Cardiac Viability Testing – A Clinical Perspective
Annual Cardiac Imaging Symposium

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WHEN DO YOU ORDER LIABILITY TESTING?
62 year old male

- Anterior STEMI – late presentation, occluded LAD with 50% mid RCA, 60% distal Cx
- Prolonged hospital course – IABP initially
- EF 20%
- Ambulating on ward with recurrent symptoms of HF
CASE 1

- Yes
- No
- I am not sure
84 year old female
New onset HF
Diffuse 3VD on coronary angiogram
EF 35%
Stable on medical therapy – NYHA FC II
CASE 2

- Yes
- No
- I am not sure
65 year old male
DM, previous CABG 10 years ago
Recurrent HF, EF 15%
NYHA FC III
Angiogram: severe native 3 VD with patent LITA but occluded SVG to RCA and OM2
Case 3

- Yes
- No
- I am not sure
How much viable myocardium do you need to see to recommend revascularization?

- 10%
- 25%
- 50%
- Depends on patient risks
What expectation do you have regarding viability and revascularization?

- If viability: then mortality with surgery = mortality with medical therapy
- If viability: mortality with surgery < mortality with medical therapy
- If no viability: mortality risk with surgery = mortality risk with medical therapy
To define and understand stunning and hibernation

Awareness of the different modalities for viability testing and relative strengths and weaknesses

Understand clinical implications of viability testing:
  + Who should have viability testing
  + How do results of viability testing alter outcome
  + How to interpret viability test results
Transient depression of contractile function secondary to acute ischemic insult

[ATP] decrease to 50% 15 minutes after ischemia

Expected to improve hours to weeks after reperfusion established

Repeated episodes of demand ischemia can lead to cumulative stunning
More persistent form of reversible contractile dysfunction due to CAD

Displays contractile recovery following revascularization

Requires the restoration of normal blood supply to improve contractile function

Traditional view of under-perfusion downregulating contraction vs. repetitive ischemic insults
ASSESSMENT OF VIABILITY
Mr. WR

- 66 year old male
  - HTN
- SOB 2 weeks prior to presentation
  - Exercise treadmill test
    - Hypotensive exercise response
- ER presentation while cath pending
  - Acute pulmonary edema – intubated
  - Rapid atrial fibrillation
Mr. WR

- 66 year old male
  - HTN
- SOB 2 weeks prior to presentation
  - Exercise treadmill test
    - Hypotensive exercise response
- ER presentation while cath pending
  - Acute pulmonary edema – intubated
  - Rapid atrial fibrillation
Mr. WR

- Initial Course in Hospital
  - Cardiogenic shock
  - Coronary angiogram
    - 99% proximal LAD with diffuse disease distally
    - RCA 90%
    - OM1 (large) occluded
    - LCx diffuse moderate-severe disease
PET Viability Results

Short Axis (Apex→Base)

Horiz Long Axis (Post→Ant)

Vert Long Axis (Sep→Lat)
PET – Viability Results

- Very little scar (0.6%)
- Significant hibernating myocardium (28%)
  - Mismatch in distal anterior wall, apex, lateral wall
- Severe reduction in systolic function
Mr. WR

- Course in Hospital
  - HF stabilized
  - Ambulated and clinically improved
- Diffuse three vessel disease with poor targets for revascularization
- Evidence of significant viability
Mr. WR

- 2 months later:
  - Elective CABG
    - LITA to LAD
    - SVG to PIV, OM1 and D1
  - Pre-discharge echo
    - EF <25% 1+ MR
    - Normal RV size and function, no PH
  - Medications
    - ECASA 81 mg, carvedilol 12.5 mg bid, coversyl 8mg qd, lipitor 80mg, lasix 40 mg bid
Refining Risk and Maximizing Benefit

- Scar
- Hibernating Myocardium

IMAGING

RISK

BENEFIT
DSE

- Low doses to demonstrate increased contractility and high doses to induce ischemia

Myocardial contrast echo

Strain rate imaging

ADVANTAGES:
- Safety, portability
- Low cost

DISADVANTAGES:
- Low resolution
- Reduced diagnostic accuracy if poor windows or significant LV impairment
Thallium

- Initial uptake depends on blood flow and sustained uptake requires integrity of cell membrane

