TO REVASCULARIZE OR NOT TO REVASCULARIZE: IMAGING FOR DECISION-MAKING IN ISCHEMIC CARDIOMYOPATHY

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Disclosures

- Novartis (consultant fees, speakers fees, research funding)
- Servier (consultant fees, speakers fees, research funding)
- Amgen (consultant fees, research funding)
A Clinical Case: Mr. GS

- 56 year old male
- Known CAD
  - Felt inoperable from previous angiogram 5 years previously
- HTN
- Dyslipidemia
- PVD
- Smoker/significant EtOH
- ICD for primary prevention with recent appropriate shock for VT

- Referred for progressive HF symptoms
  - FC III
- No chest pain, no recent ACS
- On Exam:
  - BP 95/60
  - HF 70
  - No evidence of significant volume overload

- Medications
  - Bisoprolol 10 mg daily
  - Ramipril 10 mg daily
  - Spironolactone 25 mg daily
  - Lasix 40 mg daily
  - ASA
  - Crestor 40 mg daily
ECG
Echocardiogram

**Chambers**
The left ventricle is moderately dilated. Walls are relatively thin. Left ventricular systolic function is severely reduced. Ejection Fraction by Simpson’s is 15.3%.

There is severe global hypokinesis of the left ventricle. Thin and bright LV wall segment suggests a myocardial infarction.

The right ventricle is normal in size and function. There is a pacemaker lead in the right ventricle.

The left atrium is moderately dilated. Right atrial size is normal. There is a catheter/pacemaker lead seen in the right atrium. The interatrial septum is intact with no evidence for an atrial septal defect.

**Values**
The aortic valve is normal in structure and function. No aortic regurgitation is present.

The reduced mitral leaflet separation suggests decreased flow through the mitral valve and poor cardiac output. There is a prominent "B-hump" in the mitral valve, consistent with elevated left ventricular end-diastolic pressure. There is mild (1+) mitral regurgitation. There is functional MR secondary to LV dysfunction.

The tricuspid valve is normal. There is trace tricuspid regurgitation.

The pulmonic valve is normal in structure and function. Trace pulmonic valvular regurgitation.

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**Measurement**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Diastole</td>
<td>7.0 cm &lt; 5.8 cm</td>
</tr>
<tr>
<td>LV Systole</td>
<td>6.2 cm &lt; 4.8 cm</td>
</tr>
<tr>
<td>IV Septum</td>
<td>0.99 cm &lt; 1.2 cm</td>
</tr>
<tr>
<td>Posterior Wall</td>
<td>0.97 cm &lt; 1.2 cm</td>
</tr>
<tr>
<td>Fract Short</td>
<td>11.5% &gt; 25%</td>
</tr>
<tr>
<td>Left Atrium</td>
<td>5.4 cm &lt; 4.1 cm</td>
</tr>
<tr>
<td>Aortic Root</td>
<td>3.0 cm &lt; 3.8 cm</td>
</tr>
<tr>
<td>EF MOD-bp</td>
<td>15.3% &gt; 55%</td>
</tr>
</tbody>
</table>

**Additional Measurements (2D, Doppler) & Calculations**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVED Vol</td>
<td>85.0 ml</td>
</tr>
<tr>
<td>LA vol</td>
<td>45.9 ml/m^2</td>
</tr>
<tr>
<td>LV mass(C)'d'</td>
<td>315.1 grams</td>
</tr>
<tr>
<td>LV mass(C)'d'</td>
<td>170.1 grams/m^2</td>
</tr>
<tr>
<td>MV E max vel</td>
<td>85.4 cm/sec</td>
</tr>
<tr>
<td>MV A max vel</td>
<td>40.0 cm/sec</td>
</tr>
<tr>
<td>MV E/A</td>
<td>2.1</td>
</tr>
<tr>
<td>MV dec time</td>
<td>0.14 sec</td>
</tr>
<tr>
<td>Lat Peak E' Vel</td>
<td>3.0 cm/sec</td>
</tr>
</tbody>
</table>

---

asc Aorta
Diam: 2.8 cm
Coronary Angiogram

- 99% proximal LAD with diffuse disease distally
- RCA 90%
- OM1 (large) occluded
- LCx diffuse moderate-severe disease
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https:// api.ovent.com/polling/v1/api/polls/sp-rb7kw7

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
PET Viability Results
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https:// api.event.com/polling/v1/api/polls/sp-2elpbx

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
One Year Later:

- Returned to work as a part-time machinist
- FC II
- No further HF symptoms

**Impression**

1. Respiratory Spirometry
   - PVC: 2.56 L / 64 % predicted
   - FEV1: 1.74 L / 58 % predicted
   - F EV1/FVC: 68 %
   - Resting spirometry is moderate obstructive abnormality. Breathing reserve at peak 20 % is reduced. Breathing pattern is Exaggerated beyond AT.

