Emerging role of PET in Nuclear Cardiology: PET is not only viability

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Hybrid Imaging:

Providing simple and accurate integrated measure of the effect of anatomic stenosis on coronary resistance and tissue perfusion.

Optimizing selection of patients who may ultimately benefit from revascularization.

• The combination of two data sets in equally importance for the integration of one final image.
• Referred to functional (PET/SPECT) and anatomical evaluation through Cardiac Computed Tomography Angiography (CCTA).
Applications of PET / CT in Cardiology

- **Myocardial Perfusion**
- **Correlation CCTA - PET**
- **Cardiac Function**
- **Myocardial Blood Flow**
- **Endothelial Function**
- **Myocardial Viability**
- **Inflammation of the atherosclerotic plaque**
- **Molecular Imaging**
WHERE do we stand?

- The current evidence for anatomic evaluation using CCTA remarks it's:
  - High negative predictive value
  - Moderate good capacity to predict a >50% coronary artery lesion

- Making it a very reliable form to exclude significant CAD.

- The limitations of using CCTA measures for delineating the physiologic implications of stenosis are well described i.e.
  - Moderate vasomotor tone and coronary collateral flow, both of which are known to affect myocardial perfusion, cannot be estimated by measures of stenosis severity.
WHERE do we stand?

- It has been previously described that the majority of patients are referred to diagnostic invasive coronary angiography and consequently to PCI in the absence of any sort of functional evaluation.

- Although professional guidelines call for objective documentation of ischemia prior to elective ICA and revascularization.
WHERE do we stand?

PET imaging is very important to denote the diagnostic accuracy of functional techniques, that of the case of PET MPI with an average sensitivity of 90%–92% and specificity of 85%–89% in detecting flow-limiting CAD.

- 82R Rubidium
- 15O Water
- 13N ammonia
- 18F-Flurpiridaz

Opportunity to evaluate:
1. LV myocardial perfusion
2. Absolute quantification of myocardial blood flow (ml/g/min)
3. LVEF at rest and stress
Ideal PET MPI Imaging Agent

- High cardiac uptake with minimal redistribution
- Near linear myocardial uptake vs. flow up to 5 mL/min/g or more (high first pass extraction fraction)
- High target to non-target ratio (vs. lung, liver, bowel)
- Usable for both exercise and pharmacologic stress
- Usable for quantitation of absolute myocardial flow
- Available as unit dose (\(^{18}\text{F}\)-labeled compound)
PET radionuclides of cardiological interest

Cyclotron products

- Oxygen-15  (half-life = 2.1 min)
- Nitrogen-13  (half-life = 10 min)
- Carbon-11  (half-life = 20.4 min)
- Fluorine-18  (half-life = 110 min)

Generator products

- Rubidium-82  (half-life = 76 sec)
- Gallium-68  (half-life = 68 min)
- Copper-62  (half-life = 9.7 min)
Chemical Structure of BMS747158

Mitochondrial Complex 1 (MC-1) Inhibitor

2-tert-Butyl-4-chloro-5-[4-(2-(18F)fluoro-ethoxymethyl)-benzyloxy]-2H-pyridazin-3-one

First Pass Uptake in Isolated Rabbit Hearts

BMS747158 (n=4)  
\(^{201}\text{Tl}\) (n=3) 
\(^{99}\text{mTc-sestamibi}\) (n=3) 
N13H3  
H2O15

* Indicates p<0.05

Pre-Clinical Cardiac PET Imaging with BMS747158

Normal Rat

Coronary ligation in Rat

Normal primate

First Human Study of BMS747158

Maddahi J, et al. JNM 2008
Radiation Dose Comparison – Stress and FDG

BMS747158 Preliminary Stress Dosimetry Comparison

- Mean of Adenosine Stress, Full (n=5)
- Mean of Exercise Stress, Full (n=5)
- 18F-FDG from ICRP 80

Maddahi J, et al. JACC 2009; abstract in press
Rest and Stress Myocardial SUVs

Maddahi J, et al. JACC 2009;
Adenosine

Exercise

BMS747158

Maddahi J, et al. JNM 2008; abstract in press
Applications of PET / CT in Cardiology

- Myocardial Perfusion
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- Inflammation of the atherosclerotic plaque
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WHEN?

• There is not current agreement in the appropriate indications for Hybrid Cardiac Imaging methods

• Although there is clear evidence about the incremental value of those techniques in certain groups at risk and also in those with previous history of MI and revascularization
MPI+CCTA

• Compared to CCTA alone the combination of MPI and CCTA results in a significant increase in:
  – Specificity (from 80 to 92%) and PPV (from 69 to 85%)

• Without any change in:
  – Sensitivity (95%) and NPV (97%).

• This effect was preserved across all vascular territories and on a patient-based analysis.

Sato A et al. Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease. J Nucl Cardiol 2010;17:19–26
After adjustment for clinical risk factors, obstructive plaque visualized by CCTA and abnormal MPI were independent predictors of late events.