Technetium

- Shorter half life allows for higher doses and higher energy
- Less scatter
- Can be gated to ECG to assess ventricular function

ADVANTAGES:

✓ Higher sensitivity than DSE

DISADVANTAGES:

- Exposure to ionizing radiation
- Low spatial resolution
- Attenuation artifacts
99mTc SPECT Testing

A Stress
Rest
Short axis
Apex
Mid
Base

B Stress
Rest
Horizontal long axis
Vertical long axis
PET

- Gold standard
- Presence of glucose utilization (FDG) implies metabolic activity
- Perfusion-metabolism mismatch implies viability

**ADVANTAGES:**
- Superior spatial resolution and attenuation correction

**DISADVANTAGES:**
- Lack of widespread availability
- Need to control for glucose metabolism in DM
- High cost
- Cyclotron can be needed
PERFUSION-METABOLISM MISMATCH

A  Perfusion  FDG
SA
HLA
VLA

B  Perfusion  FDG
Perfusion Defect  FDG Defect
Scar  Mismatch
Scar Score = 8%  Mismatch Score = 20%
Dobutamine stress
- protocol similar to echo
- Better endocardial border definition

Delayed Enhancement
- Use of gadolinium
- Enters lysed muscle cells and extracellular space
- May have better delineation of scar tissue than PET

ADVANTAGES:
✓ Superior spatial resolution

DISADVANTAGES:
○ cost and availability
○ long study times – breath hold
○ imaging patients with devices
<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG PET</td>
<td>93</td>
<td>58</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>SPECT</td>
<td>86</td>
<td>59</td>
<td>69</td>
<td>80</td>
</tr>
<tr>
<td>DSE</td>
<td>81</td>
<td>80</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>ceCMR</td>
<td>82</td>
<td>63</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Grade</td>
<td>Organization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viability testing should be considered in patients with heart failure, known CAD and absence of angina</td>
<td>IIa</td>
<td>ACC 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with large areas of viability should be evaluated for revascularization</td>
<td>I</td>
<td>CCS 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial viability testing should be considered in patients with ischemic CM and reduced LV function</td>
<td>Appropriate use score 9</td>
<td>AACF/ASNC/ACR/ASE/SCCT/SCMR/SNM 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac PET and CMR should be used in the evaluation and prognostication of patients with ischemic CM and LV dysfunction</td>
<td>I</td>
<td>CCS/CAR/CANM/CNCS/CanSCMR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HOW DO I PICK A TEST?

- Local expertise
- Availability
- Cost
- Patients body habitus
- Severity of LV systolic dysfunction
- Renal impairment
- Contraindicated devices
Nonrandomized studies with small sample sizes
Referral and selection bias
Lack of uniformity of medical therapy
Arbitrary definitions for viability
Lack of head-to-head comparisons between techniques
No evaluation of graft/vessel patency at time of post revascularization functional assessment
Unknown duration and severity of LV dysfunction prior to revascularization
Frequent exclusion of patients who did not get revascularized or died during revascularization
Viability Testing May Predict Improvement in LV Function

95% Confidence Intervals

- Dobutamine Echo: 5 st./195 pts
- TI-201: 3 st./95 pts
- FDG PET: 3 st./253 pts
- Tc-99m: 2 st./98 pts
Viability Testing May Predict Improvement in HF symptoms

- Magnitude of improvement in HF symptoms may relate to preoperative degree of viability
- May relate to improved quality of life

DiCarli; Circulation 1995; Shukla et al. Can J Cardiol 2011 (in press)
Effect of Revascularization on Mortality

-79.6%  
$\chi^2 = 147$  
$p < 0.0001$

23.0%  
$\chi^2 = 1.43$  
$p = 0.23$
EFFECT OF REVASCULARIZATION ON MORTALITY IN PATIENTS WITH XIAOBIITY
EFFECT OF BEXASCLARIZATION ON MORTALITY IN PATIENTS WITH NO VIABILITY

