysfunction); trace MR
- 6/2010 – **SPECT Myocardial Perfusion Imaging after Regadenoson**: No perfusion defects, no LV regional abnormality
- 6/2010 – **Stress Electrocardiography during Regadenoson**: No chest pain; limited study due to non-specific ST abnormalities in resting EKG
- 8/2011: Reportedly normal TTE and stress at JH
Clinical questions:

• What cardiac testing should we be doing in patients as part of the renal transplant assessment?
  • Non-invasive vs. invasive testing – risk of CIN in this population really challenges us to prove that invasive testing is beneficial

• Who should get tested?
  • High-risk - ?low-risk
  • Symptomatic - ?asymptomatic

• How often should we be repeating the tests?

• What should we do with positive results?
  • Revascularization?
  • Prior to transplant or post-transplant?
Background

- Longitudinal study of mortality in >200,000 patients with ESRD
- Compared outcomes of the 23,000 patients who received a cadaveric renal transplant to 46,000 patients on HD who were on the waiting list
- Relative risk of death was 0.32 in transplant recipients c/t pts continued on dialysis (after an initial period of higher risk post-operatively)

NEJM, 1998
Background

- The incidence of cardiovascular disease is high after renal transplantation
  - Annual rate of fatal or nonfatal CVD events is 3.5–5.0% in kidney transplant recipients (higher than in the general population)
  - By 36 months after transplantation, nearly 40% of patients have experienced a CVD event
  - CVD is the leading cause of death after renal transplantation

- Most of the traditional risk factors including cigarette smoking, DM, HTN, dyslipidemias are present

- In addition, most have had CKD for an extended period of time prior to transplantation, and have thereby acquired additional CVD risk by the time they undergo transplantation
Table 1. Causes of death following renal transplantation

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Percentage of total deaths</th>
</tr>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>42</td>
</tr>
<tr>
<td>Malignancy</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>18</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 2. Mechanisms of cardiovascular disease following renal transplantation

<table>
<thead>
<tr>
<th>Atheroma</th>
<th>Left ventricular hypertrophy</th>
<th>Vascular calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Hypertension</td>
<td>Hyperphosphataemia (pre-transplant)</td>
</tr>
<tr>
<td>Male gender</td>
<td>Anaemia (pre-transplant)</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Fluid overload (pre-transplant)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Arterio-venous fistula</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>DD genotype of ACE</td>
<td></td>
</tr>
<tr>
<td>Lack of exercise</td>
<td></td>
<td></td>
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<tr>
<td>Hyperglycaemia</td>
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<tr>
<td>Hyperhomocystinaemia</td>
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</tbody>
</table>
Occult CAD in CKD patients

- Study of 30 patients with CKD stage 5 at the time of initiation of renal replacement therapy
  - No h/o angina or myocardial infarction
  - Significant (>50% CAS) was found in 16/30 pts (53%)
  - Among the 16 patients with significant CAS, five had severe CAS with luminal narrowing of 90%
  - When stress cardiac scintigraphy was done in these five patients with severe CAS, it was positive in two patients and negative in three patients (sensitivity 40%)
- Conclusion: Patients with CKD are at very high risk of CAD even prior to starting HD, and the risk only increases with dialysis

Otake, JASN 2005
Nuclear stress tests

- 41 patients with ESRD who were referred for cardiac catheterization as part of the renal transplant assessment
  - “High risk”: long-standing DM, h/o chest pain, or age >40
  - 56% DM nephropathy
  - All on dialysis at time of referral
- All patients prospectively underwent Dipyridamole stress/SPECT test within one week of coronary angiography
- 19 patients were found to have an obstructive lesion >50%
  - 7/19 had a positive stress (sensitivity 37%)
  - 7/26 patients without significant lesions had false-positive stress (specificity 73%)
  - 7/10 patients with multi-vessel disease had false-negative stress (sensitivity 30%)
- Patients were followed clinically for 25 +/- 14 months
  - 12 patients died, 6 from cardiac causes; of those 6, all had lesions on coronary angiography but 5/6 had normal stress tests

