Cardiac Assessment of Stunning-Hibernating Myocardium and Sympathetic Innervation

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• Approaches to Myocardial Viability by PET/CT
• Clinical Implications of Myocardial Viability
• Pathophysiologicaal Considerations
• Clinical Impact in Ischemic Cardiomyopathy
• Role of Assessment of Abnormal Sympathetic Innervation in Heart Failure Patients
Clinical Example

• 68 yrs old diabetic patient with exertional dyspnea who was referred for evaluation of ischemic heart disease by means of 99m- Tc SPECT perfusion imaging.

CVRF: diabetes, history of smoking, and hypercholesterolemia.

PM-implantation due to sick-sinus-syndrom
99mTc-SPECT Perfusion Images
Polar Map and 3D Display

Stress

Rest
Display of FDG-PET/CT Images

vertical long axis

short axis

horizontal long axis
Diagnosis

Antero-septo-apical and infero-septal:

- Fixed defect (99mTc-SPECT) and viable myocardium (≈80%) (FDG-PET).

⇒ Findings are indicative of an extensive « mismatch » or hibernating myocardium!

(≈55% of LV)
Coronary Angiography

- Two Proximal LAD lesions ≈ 90%
- LCx with ≈ 40-50%
- RCA ≈ 90%

⇒ PCI with stent implantation of LAD and RCA lesions

Echocardiography

- Follow-Up exam with improvement of global LV-EF from 25% to 40%.
71 year old patient with severe heart failure and dyspnea who was referred for evaluation of ischemic heart disease by means of Tc- SPECT perfusion imaging.
3D Display of Tc- SPECT
Display of FDG-PET/CT Images
Pitfall!

• Glucose utilization in normal myocardium is suppressed by high circulating free fatty acids (FFA) and low insulin-levels

• The current FDG-PET/CT exam was performed WITHOUT insulin!

⇒ The absence of FDG-uptake in the antero-basal wall (while perfusion was normal) reflects regional FFA utilization preventing the FDG-uptake!
Glucose Loading Protocol for Cardiac FDG-PET Viability Study

Measurement of plasma glucose

- < 6 mmol/l: 25g dextrose i.v.
- 6-12.5 mmol/l: 13g dextrose i.v.
- >12.5 mmol/l: Insuline s.c.*

Measurement of plasma glucose

- < 8 mmol/l: 5-10 mCi FDG Injection i.v.
- >8 mmol/l: Insuline s.c.*

PET Acquisition

*Humalog Dosis  Plasma glucose
3 IE   8.0-9.0 mmol/l
4 IE   9.0-10 mmol/l
5-6 IE 10-11 mmol/l
6-7 IE >11 mmol/l
Reversible Contractile Dysfunction

• Normal blood flow  
  or  
• Normal glucose utilization 
  or  
• Reduced blood flow combined with enhanced glucose utilization 
  = “mismatch”

Irreversible Contractile Dysfunction

• Severely reduced blood flow  
  or  
• Severely reduced glucose utilization 
  or  
• Reduced blood flow combined with reduced glucose utilization 
  = “match”

(Courtesy of H. Schelbert)
N-13 ammonia PET-perfusion images

Glucose metabolism by FDG-PET

normal

irreversible dysfunction = “Match” (Scar Tissue)

reversible dysfunction = “Mismatch” (Hibernation)

(Courtesy of H. Schelbert)
Higher Sensitivity of FDG-PET in the Detection of Viable Myocardium than TI-201 SPECT Perfusion Imaging

(Brunken R. Circulation 1992;86:1357)

In patients with ischemic cardiomyopathy and LVEF < 30% TI-201 SPECT redistribution images may underestimate viability

- Impaired sarcolemma function
- Severe hypoperfusion may limit TI-201 delivery
- Attenuation of low energy photons of TI-201 in dilated ventricles
Improvement in LVEF by Severity of LV Dysfunction

14 Investigations

PRE-SX LVEF > 35%
+19%
+8.4 EF units

PRE-SX LVEF < 35%
+42%
+11.6 EF units

LVEF %

PRE  POST  PRE  POST
Schöder et al, UCLA School of Medicine

Amount of Viability and LVEF Improvement

\[ y = 4.6 + 1.07x \]

\[ r = 0.65 \]

\[ p < 0.001 \]
Survival by Viability and Treatment

With PET Mismatch

Survival Probability

Time (months)

CABG

Medical

p = 0.007

Without PET Mismatch

Survival Probability

Time (months)