Inaba, JNC 2010
## Treatment and Survival Rates

<table>
<thead>
<tr>
<th></th>
<th>Total Patients, n</th>
<th>Weighted Average Annual Mortality</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical therapy viability present</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSE&lt;sup&gt;99,105&lt;/sup&gt;</td>
<td>362</td>
<td>11.23</td>
<td>7.98–14.48</td>
</tr>
<tr>
<td>PET&lt;sup&gt;106&lt;/sup&gt;</td>
<td>50</td>
<td>6.25</td>
<td>0.00–12.96</td>
</tr>
<tr>
<td>99mTc-sestamibi&lt;sup&gt;39,107&lt;/sup&gt;</td>
<td>110</td>
<td>11.17</td>
<td>5.29–17.06</td>
</tr>
<tr>
<td>99mTc-sestamibi + PET-FDG&lt;sup&gt;108&lt;/sup&gt;</td>
<td>30</td>
<td>10.33</td>
<td>0.00–21.23</td>
</tr>
<tr>
<td>201TI rest, reinjection: DSE&lt;sup&gt;109&lt;/sup&gt;</td>
<td>43</td>
<td>9.67</td>
<td>0.83–18.50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>595</td>
<td>10.64</td>
<td>8.17–13.12</td>
</tr>
<tr>
<td><strong>Medical therapy viability absent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSE&lt;sup&gt;99,101-105&lt;/sup&gt;</td>
<td>447</td>
<td>12.05</td>
<td>9.03–15.06</td>
</tr>
<tr>
<td>99mTc-sestamibi&lt;sup&gt;107&lt;/sup&gt;</td>
<td>27</td>
<td>13.85</td>
<td>0.82–26.87</td>
</tr>
<tr>
<td>99mTc-sestamibi + PET-FDG&lt;sup&gt;108&lt;/sup&gt;</td>
<td>26</td>
<td>3.33</td>
<td>0.00–10.23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>500</td>
<td>11.69</td>
<td>8.87–14.51</td>
</tr>
<tr>
<td><strong>Revascularization viability present</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSE&lt;sup&gt;98,99,105&lt;/sup&gt;</td>
<td>338</td>
<td>3.09</td>
<td>1.24–4.93</td>
</tr>
<tr>
<td>PET&lt;sup&gt;106&lt;/sup&gt;</td>
<td>43</td>
<td>7.5</td>
<td>0.00–15.37</td>
</tr>
<tr>
<td>99mTc-sestamibi&lt;sup&gt;39,107&lt;/sup&gt;</td>
<td>171</td>
<td>3.16</td>
<td>0.54–5.78</td>
</tr>
<tr>
<td>99mTc-sestamibi + PET-FDG&lt;sup&gt;108&lt;/sup&gt;</td>
<td>42</td>
<td>0</td>
<td>0.00–0.00</td>
</tr>
<tr>
<td>201TI rest, reinjection: DSE&lt;sup&gt;109&lt;/sup&gt;</td>
<td>94</td>
<td>1.67</td>
<td>0.00–4.25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>699</td>
<td>3.71</td>
<td>2.31–5.12</td>
</tr>
<tr>
<td><strong>Revascularization viability absent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSE&lt;sup&gt;98,99,101-105&lt;/sup&gt;</td>
<td>348</td>
<td>8.78</td>
<td>5.80–11.75</td>
</tr>
<tr>
<td>99mTc-sestamibi&lt;sup&gt;107&lt;/sup&gt;</td>
<td>50</td>
<td>8.77</td>
<td>0.93–16.61</td>
</tr>
<tr>
<td>99mTc-sestamibi + PET-FDG&lt;sup&gt;108&lt;/sup&gt;</td>
<td>25</td>
<td>3.33</td>
<td>0.00–10.37</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>423</td>
<td>8.45</td>
<td>5.80–11.10</td>
</tr>
</tbody>
</table>

Inaba, et al. J Nucl Cardiol 2010;17(4) 646
Figure 3: “Survival Curves” (on the Basis of Time to First Occurring Outcome of the Composite Event)

Mantel-Haenszel (log-rank) test for differences between 2 survival curves; chi-square = 2.1, hazard ratio = 0.78, 95% CI 0.58 to 1.1, p = 0.15. PET = positron emission tomography.

Figure 4: “Survival” Curves (on the Basis of Time to Cardiac Death) for All Subjects

Mantel-Haenszel (log-rank) test for differences between 2 survival curves; chi-square = 1.3, hazard ratio = 0.72, 95% CI 0.4 to 1.3, p = 0.25. PET = positron emission tomography.

