Myocardial viability detected with SPECT perfusion imaging

Raffaele Giubbini

Chair and Nuclear Medicine Unit
University and Spedali Civili
Brescia - Italy

giubbini@med.unibs.it
The sleeping heart: Hibernating Myocardium

PRE-OPERATIVE
Single vessel disease - Occluded L.A.D.

CONTROL
LVEDV = 128
EF = 0.37

POST NTG
LVEDV = 101
EF = 0.51

8 MONTHS
After Surgery
Patient Coronary Bypass Graft to L.A.D.

LVEDV = 104
EF = 0.76

What is viable?

a) Normal
b) Ischemic
c) Stunned
d) Short-term hibernation (repetitive stunning)
e) Chronic hibernation
f) maimed-embalmed

NB:
- From c) to e) not contracting viable cells (tissue)
- c) spontaneous recovery
- d) & e) variable grade of recovery only after revascularization
Rest myocardial blood flow (rMBF)

- **Normal** ($\approx 0.8 \text{ ml/gr/min}$)
  a) Stunned
  b) Short-term hibernation

- **Reduced**
  a) Chronic hibernation
  b) Maimed-embalmed
CORONARY RESERVE

a) **Stunned**: preserved with variable degrees

b) **Short-term hibernation**: impaired or abolished

c) **Chronic hibernation**: preserved at low level (flow down-regulation)
PHYSIOPATHOLOGICAL CONSEQUENCES

- loss of contractility
- preservation of ultrastructure (stunned & short-term hibernation)
- progressive undifferentiation (chronic hibernation \(\rightarrow\) loss of contractyle proteins, fibrosis)
- preserved function of cell membrane
- metabolic shift (predominant in chronic hibernation, variable in stunning)
- apoptotic trend
Goals of Assessing Myocardial Viability

To select pts candidate to revascularization procedures in order to achieve an improvement in:

- **Perfusion**
- **Systolic function**
- **Symptoms & Natural history** (independently of the improvement in global systolic function)
  - diastolic performance,
  - improvement in systolic and diastolic function during stress,
  - stabilization of the arrhythmic milieu,
  - prevention of MI and potential attenuation of progressive remodeling in pts with LV dysfunction
Assessment of Myocardial Viability

**Membrane integrity:**
uptake of Thallium and Rubidium

**Metabolic activity:**
Fatty acids
PET, uptake of F-fluorodeoxyglucose (FDG) is a marker of glucose metabolism

**Blood Flow**
$^{11}N\text{H}_3$, $^{99m}\text{Tc}$-Sestamibi, $^{99m}\text{Tc}$-tetrofosmin

**Contractyle reserve**
Low Dose Dobutamine RWM analysis

**Morphology**
MR hyperenhancement
Assessment of Myocardial Viability

- Membrane integrity
- Metabolic activity
- Contractile reserve
- Blood Flow
- Morphology
ROC analysis for hyperenhancement, end-diastolic wall thickness, and wall thickening for detection of transmural defects (area for ES wall thickness, 0.843)

System Resolution

F18

NH3 TC99M

RB

TL

15 mm  8 mm  5 mm
MARKERS of VIABILITY

♥ Tracer uptake > 50%
♥ Thallium RED/REINJ > 10%
♥ Improved uptake after nitrates with Tc Mibi/Tetro
Hibernating Myocardium
Nitrate MPI

PATIENT 1

CONTROL

NTG

PATIENT 2

CONTROL

NTG

SHORT AXIS

VLA
Nitrate sestamibi imaging in ischemic LV dysfunction

EF Change After Revascularization (%) vs. Nitrate-induced Defect Change (%)

$r = 0.94$
$p < 0.0001$

Markers of Hibernation

Blood-flow – Metabolism mismatch

Blood Flow

Ischemic

Normal

Blood Flow

Normal

Intervention

Days

50

Metabolism

Hypermetabolic

Normal

Intervention

Days

50

Metabolism

Normal

Intervention

Days

50
Top, Three short-axis views (apical, equatorial, and basal) of a PET viability study with assessment of rest perfusion (NH3) and glucose metabolism (FDG)

Accuracy of imaging techniques to predict functional recovery after revascularization in patients with chronic ischemic LV dysfunction

Bax JJ et al. JACC 1997;30:1451

Bax et al. Curr Probl Cardiol 2001;26:141-86
Sensitivity, specificity, and predictive accuracies of non-invasive tests, singly and in combination, for diagnosis of hibernating myocardium
### Sensitivity, specificity and predictive accuracies of the tests