2. Cardiovascular
   - exercised for 7:28 on the slow ramp protocol, stopping because of dyspnea.
   - Blood Pressure:
     - Rest: 134 / 76 mmHg
     - AT: 130 / 64 mmHg
     - Peak: 150 / 66 mmHg
   - Heart Rate:
     - Rest: 81 bpm
     - AT: 91 bpm
     - Peak: 118 bpm
   - Heart rate reserve at peak exercise is 38 %

3. Metabolic
   - The test was maximal with an RER of 1.19. The peak VO₂ achieved was 16.1 ml/kg/min or 4.6 METs.
   - The anaerobic threshold is 2.4 METs or 30 % predicted maximal VO₂ uptake.
   - The O₂ pulse at peak is 11.8 which is reduced. The O₂ saturation 97% at rest and 99% at peak.

**Additional Measurements (2D, Doppler) & Calculations**

- LV Diastole: 6.7 cm < 5.8 cm
- LV Systole: 6.2 cm < 4.5 cm
- RV Septum: 0.91 cm < 1.4 cm
- Posterior Wall: 1.08 cm < 1.2 cm
- Fract Short: 8.1 % > 26%
- Aortic Root: 2.7 cm < 3.8 cm

- LA vol: 68.8 ml
- LV mass(C/d): 260.4 grams
- RVSP(TR): 91.7 cm/sec
- LA vol index: 39.0 ml/m²
- LV mass(C/d): 140.1 grams/m²
- MV A max vel: 38.8 cm/sec
- MV E/A: 2.4
- MV dec time: 0.13 sec
- LA Peak E' Vel: 3.5 cm/sec
- Septal Peak E': 3.3 cm/sec

**Chambers**

- The left ventricle is moderately dilated. There is eccentric left ventricular hypertrophy. Left ventricular systolic function is severely reduced. Ejection Fraction is 17.5%. The ejection fraction is calculated using Teichholz method. The E/Ea ratio suggests that LA pressure is elevated. There is severe global hypokinesis of the left ventricle.

- There is severe (grade 3 or 4- restrictive) diastolic dysfunction.
- There is a pacemaker lead in the right ventricle. The right ventricle is normal size. The right ventricular systolic function is mildly reduced.
- The left atrium is mildly dilated. Right atrial size is normal. The interatrial septum is intact with no evidence for an atrial septal defect.
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https:// api.cvent.com/polling/v1/api/polls/sp-kg4yfq

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Refining Risk and Maximizing Benefit

Medical therapy
better

Surgical therapy
better

Intensity
Normalcy

age
scar
LVEF / HF symptoms
angina
CAD

Adapted from Rouleau: Can J Cardiol 2014; 281-287
Where is the Evidence that a Viability Based Strategy Improves Long-Term Outcomes?
Stunning, Hibernation and Viability

Triad of Hibernation

- Reduced MBF and MFR
- Flow limiting stenosis
- no irreversible damage

Hibernation

Viability

revascularization
Spectrum of Myocardial Dysfunction in Ischemic Cardiomyopathy

Repetitive ischemia

Persistent Repetitive ischemia

Cell death

Normal myocardium

Stunned myocardium

Hibernating myocardium

Myocardial Scar

Severe CAD

Adapted from: Shah Eur Heart J; 2013:34:1323
Multiple Modalities Available to Assess for “Viability”

Schinkel; Curr Prob Cardiol 2007;32:375
# Imaging Modalities to Assess Myocardial Viability