Beanlands; JACC 2007;50:2002
Adherence to Recommendations

Figure 7  “Survival Curves” (on the Basis of Time to First Occurring Outcome Out of the Composite Event)

The positron emission tomography adherence group versus standard care arm. Mantel-Haenszel (log-rank) Test for differences between 2 survival curves; adjusted hazard ratio = 0.62, 95% CI 0.42 to 0.93, p = 0.019.

Beanlands; JACC 2007;50:2002
• Renal function
• LV function (trend)
• Interaction of hibernation with revascularization

Beanlands; JACC 2007;50:2002
**Does Experience Matter?**

**A**

HR = 0.34, 95% CI = (0.16, 0.72), p = 0.005

**B**

Interaction test p = 0.016

**Table 1.** Optimal cutoff values for the presence of viability leading to improved survival with revascularization over medical therapy

<table>
<thead>
<tr>
<th>Imaging techniques (number of studies)</th>
<th>Mean viable myocardium (SD), %</th>
<th>Optimal threshold for viability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET overall (N = 7)</td>
<td>21 (13)</td>
<td>25.8 (16.6–35.0)</td>
</tr>
<tr>
<td>PET with FDG/NH3 (N = 3)</td>
<td>20 (15)</td>
<td>22.5 (10.1–34.8)</td>
</tr>
<tr>
<td>PET with FDG/Tc-99m (N = 3)</td>
<td>22 (16)</td>
<td>29.2 (20.7–37.8)</td>
</tr>
<tr>
<td>Stress echo overall (N = 8)</td>
<td>32 (24)</td>
<td>35.9 (31.6–40.3)</td>
</tr>
<tr>
<td>Stress echo with LDDE (N = 4)</td>
<td>33 (28)</td>
<td>33.6 (27.4–39.8)</td>
</tr>
<tr>
<td>Stress echo with HDDE (N = 2)</td>
<td>35 (31)</td>
<td>44.1 (37.2–50.9)</td>
</tr>
<tr>
<td>SPECT overall (N = 6)</td>
<td>38 (25)</td>
<td>38.7 (27.7–49.7)</td>
</tr>
<tr>
<td>SPECT with TI-201 (N = 5)</td>
<td>41 (35)</td>
<td>38.0 (26.2–49.7)</td>
</tr>
</tbody>
</table>

*Echo, Echocardiography; FDG, fluorine-18 fluorodeoxyglucose; HDDE, high-dose dobutamine echocardiography; LDDE, low-dose dobutamine echocardiography; NH₃, nitrogen-13 ammonia; PET, positron emission tomography; SD, standard deviation; Tc-99m, technetium-99m; and TI-201, thallium-201.*

*Inaba, J Nucl Cardiol 2010*
How much viability is present?

**Patient A**
- Raw Perfusion
- Raw FDG
- Normalized Perfusion
- Normalized FDG
- Scar Map: Scar Score = 31%
- Mismatch map: Mismatch Score = 3%

**Patient B**
- Raw Perfusion
- Raw FDG
- Normalized Perfusion
- Normalized FDG
- Scar Map: Scar Score = 8%
- Mismatch map: Mismatch Score = 18%
INCREASING BENEFIT WITH INCREASING HIBERNATION
Increasing Benefit with Increasing Hibernation

A

<table>
<thead>
<tr>
<th>Mismatch &lt;7%</th>
<th>Mismatch ≥7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=59</td>
<td>N=24</td>
</tr>
<tr>
<td>31%</td>
<td>13%</td>
</tr>
<tr>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Mismatch &lt;7%</th>
<th>Mismatch ≥7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=59</td>
<td>N=24</td>
</tr>
<tr>
<td>12% (Protocol Revascularization)</td>
<td>11% (Medical Therapy)</td>
</tr>
<tr>
<td>N=83</td>
<td>N=16</td>
</tr>
<tr>
<td>13%</td>
<td>0%</td>
</tr>
</tbody>
</table>

D'Egidio JACC 2009;2:1060
STICH Results

Figure 1. Kaplan–Meier Curves for the Probability of Death from Any Cause.