CABG

Medical

NS

Patients at Risk

CABG 26 22 20 20 19 11

Medical 17 7 3 3 3 3

17 16 14 13 8 4

33 28 25 17 13 7

Death Rates for Patients with and without Myocardial Viability treated by Revascularization or Medical Therapy

(Allman KC et al. JACC 2002)
Restoration of Coronary Flow in Ischemic Cardiomyopathy

*Therapeutic Goals*

- Reduce Cardiac Morbidity and Mortality
- Relief of CHF Symptoms
- Improve Quality of Life
Restoration of Coronary Flow in Ischemic Cardiomyopathy

Criteria

- Adequate Viable Myocardium
  (> 4 Segments or > 20% of LV)
- Adequate Target Vessels
- LVEDD < 75 mm
Algorithm to Stratify Patients with Ischemic Cardiomyopathy for Treatment Options

Echocardiography and LVEF < 30%

- SPECT and/or PET
  - Viability \( \geq 20\% \) of LV *
    - PCI and/or CABG
  - Angiography
    - No Viability
      - Aggressive Medical Treatment
        - No Improvement
        - Transplantation
    - Sufficient Coronary Anatomy
      - Insufficient Coronary Anatomy

(*Viability defined as \( \geq 4 \) segments of mismatch between reduced perfusion and viability)
PCI or CABG in Ischemic Cardiomyopathy

When Large Reversible Component is Present

- Improvement of Global Left Ventricular Function
- Amelioration or Relief of CHF Symptoms
- Reduction in long-term Cardiac Mortality
- Lower Peri-Operative Mortality and Morbidity
Effects of Viability on Therapeutic Strategy

(Courtesy of H. Schelbert)

Beanlands et al, Am J Card 1997
Factors potentially affecting the Effect of Flow Restoration on Viable but Dysfunctional Myocardium

1. Timing of coronary revascularization.

2. Extent and severity of myocardial ischemia in dysfunctional but viable myocardium.

3. Myocardial remodeling.

4. Left-ventricular dilation.
PARR-2 (randomized-controlled) Trial: Survival Curves for Composite Outcome (Cardiac Death, Myocardial Infarction, or Recurrent Hospitalization) within 1 year!

Overall Study

Hazard Ratio (HR): 0.78 (95% CI: 0.58–1.1; P = 0.15)

Post Hoc Analysis: PET Recommendations vs. Standard Arm

HR = 0.62 (95% CI: 0.42–0.93; P = 0.019)

(Beanlands RS et al. J Am Coll Cardiol 2007)
Examples of Images and Reconstructed Polar Maps

(D’Egidio G et al. J Am Coll Cardiol Img 2009)
Interaction Hazard Ratios and 95% Confidence Interval at Various Levels of Mismatch

(D’Egidio G et al. J Am Coll Cardiol Img 2009)
Early Versus Delayed Revascularization in Ischemic Cardiomyopathy Patients with Substantial Viability

- Patients (n=85) with ischemic cardiomyopathy and substantial viability (25% of the left ventricle) on dobutamine stress echocardiography underwent surgical revascularization.
- Patients were divided into 2 groups: early (≤1 month) and late (>1 month) revascularization.
- 40 patients underwent early (groups I: 20  12 days) and 45 late (group II: 85  47 days) revascularization.
- LVEF was determined using radionuclide ventriculography before and 9 to 12 months after revascularization.
- Follow-up was performed up to 2 years.

(Bax JJ et al. Circulation 2003)
Inotropic Response to Dobutamine in Dysfunctional Myocardial Segments determined with Echocardiography

**Typical Biphasic Response** (septum and apex) suggestive of hibernating-stunned myocardium!

Increase in function: ↑ ; Deterioration: ↓  

*(Nihoyannopoulos P. EHJ 2011)*
Viability Criteria as assessed with dobutamine-stress Echocardiography

1. **Biphasic response** (improvement of wall motion during low dose (5 and 10 g/kg/min), followed by worsening of wall motion during high dose dobutamine).

2. **Sustained improvement** (improvement during low and/or high dose dobutamine without subsequent deterioration of wall motion);

3. **Worsening** (immediate deterioration of wall motion during dobutamine infusion).