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Sens%</th>
<th>Spec%</th>
<th>PPV%</th>
<th>NPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early improvement of contraction (immediately after CABG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic wall thickness</td>
<td>98</td>
<td>24</td>
<td>59</td>
<td>91</td>
</tr>
<tr>
<td>Dobutamine echocardiography</td>
<td>82</td>
<td>82</td>
<td>83</td>
<td>80</td>
</tr>
<tr>
<td>Thallium-201 scintigraphy</td>
<td>83</td>
<td>51</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td>Combination of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWT+DOB</td>
<td>100</td>
<td>59</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>DWT+TL</td>
<td>99</td>
<td>29</td>
<td>68</td>
<td>95</td>
</tr>
<tr>
<td>DOB+TL</td>
<td>99</td>
<td>77</td>
<td>83</td>
<td>98</td>
</tr>
<tr>
<td>DWT+DOB+TL</td>
<td>100</td>
<td>51</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Short-term improvement of contraction (3 months after CABG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic wall thickness</td>
<td>99</td>
<td>24</td>
<td>54</td>
<td>97</td>
</tr>
<tr>
<td>Dobutamine echocardiography</td>
<td>79</td>
<td>72</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>Thallium-201 scintigraphy</td>
<td>81</td>
<td>46</td>
<td>57</td>
<td>73</td>
</tr>
<tr>
<td>Combination of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWT+DOB</td>
<td>100</td>
<td>46</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>DWT+TL</td>
<td>100</td>
<td>30</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>DOB+TL</td>
<td>99</td>
<td>64</td>
<td>69</td>
<td>98</td>
</tr>
<tr>
<td>DWT+DOB+TL</td>
<td>100</td>
<td>37</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>Late improvement of contraction (12 months after CABG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic wall thickness</td>
<td>100</td>
<td>28</td>
<td>61</td>
<td>100</td>
</tr>
<tr>
<td>Dobutamine echocardiography</td>
<td>74</td>
<td>74</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>Thallium-201 scintigraphy</td>
<td>74</td>
<td>43</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Combination of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWT+DOB</td>
<td>100</td>
<td>51</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>DWT+TL</td>
<td>100</td>
<td>30</td>
<td>69</td>
<td>100</td>
</tr>
<tr>
<td>DOB+TL</td>
<td>88</td>
<td>65</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>DWT+DOB+TL</td>
<td>100</td>
<td>42</td>
<td>76</td>
<td>100</td>
</tr>
</tbody>
</table>
MYOCARDIAL VIABILITY
and

♥ FUNCTIONAL RECOVERY After REVASCULARIZATION

♥ IMPROVEMENT in HEART FAILURE SYMPTOMS - EXERCISE CAPACITY and PROGNOSIS

♥ VENTRICULAR REMODELLING
Hibernating Myocardium
prediction of functional recovery

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>No. of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc99m-MIBI</td>
<td>83 (78-97)</td>
<td>69 (63-74)</td>
<td>10</td>
</tr>
<tr>
<td>DSE</td>
<td>84 (82-86)</td>
<td>81 (79-84)</td>
<td>16</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>86 (83-89)</td>
<td>47 (69-74)</td>
<td>7</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>90 (87-93)</td>
<td>73 (69-74)</td>
<td>12</td>
</tr>
</tbody>
</table>

W.Wijns, PG.Camici NEJM 1998;339:176
MRI hyperenhancement technique (top) and PET viability study (bottom) covering the complete heart

Bland-Altman analysis of the visual (top) and quantitative (bottom) comparison of MRI with PET for estimating defect severity

Accuracy of MCE and LGE-MR in prediction of myocardial function recovery after bypass surgery

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dysf. seg. Aki seg</td>
<td>dysf seg Aki seg</td>
</tr>
<tr>
<td>MCE preserved perfusion</td>
<td>87 78</td>
<td>42 72</td>
</tr>
<tr>
<td>(grade 1+2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGE-MR viable myocardium</td>
<td>91 88</td>
<td>35 52</td>
</tr>
<tr>
<td>(grade 1+2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Tousek P et al. International Journal of Cardiology, in press*
Accuracy of nitrate myocardial perfusion imaging in predicting recovery of LV function

<table>
<thead>
<tr>
<th>Author</th>
<th>Tracer</th>
<th>Miocardial Infarction (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior et al.</td>
<td>Thallium</td>
<td>NA</td>
<td>92</td>
<td>78</td>
</tr>
<tr>
<td>Bisi et al.</td>
<td>Sestamibi</td>
<td>100</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>Bisi et al.</td>
<td>Sestamibi</td>
<td>100</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>Maurea et al.</td>
<td>Sestamibi</td>
<td>100</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Li et al.</td>
<td>Sestamibi</td>
<td>100</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>Li et al.</td>
<td>Sestamibi</td>
<td>100</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>Total (117 patients)</td>
<td></td>
<td></td>
<td>90</td>
<td>83</td>
</tr>
</tbody>
</table>
LDD nitrate-enhanced Tc99m-Sestamibi G-SPECT vs. LDDE for detecting reversible dysfunction in ischemic cardiomyopathy

Is a critical mass of viable myocardium necessary to observe an improvement of global LV function after revascularization?
Extent and Severity of Perfusion Defects

- Extended defect
- Severe defect
LVEF significantly increased after surgery only in group A.