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy</td>
<td>602</td>
<td>532</td>
<td>487</td>
<td>435</td>
<td>312</td>
<td>154</td>
<td>80</td>
</tr>
<tr>
<td>CABG</td>
<td>610</td>
<td>532</td>
<td>486</td>
<td>459</td>
<td>340</td>
<td>174</td>
<td>91</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.86 (95% CI, 0.72–1.04)
P = 0.12

CABG denotes coronary-artery bypass grafting.
STICH Results

CV Death: 28% CABG vs. 33% medical

CV Death/admission: 58% CABG vs. 68% medical

STICH Viability

Mortality 56% medical vs. 41% CABG

Mortality 35% medical vs. 31% CABG

Bonow et al. N Engl J Med 2011; April
## STICH Viability

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Deaths</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without viability</td>
<td>114</td>
<td>58</td>
<td>0.70 (0.41–1.18)</td>
<td>0.53</td>
</tr>
<tr>
<td>With viability</td>
<td>487</td>
<td>178</td>
<td>0.86 (0.64–1.16)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios compare CABG Better to Medical Therapy Better.
### STICH Viability vs. PARR 2

<table>
<thead>
<tr>
<th>Patient population</th>
<th>STICH: accepted for revascularization</th>
<th>PARR2: decisions about revascularization unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25% single vessel</td>
<td>90% 2, 3 or left main</td>
</tr>
<tr>
<td></td>
<td>7% renal disease</td>
<td>More comorbid burdens</td>
</tr>
<tr>
<td>Viability testing</td>
<td>SPECT or dobutamine echo</td>
<td>PET</td>
</tr>
<tr>
<td>Report</td>
<td>No report of ischemia or hibernation</td>
<td>Ischemia/hibernation reported</td>
</tr>
</tbody>
</table>

The Bottom Line

- Does revascularization make sense?
  - STICH supports selected role for revascularization
Can viability testing help to refine selection process?

- Optimal treatment of patients with HF and moderate-severe LV dysfunction is variable
- In significant amounts of viability revascularization should be considered
- Depends on:
  - Patients comorbidities
  - Patient preference
  - Experience of centre
The Bottom Line

Moderate or Severe LV Dysfunction?

- moderate angina with high risk anatomy
  - Viability Test
    - Low degree of Viability
      - Medical therapy
      - Transplantation assessment
    - Moderate or large degree of Viability
      - No absolute contraindications for revascularization
      - Surgical disease?
        - Revascularization

- Heart failure symptoms
  - No absolute contraindications for revascularization

Patients presenting with new or worsening symptoms/signs of HF (n=2550) (with one of three clinical questions)

Level I Projects

I-A (n=1095)

Unknown Coronary Anatomy
Clinical Question: Is there obstructive CAD?

I-C (n=766)

Known CAD/LVEF <40%
Clinical Question: Is there ischemia/hibernation?

(n=367) Yes

CTA vs. STD**

(n=250) No

Known or suspected NICM or HFPSF
Clinical Question: What is the cause of CM* or HF?

(n=939)

MRI/PET vs. STD**

(n=1485)

Primary Outcome: Composite Clinical Endpoint

I-B (n=689)

Primary Outcome: Resource utilization

Primary Outcome: Specific Diagnosis

Follow-up all level one patients
Outcomes: composite clinical endpoints (cardiac death, MI, Arrest, hospitalization), QoL, LV Function, Cost, resource utilization, safety.

• CM = Cardiomyopathy
• ** STD = Standard care which is: I-A: SPECT perfusion; I-B: Echo +/- selective CMR; I-C: coronary angiography
Does patient need viability and/or ischemia testing?

**Standard Imaging**
- Echocardiography
- SPECT (tech or thallium)

**Advanced Imaging**
- CMR
- FDG PET
High procedural risks associated with revascularization in low EF patients provides rationale for risk stratification

Most established viability techniques are PET, SPECT and echo

- MRI and CT gaining ground
- Best test is individualized
Several consistent findings regarding viability testing:

- Medically treated patients have lowest survival.
- Patients with viability have better survival with revascularization than medical therapy.
- Viability imaging can predict global, regional LV recovery and patient functional improvement.
More robust trial data needed to address the role of viability imaging in HF

+ IMAGE HF