<table>
<thead>
<tr>
<th>Modality</th>
<th>Mechanism</th>
<th>Findings to Suggest Viability</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR</td>
<td>LGE Wall thickness</td>
<td>LGE&lt;50% wall thickness Systolic thickening of a dyskinetic segment</td>
<td>A: highly sensitive, no radiation, assess valves</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: limited availability, cost, devices, renal failure</td>
</tr>
<tr>
<td>Dobutamine echo (CMR)</td>
<td>Contractile reserve</td>
<td>Improvement by visual or strain rate imaging</td>
<td>A: highly specific, widely available, no radiation, assess ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: interobserver variability, dobutamine risks</td>
</tr>
<tr>
<td>SPECT Thallium-201</td>
<td>Perfusion: sarcolemma membrane integrity (K analogue)</td>
<td>Tracer uptake:&gt;50% of max</td>
<td>A: available, moderate cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: radiation dose, moderate sensitivity with low specificity</td>
</tr>
<tr>
<td>Technetium-99m labeled tracers</td>
<td>Mitochondrial membrane integrity</td>
<td>&gt;50-65% maximum</td>
<td>A: available, cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: moderate accuracy</td>
</tr>
<tr>
<td>PET</td>
<td>Perfusion: 13NH3, 82Rb, 150-water Glucose utilization: FDG</td>
<td>Flow-metabolism mismatch = hibernation Match =nonviable</td>
<td>A: highly sensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D: limited availability, high cost, complex in diabetics</td>
</tr>
</tbody>
</table>
How Do I Pick a Test?

- Moderate LV dysfunction – any modality with local expertise
- Severe LV dysfunction – nuclear methods (SPECT, PET) or CMR LGE – more sensitive than contractile reserve
- Renal failure (GFR<30) or CMR incompatible devices – avoid CMR
- Critical left main or proximal 3VD – avoid dobutamine
- Equivocal or negative results on another viability test – consider PET or CMR as highly sensitive methods
Effect of Revascularization on Mortality

-79.6%  
$x^2 = 147$  
$p < 0.0001$

23.0%  
$x^2 = 1.43$  
$p = 0.23$

Allman, JACC 2002
Effect of Revascularization on Mortality in Patients with Viability

Inaba, et al. J Nuc Cardiol 2010;17(4) 646
Effect of Revascularization on Mortality in Patients with NO Viability

<table>
<thead>
<tr>
<th>Group</th>
<th>Weighted Average Annual Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy – viability present</td>
<td>10.64 (8.17 - 13.12)</td>
</tr>
<tr>
<td>Medical therapy – viability absent</td>
<td>11.69 (8.87 – 14.51)</td>
</tr>
<tr>
<td>Revascularization – viability present</td>
<td>3.71 (2.31, 5.12)</td>
</tr>
<tr>
<td>Revascularization – viability absent</td>
<td>8.45 (5.80, 11.10)</td>
</tr>
</tbody>
</table>

*Inaba, et al. J Nuc Cardol 2010;17(4) 646*
Limitations of the literature on viability testing

- Nonrandomized studies with small sample sizes
- Referral and selection bias
- Lack of uniformity of medical therapy
- 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 and Prognosis: The PARR 2 Trial

Time to Composite Endpoint
(CV death, MI, cardiac admission)

Time to Cardiac Death

Beanlands; JACC 2007;50:2002
Adherence to Recommendations

**Adherence Rates**

- **High** (n=58)
- **Moderate** (n=163)
- **Low** (n=46)

**Time to Composite Endpoint**

- HR 0.62
- 95% CI 0.42 to 0.93
- P=0.019

*Beanlands; JACC 2007;50:2002*
Long Term Follow-Up of PARR-2

**Whole Cohort**

**Patients who Adhered to Imaging Recommendations**

McCardle at al. Circ CV Imag 2016
Increasing Benefit with Increasing Hibernation
Increasing Benefit with Increasing Hibernation

A

% of Patients with Primary Outcome

<table>
<thead>
<tr>
<th>Mismatch &lt;7%</th>
<th>Mismatch ≥7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=59</td>
<td>N=83</td>
</tr>
<tr>
<td>31%</td>
<td>56%</td>
</tr>
<tr>
<td>29%</td>
<td>13%</td>
</tr>
</tbody>
</table>

p=0.015

B

% of Patients Suffering Cardiac Death

<table>
<thead>
<tr>
<th>Mismatch &lt;7%</th>
<th>Mismatch ≥7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=59</td>
<td>N=83</td>
</tr>
<tr>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>0%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Brown: Protocol Revascularization  Yellow: Medical Therapy

D'Egidio JACC 2009;2:1060
STICH Results

![Graphs showing Kaplan-Meier curves for CV Death and CV Death/admission]

**Figure 1.** Kaplan–Meier Curves for the Probability of Death from Any Cause. CABG denotes coronary-artery bypass grafting.