No significant difference in the pre-operative LVEF between the groups.

Ragosta et al. Circulation. 1993;87:1630-1641
Change in global LV ejection fraction after revascularization in patients with ≥4 and in those with <4 viable segments

Cuocolo et al. J Nucl Cardiol 2000
Relation between viable myocardium (defined as improved wall motion after revascularization) and the magnitude of regional sestamibi activity

Spearman rank correlation $p < 0.0001$

Percentage of Viable Regions

Regional Sestamibi Activity

Acampa et al. J Nucl Cardiol 2000
MYOCARDIAL VIABILITY
and

♥ FUNCTIONAL RECOVERY After REVASCULARIZATION
♥ IMPROVEMENT in HEART FAILURE SYMPTOMS - EXERCISE CAPACITY
♥ PROGNOSIS
♥ VENTRICULAR REMODELLING
Myocardial viability to predict improvement in exercise capacity

Percentage of LV with PET mismatch

Delay in Revascularization Is Associated With Increased Mortality Rate in Patients With Severe Left Ventricular Dysfunction and Viable Myocardium on Fluorine 18-Fluorodeoxyglucose Positron Emission Tomography Imaging
Prognostic value of tomographic rest-redistribution Tl-201 imaging in medically treated patients with coronary artery disease and left ventricular dysfunction

Mantel-Cox = 5
P = 0.03

J Nucl Cardiol 1996; 3:150-6
Death Rates with and without Viability
Revascularization vs. Medical Therapy

Cardiac Death Rates (%/yr)

<table>
<thead>
<tr>
<th>Viable</th>
<th>Non-Viable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revasc</td>
<td>Medical Rx</td>
</tr>
<tr>
<td>Revasc</td>
<td>Medical Rx</td>
</tr>
<tr>
<td>3.2</td>
<td>7.7</td>
</tr>
<tr>
<td>16.0</td>
<td>6.2</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 147, \quad p < .0001 \]

\[ \chi^2 = 1.43, \quad p = 0.23 \]

Allman KC et al. JACC 2002;1151-8
Event rate according to the presence/absence of viable tissue on FDG PET and treatment

- Di Carli M. (Am J Cardiol 1994)
- Eitzman D. (JACC 1992)
- Lee KS. (Circulation 1994)
- Yoshida K. (JACC 1994)
- Vom Dahl J. (J Nucl Med 1997)
- Tamaki N. (JACC 1993)
- Pagano D. (Heart 1999)
Survival benefit after revascularization is independent of left ventricular ejection fraction improvement in patients with previous myocardial infarction and viable myocardium

<table>
<thead>
<tr>
<th>Variable</th>
<th>chi²</th>
<th>Hazards ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction at baseline</td>
<td>1.4</td>
<td>1.0</td>
<td>0.9–1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Viable segments</td>
<td>6.7</td>
<td>1.2</td>
<td>1.1–1.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-viable segments</td>
<td>0.1</td>
<td>0.9</td>
<td>0.7–1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>12.2</td>
<td>0.3</td>
<td>0.1–0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Survival benefit after revascularization is independent of left ventricular ejection fraction improvement in patients with previous myocardial infarction and viable myocardium.
Hibernating myocardium: chronically adapted to ischemia but vulnerable to sudden death

I-123 MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator

Denervation in areas of myocardial viability
MYOCARDIAL VIABILITY and

♥ FUNCTIONAL RECOVERY After REVASCULARIZATION
♥ IMPROVEMENT in HEART FAILURE SYMPTOMS - EXERCISE CAPACITY AND PROGNOSIS
♥ VENTRICULAR REMODELLING
PTCA+Stent

Pre-PTCA Post-PTCA
Value of gated-SPECT in the analysis of regional wall motion of the interventricular septum after coronary artery by-pass grafting

ARE THERE IMPORTANT DIFFERENCES BETWEEN NON INVASIVE TESTING MODALITIES IN RISK STRATIFICATION?
Reasons for Discrepancies in Techniques for Identifying Viability