→ substantial viability in the presence of 4 or more dysfunctional but viable segments (25% of the LV)
Impact on Left-Ventricular Ejection Fraction (LVEF)

- Group I: early
- Group II: late

Revascularization

LVEF (%)

- p<0.05
- p = ns

(Bax JJ et al. Circulation 2003)
Impact on Mortality and Rehospitalization

(Bax JJ et al. Circulation 2003)
Left Ventricular Remodeling, Viable Myocardium, Improvement in LV-Function After Revascularization and Prognosis

Change in LVEF (%) after Revascularization

LV Endsystolic Volume (ml)

Δ LVEF = 18.4 - 0.1 ESV
P < 0.001

(Bax JJ et al. Circulation 2004)
Discrepancy between Information derived from contrast enhanced MRI and Nuclear Imaging

Patient with inferior subendocardial scar tissue on contrast enhanced MRI (a)

Severe reduction in 99mTc-tetrofosmin activity (b)

Preserved 18F-FDG activity (c)

Ischemically jeopardized or hibernating myocardium (Roes SD et al. Eur J Nucl Med Mol Imaging 2009)
FDG-PET/ SPECT approach to identify and denote hibernating myocardium may be more accurate or easier to evaluate of myocardial viability in the « intermediate » range than CMR

- Investigations by
  and
**MRI and Necrosis**

I. **Acute T2W**
   - Edema anterior wall

II. **Acute LGE**
   - Compact Enhancement

II. **Late LGE**
   - Reduced Enhancement

(Dall'Armellina et al. Circ Cardiovasc Imaging 2011)
Edema in Patients with Myocardial Infarction

⇒ Edema may lead to overestimation of infarct size with DE-MRI!

(Dall'Armellina et al. Circ Cardiovasc Imaging 2011)
201-Thallium Reinjection Imaging for Assessment of Myocardial Viability

Relationship between Recovery of LV Function after Revascularization and Viability Imaging

(A) Contrast-Enhanced CMR

- Percent of Segments Improving after Revascularization
  - 0%: 86%
  - 1-25%: 65%
  - 26-50%: 43%
  - 51-75%: 10%
  - 76-100%: 0%

(B) Rest-Redistribution

- Percent of Segments Improving after Revascularization
  - >80%: 83%
  - 71-80%: 75%
  - 61-70%: 69%
  - 51-60%: 56%
  - 41-50%: 17%
  - <40%: 0%

(C) Stress-Redistribution-Reinjection

- Percent of Segments Improving after Revascularization
  - Normal: 91%
  - Complete: 96%
  - Partial: 63%
  - Mild to Moderate: 30%
  - Severe: 0%

(Dilsizian V. J Nucl Cardiol 2007)
Pooled Analysis of different Modalities of Viability Assessment for predicting Improvement in Left-Ventricular Function

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Mean sensitivity (%)</th>
<th>Mean specificity (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
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<tr>
<td>Dobutamine echocardiography</td>
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<tr>
<td>$^{201}$TI-SPECT</td>
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<td>54</td>
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<td>$^{99m}$Tc-SPECT</td>
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<td>FDG-PET</td>
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<td>MRI diastolic wall &lt;6 mm</td>
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<td>Dobutamine MRI</td>
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$^{201}$TI = thallium-201; $^{99m}$Tc = technetium-99m; FDG = fluorine-18-labeled fluorodeoxyglucose; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SPECT = single-photon emission computed tomography

(Schinkel et al. Curr Probl Cardiol 2007)
Comparison of Sensitivities and Specificities of various Techniques for the Prediction of Recovery of Regional Function after Revascularization

(Schinkel AF et al. Curr Probl Cardiol 2007;32: 375)
Assessment of Sympathetic Innervation in Heart Failure Patients
Study Results in a Representative Animal With Inducible VT

(Sasano T et al. J Am Coll Cardiol 2008)
PET Defect Sizes in Animals with and without Inducible Ventricular Tachycardia

(Sasano T et al. J Am Coll Cardiol 2008)
Examples of Planar Cardiac 123I-mIBG Images

Ji SY and Travin M.I J Nucl Cardiol 2010
Major Cardiac Event Rates (MCE) over 2 Years in relation to LVEF and 123I-mIBG H/M.

Cardiac events:
- cardiac death, transplant, and potentially lethal arrhythmias based on implantable cardioverter defibrillator discharge.

Relationship of LVEF and H/M to 2-year Cardiac Mortality in the ADMIRE-HF Study

Chirumamilla A, Travin MI. Semin Nucl Med 2011
Better predictor of lethal arrhythmias/Cardiac death than LVEF, NYHA class, and ECG alterations.

123I-mIBG can identify a low risk subgroup with an extremely low incidence of lethal ventricular arrhythmias and cardiac death and, therefore, may not necessarily require an ICD.

Autonomic imaging may provide important information in the decisionmaking process as regards the necessity of ICD implantation in heart failure patients.