Marwick, et al.
Transplantation, 1990
Dobutamine stress echo

- 50 patients with ESRD awaiting renal transplant who were considered high-risk for CAD:
  - ERSD 2/2 DM nephropathy (39 patients)
  - ESRD from other cause with inability to perform treadmill exercise and two or more risk factors for CAD (11 patients)
- Patients underwent DSE followed by coronary angiography; angiography was deferred until initiation of dialysis in patients not yet on HD
  - 47 patients had CA within 2 weeks of DSE
  - The 3 pts who were not dialysis dependent at time of DSE had CA at 69, 85, and 250 days post DSE
- Angiography results were reported as 50% or greater, greater than 70% stenosis by QCA and >75% diameter stenosis by visual estimation

20/50 DSE were found to be positive for inducible ischemia
27/50 patients (54%) had at least one stenosis of 50% or greater by QCA in a coronary artery or major branch
12/50 (24%) had one stenosis or more of greater than 70% by QCA
16/50 (32%) had one stenosis or more of greater than 75% by visual estimation
Long term outcomes

• Followed the patients for a mean of 22.5 +/- 10.1 months
• There was no difference in survival for the all-cause death end point in relation to angiographic or DSE findings
• For the end point of cardiac death and MI, there was a non-significant trend toward worse survival in patients with a positive DSE
Non-invasive vs. Invasive Screening

• Of 380 renal transplant candidates, 150 determined to be “high-risk” were referred for Coronary angiography
  • Age >50, DM, angina, previous MI or CVA, LV dysfunction, or extra-cardiac atherosclerosis
• 126 patients completed at least one cardiac test (stress echo, nuclear stress, angiography); 88 patients had all three tests, 106 had CA
• Stratified into high-risk and low-risk groups
  • 61 High-risk: patients with DM and/or cardiac alterations
  • 65 Low-risk: patients whose sole reasons for protocol inclusion was age >50
• Minimum and mean follow-up periods of 6 and 26 months

De Lima, et al. HTN 2003
• Significant CAD was found by CA in 44/126 (42%)
A total of 18 cardiac events were observed in the 126 study participants.
DSE and Exercise EKG

- Prospective study of 125 patients with ERSD in a single center who presented for evaluation for renal transplant
- All patients had EKG, Exercise stress test, Echocardiogram, Dobutamine Echo, and Coronary angiography
  - 39% were diabetic
  - 45% were pre-dialysis; of the patients on dialysis, mean time was 2.7 months
- Mean follow-up of 1.6 +/- 0.6 years

**Table 3. Baseline and exercise ECG data in those with and without severe CAD**

<table>
<thead>
<tr>
<th></th>
<th>Severe CAD (n = 36)</th>
<th>Non-severe CAD (n = 89)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal resting ECG</td>
<td>27 (77%)</td>
<td>14 (26%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total exercise time (min)</td>
<td>5.2 ± 1.7</td>
<td>6.5 ± 2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Limiting angina</td>
<td>8 (22%)</td>
<td>12 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>136 ± 42</td>
<td>143 ± 53</td>
<td>NS</td>
</tr>
<tr>
<td>Peak systolic blood pressure (mmHg)</td>
<td>163 ± 59</td>
<td>174 ± 46</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal ST change (mm)</td>
<td>0.25 ± 0.58</td>
<td>0.14 ± 0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Duke score</td>
<td>2.7 ± 4.3</td>
<td>4.8 ± 3.8</td>
<td>NS</td>
</tr>
</tbody>
</table>
Fig. 2. Kaplan-Meier survival curves according to the resting ECG, DSE result, presence of CAD and severe CAD.
Meta-analysis of studies of non-invasive testing compared to coronary angiography:

Wang, AKJD 2001
• MPS: AUC 80%, sensitivity 69%, specificity 77%

• DSE: AUC 92%; sensitivity 80%, specificity 89%
Figure 1. Myocardial infarction. (A) Positive versus negative tests; (B) Reversible defects versus negative tests; (C) Fixed defects versus negative tests; (D) Reversible versus fixed defects.