10 Patients with severe ischemic cardiomyopathy (mean LVEF 27%) scheduled for prompt heart transplantation

The percentage of live myocytes per segment needed for LDDE or Dobutamine MRI to identify viability was higher than Thallium (40% vs. 32%)
The highest agreement was between LDDE and Dobutamine MRI (91%)

The demonstration of improved contractility (contractile reserve) requires more live myocytes than what’s needed for the same segment to effectively uptake Thallium

Zamorano et al. Am J Cardiol 2002;90:455-459
PET-SPECT flow chart

Dipyridamole $^{13}$N-ammonia/ rest $^{18}$FDG PET
Dipyridamole/rest $^{99m}$Tc-SeptaMibi SPECT

blinded polar maps
randomization

PET strategy                                  SPECT strategy
PTCA  CABG  drug                               PTCA  CABG  drug

26 months follow up first cardiac event
• cardiac death
• myocardial infarction
• revascularization

H.J. Siebelink et al. Groningen University Hospital, The Netherlands. JACC 2001
Cardiac event free survival
all patients

H.J. Siebelink et al. Groningen University Hospital, The Netherlands. JACC 2001
### ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging

**Table 17. Recommendations for Radionuclide Techniques to Assess Myocardial Viability**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Test</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Predicting improvement in regional and global LV function after revascularization</td>
<td>Stress/redistribution/reinjection Tl-201</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Rest-redistribution imaging</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perfusion plus PET FDG imaging</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resting sestamibi imaging</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gated-SPECT sestamibi imaging</td>
<td>IIa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late Tl-201 redistribution imaging</td>
<td>IIIb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(after stress)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dobutamine RNA</td>
<td>IIIb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postexercise RNA</td>
<td>IIIb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pos nitroglycerin RNA</td>
<td>IIIb</td>
<td></td>
</tr>
<tr>
<td>2. Predicting improvement in heart failure symptoms after revascularization</td>
<td>Perfusion plus PET FDG imaging</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>3. Predicting improvement in natural history after revascularization</td>
<td>Tl-201 imaging (rest-redistribution and stress/redistribution/reinjection)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Perfusion plus PET FDG imaging</td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

FDG indicates fluorodeoxyglucose; PET, positron emission tomography; RNA, radionuclide angiography; SPECT, single-photon emission computed tomography; Tl-201, thallium-201.
Assessment of viability
Why nuclear imaging?

<table>
<thead>
<tr>
<th>Prons</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>♥ Real 3-D imaging</td>
<td>♥ Poor spatial resolution</td>
</tr>
<tr>
<td>♥ Standardization</td>
<td>♥ (Uptake related to residual blood flow)</td>
</tr>
<tr>
<td>♥ Qualitative and quantitative analysis</td>
<td></td>
</tr>
<tr>
<td>♥ Simultaneous evaluation of perfusion,</td>
<td></td>
</tr>
<tr>
<td>viability and LV function</td>
<td></td>
</tr>
<tr>
<td>♥ High sensitivity</td>
<td></td>
</tr>
<tr>
<td>♥ Reproducibility</td>
<td></td>
</tr>
<tr>
<td>♥ Accuracy demonstrated in large body of</td>
<td></td>
</tr>
<tr>
<td>literature</td>
<td></td>
</tr>
<tr>
<td>♥ Prognostic impact</td>
<td></td>
</tr>
<tr>
<td>♥ Availability</td>
<td></td>
</tr>
<tr>
<td>♥ Feasibility</td>
<td></td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGE

Radionuclide techniques are a simple, reproducible, widely validated and very sensitive method for detecting viable myocardium: SPECT imaging with Thallium or Tc-labelled agents may be the first step to detect hibernating myocardium in asynercic areas.

In patients with the most severe depression in LVEF and very high revascularization risk, PET-FDG imaging may also be advisable.
Patients with CHF, LV dysfunction and a significant extent of myocardial viability are a very high risk Pt subset for cardiac death.

There is substantial evidence supporting the concept that radionuclide imaging of myocardial viability can provide important prognostic information in patients with CHF and LV dysfunction and that it can drive decision making as a strong predictor of the potential benefit of revascularisation.
Hamish, why don't you play with Donald anymore?

Would you want to play with someone who lies, moves his ball and cheats on his score?

No, never!

Neither would Donald...

cutting edge cartoons

Hamish McDivot & Sandy Bunker©
REST-REDISTRIBUTION

Early images

uptake defect at rest: fibrosis? hypoperfusion at rest?

• Redistribution and “fill-in” phenomena
• Reduced wash-out

Late images (>4h)

hypoperfusion at rest (hibernation)

Fibrosis