- **CV Death:** 28% CABG vs. 33% medical
  - Hazard ratio, 0.81 (95% CI, 0.66–1.00) \( P = 0.65 \)

- **CV Death/admission:** 58% CABG vs. 68% medical
  - Hazard ratio, 0.74 (95% CI, 0.64–0.85) \( P < 0.001 \)

STICHES Long Term Extension Study

A Death from Any Cause (Primary Outcome)

Hazard ratio, 0.84 (95% CI, 0.73–0.97)
P=0.02 by log-rank test

No. at Risk
Medical therapy 602 532 487 435 404 357 315 274 248 164 82 37
CABG 610 532 487 460 432 392 356 312 286 205 103 42

B Death from Cardiovascular Causes

Hazard ratio, 0.79 (95% CI, 0.66–0.93)
P=0.006 by log-rank test

C Death from Any Cause or Cardiovascular Hospitalization

Hazard ratio, 0.72 (95% CI, 0.64–0.82)
P<0.001 by log-rank test

STICH Viability

**Mortality 56% medical vs. 41% CABG**

**Mortality 35% medical vs. 31% CABG**

- **Without Myocardial Viability**
  - Medical therapy (33 deaths)
  - CABG (25 deaths)

- **With Myocardial Viability**
  - Medical therapy (95 deaths)
  - CABG (83 deaths)

**Subgroup**

- **Without viability**
  - No.: 114
  - Deaths: 58

- **With viability**
  - No.: 487
  - Deaths: 178

**Hazard Ratio (95% CI)**

- **CABG** Better: 0.70 (0.41−1.18)
- **Medical Therapy Better**: 0.86 (0.64−1.16)

**P Value for Interaction**: 0.53

*Bonow et al. N Engl J Med 2011; April*
## Comparing STICH to PARR2

<table>
<thead>
<tr>
<th>Variable</th>
<th>STICH Sub-study</th>
<th>PARR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Randomized?</td>
<td>No</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>60.7</td>
<td>63</td>
</tr>
<tr>
<td>Male Sex (%)</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Previous CABG (%)</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Multi-vessel disease (%)</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>DM (%)</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>GFR&lt;60 (%)</td>
<td>7.5</td>
<td>34</td>
</tr>
<tr>
<td>Mean serum creatinine</td>
<td></td>
<td>108</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Viability testing</td>
<td>SPECT or dobutamine echo 81% viable</td>
<td>PET 22% viable</td>
</tr>
<tr>
<td>Report</td>
<td>No report of ischemia or hibernation</td>
<td>Ischemia/hibernation reported</td>
</tr>
</tbody>
</table>
What Other Clinical Factors Can Help Guide Us in Decision Making?
Extent of Disease May Predict Benefit

**Central Illustration.** Schematic Representation of the Clinical Implications of the Present Study Findings

*These thresholds are simply the medians of the LV function variables in the present study and have not been validated prospectively in an independent patient population. This algorithm should only be applied conceptually to support the notion that, among patients with ischemic LV systolic dysfunction, the benefit of surgical revascularization is greater when the disease process is more advanced (see text for more detail). CAD = coronary artery disease; EF = ejection fraction; ESVI = end-systolic volume index.

Panza et al. J Am Coll Cardiol 2014; 64:553
Extent of Disease May Predict Benefit

Figure 3. Kaplan-Meier rate estimates of all-cause mortality among patients with 2–3 (top panel) and 0–1 (bottom panel) prognostic factors. In each panel, study patients are divided according to the treatment arm (CABG or OMT) to which they were randomized.

Panza et al. J Am Coll Cardiol 2014; 64:553
Is Ischemia Testing Relevant?

Sub-group | N  | Events | Hazard Ratio | 95% CI     |
-----------|----|--------|--------------|------------|
No Ischemia| 143| 53     | 0.72         | 0.42, 1.25 |
                | 256| 103    | 0.83         | 0.56, 1.23 |

Interaction with Treatment
P-value = 0.643

Panza; J Am Col Cardiol 2013; 61: 1860
Inducible Ischemia vs. Hibernating Myocardium

Ling; Circ CV Imaging 2013; 6:363
Does The Presence of Angina Matter?

The presence of angina did not significantly affect mortality in patients assigned to CABG. However, when crossovers were considered, the observed reduction in mortality with CABG was significant and of similar magnitude in patients with and without angina. Finally, CABG improved angina compared with medical therapy alone. These findings have important clinical implications given the paucity of prior evidence to guide decision making in patients with angina and LV systolic dysfunction.