Figure 2. Cardiac death. (A) Positive versus negative tests; (B) Reversible defects versus negative tests; (C) Fixed defects versus negative tests; (D) Reversible versus fixed defects.
Diabetes and ESRD

- 280 consecutive patients with DM and ESRD who were renal transplant candidates at a single center
- All patients underwent non-invasive testing with either dipyridamole or exercise (n=21) stress, as well as coronary angiogram; only patients who underwent both were included in the analysis
- Patients were followed for a mean of 4 yrs
- Primary Endpoint: The ability of clinical parameters and non-invasive testing to detect angiographic CAD
- Secondary Endpoints: All-cause mortality, myocardial infarction, unstable angina, CVA, significant arrhythmia, and revascularization

Welsh, et al.
Transplantation, 2011
• A positive myocardial perfusion study was strongly predictive of the presence of CAD (> or = 70%): specificity 93.1% and positive predictive value 87.7%

• A negative myocardial perfusion scan occurred in:
  • 50.3% of patients with CAS > 50%
  • 35.4% with CAD > 70%
  • 41.8% of patients with a Duke angiographic score >= 4

• Negative predictive value was 64.6%

**TABLE 2. Myocardial perfusion imaging and degree of coronary artery stenosis**

<table>
<thead>
<tr>
<th>CAD (n=234)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reversible defect</td>
<td>Fixed defect</td>
<td>Reversible/fixed defect</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>≥50%</td>
<td>40 (90.9)</td>
<td>87 (53.4)</td>
<td>28 (96.6)</td>
</tr>
<tr>
<td>≥70%</td>
<td>37 (84.1)</td>
<td>65 (39.8)</td>
<td>28 (96.6)</td>
</tr>
<tr>
<td>DUKE score ≥4</td>
<td>30 (73.2)</td>
<td>42 (45.6)</td>
<td>20 (71.4)</td>
</tr>
</tbody>
</table>

All data are presented as N (%). All pair values were statistically significant (P<0.005).
CAD, coronary artery disease; DUKE, Duke angiographic score.
After a mean follow-up of 4 yrs, 82 of 280 (29%) patients had a major cardiac event.

In multivariable Cox regression analysis, angiographic evidence of CAD (hazard ratio 1.81 [1.016 –3.23], p = 0.044) was the only predictor of major adverse cardiac events.

Concluded that in this high risk group with high incidence of CAD, myocardial perfusion imaging has little utility.
Interval Testing?

- Study of 193 patients with CKD who underwent DSE for risk stratification
- Followed for 40 months
- At 2 yrs, negative DSE had good negative predictive value, but events increased significantly after 24 months
Coronary revascularization prior to transplant?

- Prospective study of 26 patients with IDDM and ESRD who had coronary angiography as routine screening in assessment for renal transplant

- Included patients who were found to have lesions that were hemodynamically significant and suitable for revascularization, with LVEF > 35%, and atypical chest pain or no symptoms

- Randomized to revascularization vs medical management
  - Revascularization: Angioplasty if possible or CABG
  - Medical mgt: Calcium-channel blocker and ASA

Lancet, 1992
Study was terminated early due to imbalance of events between groups and slow recruitment
Current Guidelines – American Society for Transplantation, 2001

• “Non-invasive tests play an important role in assessing IHD risk in renal transplant candidates, although these tests are less than perfect in predicting angiographically documented coronary disease or IHD events.”

• “A high pretest likelihood of cardiac events in ESRD patients with indicators of IHD, diabetes and/or multiple CVD risk factors could make the use of thallium scintigraphy reasonable in this setting. Dobutamine echocardiography may be an acceptable and more cost-effective alternative to thallium scintigraphy.”

• No definitive guidelines on when to use invasive testing
Guidelines for surveillance:

III. 3. Cardiac evaluation
IV. a. Nondiabetic

V. i. Asymptomatic: no tests, unless the patient has at least two of the following risk factors: on dialysis >3 years, primary disease with known arteriosclerotic risk (e.g., lupus), male > age 45, ischemic heart disease in a first-degree relative, current cigarette smoking, hypertension, fasting total cholesterol >200 mg/dl, high-density lipoprotein cholesterol <35 mg/dl, and left ventricular hypertrophy (if >=2 risk factors are present, cardiac stress test every 1–2 years)

VI. ii. Asymptomatic > age 50: cardiac stress test every 1–2 years

VII. iii. Asymptomatic with cardiac disease (e.g., known ischemic heart disease or valvular heart disease): yearly stress echo

VIII. iv. Symptoms with initial evaluation revealing disease not at a stage that needed to be treated: yearly cardiac stress test

IX. b. Diabetic: yearly adenosine thallium or dobutamine echo
Questions that remain:

- Who should undergo invasive testing?
- At what frequency should patients on the renal transplant list undergo surveillance testing, and with what modality?
- When non-severe disease is found, when should patients undergo revascularization (pre- or post-transplant)?

- Future studies needed...
Thank you