Among patients with severe LV dysfunction, CABG is associated with an early risk of serious complications, including death. Findings from this study challenge the perceived benefit-risk balance for CABG in patients with and without angina. Although revascularization should be considered for symptom relief for patients with heart failure and angina recalcitrant to pharmacological therapy, this analysis suggests that insofar as subsequent prognosis is concerned, the presence or absence of angina should not be used as a discriminating factor to decide for or against revascularization as an initial treatment.

Graphs and tables showing the cumulative risk of all-cause death over time for patients with and without angina at baseline, along with hazard ratios and p-values for interaction.
Image 1A Study: AIMI-HF Study: RCT Evaluating Standard vs. Advanced Imaging in Patients with Ischemic CM

O’Meara E, Mielniczuk LM et al. Trials 2013; 14:332
Can Biomarkers Aid in Decision Making?
Can Biomarkers Aid in Decision Making?

A

\[
\begin{align*}
\text{Log NT-proBNP (pg/mL)} & \\
<10\% & : 2815.0 \text{ pg/mL (1319-3867)} \\
\geq 10\% & : 1939.0 \text{ pg/mL (1007-6218)} \\
\end{align*}
\]

\[n=10 \quad n=29\]

B

\[
\begin{align*}
\text{Global LV Scar (\%)} & \\
\text{Log NT-proBNP (pg/mL)} & \\
\end{align*}
\]

\[r=-0.05 \quad p=0.78\]

C

\[
\begin{align*}
\text{Log hs-cTnT (pg/mL)} & \\
<10\% & : 36.81 \text{ pg/mL (24-42)} \\
\geq 10\% & : 34.18 \text{ pg/mL (16-42)} \\
\end{align*}
\]

\[n=10 \quad n=29\]

D

\[
\begin{align*}
\text{Global LV Scar (\%)} & \\
\text{Log hs-cTnT (pg/mL)} & \\
\end{align*}
\]

\[r=-0.10 \quad p=0.54\]

Zelt JE, Mielniczuk LM, Can J Cardiol 2017; 1478-88
Coronary Disease Spectrum

Severe LV dysfunction
- Significant scar
- Predominant HF symptoms

Patients with severe CAD:
- Only demonstration of viability may be necessary

Mild-moderate CAD
- Ischemia testing may be of benefit

Normal LV function
- Significant CAD
- Presence of angina

Some degree of LV dysfunction
- Mixture of hibernating myocardium
- Evidence of ischemia or symptoms of angina
## Decision Making for Viability Assessments

<table>
<thead>
<tr>
<th>Viability Testing Unlikely to Add Useful Information</th>
<th>Viability Testing May Be Helpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger patients</td>
<td>Older patients</td>
</tr>
<tr>
<td>HFrEF with &gt;class II angina</td>
<td>HFrEF with no angina</td>
</tr>
<tr>
<td>Moderate-severe ischemia on provocative testing</td>
<td>No evidence of ischemia</td>
</tr>
<tr>
<td>EF&gt;40%</td>
<td>EF&lt;40%</td>
</tr>
<tr>
<td>Left main coronary disease</td>
<td>Chronic total occlusions</td>
</tr>
<tr>
<td>No or limited co-morbidities</td>
<td>Severe/multiple co-morbid disease</td>
</tr>
</tbody>
</table>
Decision Making for Revascularization in Heart Failure

Favors Medical Therapy
Severe Renal Insufficiency
Smaller LVESVI ($<79 \text{ ml/m}^2$)
Higher LVEF ($>28\%$)
Single-Vessel Coronary Disease
Limited Functional Capacity
(6MWD $<300$ meters, KCCQ
Physical Ability Score $\leq 55$)
More Viable Myocardium
Ischemic Burden
Biomarker Level (BNP, STNFR-1)
Less Viable Myocardium
Increased MI Risk
Increased Risk of Sudden Cardiac Death
Moderate to Severe Mitral Regurgitation
Preserved Functional Capacity
(6MWD $>300$ meters, KCCQ
Physical Ability Score $>55$)
Lower LVEF ($\leq 27\%$)
Three-Vessel Coronary Disease
Larger LVESVI ($\geq 79\text{ ml/m}^2$)

Favors CABG + Medical Therapy
Concluding Remarks

- Viability testing is not for everyone
  - To be considered when it may impact management decisions
- The field has evolved significantly over 20 years
  - Over-reliance on viability info not needed to guide decisions
  - Personalized approaches to revascularization are needed
- Future Directions
  - Role of biomarkers
  - Method of revascularization
  - Novel imaging techniques
  - Heart team and artificial intelligence approaches for complex decisions