An annual event rate of 1% was found in those with concordantly normal CCTA and MPI, and conversely those with concordantly abnormal CCTA and MPI had an event rate of 9%.

With significant incremental improved prediction of risk by the combination of the two modalities.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F[STRESS] ml/min/g</th>
<th>relative [% of Max]</th>
<th>F[REST] ml/min/g</th>
<th>relative [% of Max]</th>
<th>CFR S/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>1.3515</td>
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<td>0.5796</td>
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<td>2.332</td>
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<tr>
<td>1. basal anterior</td>
<td>1.6392</td>
<td>67.0</td>
<td>0.4329</td>
<td>56.8</td>
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<tr>
<td>2. basal anteroseptal</td>
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<td>0.6056</td>
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<td>7. mid anterior</td>
<td>1.5417</td>
<td>63.0</td>
<td>0.5645</td>
<td>74.0</td>
<td>2.731</td>
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<tr>
<td>8. mid anteroseptal</td>
<td>0.9609</td>
<td>39.3</td>
<td>0.6441</td>
<td>84.4</td>
<td>1.492</td>
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<tr>
<td>13. apical anterior</td>
<td>1.3385</td>
<td>54.6</td>
<td>0.605</td>
<td>79.3</td>
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<tr>
<td>14. apical septal</td>
<td>0.7078</td>
<td>28.9</td>
<td>0.6019</td>
<td>78.9</td>
<td>1.176</td>
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<tr>
<td>17. apex</td>
<td>1.1116</td>
<td>45.5</td>
<td>0.6507</td>
<td>85.3</td>
<td>1.708</td>
</tr>
</tbody>
</table>

FLOW RESERVE [ Pathology < 2.0 , Grey Zone 2.0 - 2.5 , Normal > 2.5 ]
# Myocardial Blood Flow Quantification Software

## N=9 (normals)

<table>
<thead>
<tr>
<th></th>
<th>Stress Flow (LAD/LCX/RCA)</th>
<th>Rest Flow (LAD/LCX/RCA)</th>
<th>CFR (LAD/LCX/RCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (QPET)</td>
<td>2.25/2.25/2.27</td>
<td>0.57/0.60/0.59</td>
<td>4.02/3.88/3.99</td>
</tr>
<tr>
<td>B (SyngoMBF)</td>
<td>3.21/3.22/3.34</td>
<td>0.86/0.83/0.88</td>
<td>3.89/3.98/3.97</td>
</tr>
<tr>
<td>C (PMOD)</td>
<td>3.20/3.41/3.33</td>
<td>0.80/0.75/0.80</td>
<td>4.1/4.83/4.38</td>
</tr>
</tbody>
</table>

## N =18 (all)

<table>
<thead>
<tr>
<th></th>
<th>Stress Flow r/Slope/Intercept</th>
<th>Rest Flow r/Slope/Intercept</th>
<th>CFR r/Slope/Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs. B</td>
<td>0.92/0.71/0</td>
<td>0.84/0.66/0</td>
<td>0.86/0.96/0</td>
</tr>
<tr>
<td>A vs. C</td>
<td>0.85/0.60/0.3</td>
<td>0.88/0.59/0.1</td>
<td>0.89/0.77/0.6</td>
</tr>
<tr>
<td>C vs. B</td>
<td>0.9/0.98/0.0</td>
<td>0.76/0.89/0.1</td>
<td>0.78/1.00/0.1</td>
</tr>
</tbody>
</table>

Presented on the ASNC2010 in Philadelphia, EU.
CTA: Positive and negative predictive value for ischemia

Min JK et al, *J. Am. Coll. Cardiol. Img.* 2010;3;305-315
Risk of cardiac death
Relation to inducible ischemia on SPECT

Evaluation of Ischemic Burden Remains the Main Stay for Management of a Patient With Stable CAD
Evaluation of CAD symptoms

- Low-Int Lk (.15-0.5)
  - CTA
  - High NPV
- High Int Lk (0.5-0.85)
  - CTA, MPI Imaging
  - High Diagnostic Value
- High Lk (>0.85)
  - Guide Management

Courtesy MF Di Carli
PET/CTA: A Sequential Approach

CT Scan

Normal

Mild/moderately abnormal

Ischemia evaluation

Suspect microvascular dysfunction

Medical Therapy

Severely abnormal

Invasive Angiogram ± revascularization
Atherosclerosis

Asymptomatic

Endothelial Damage

Atherosclerosis

Endothelial Dysfunction

Chronic Atherosclerosis

ACS

HF

Myocardial Damage

Atherotrombosis
Metodología

REST
ENDEVI >1.5

CPT

STRESS
CFR >2.5
Endothelial Dysfunction

- Diabetes Mellitus 2
- Dyslipidemia
- Hypertension
- Tobacco
- Metabolic Syndrome
- Others
MBF (mean±SE) after adjustment for mean group differences in MBF at rest, age, gender, and BMI by ANCOVA. A, In response to adenosine or dipyridamoloe and compared with IS control group, MBF was decreased significantly in DM (−17%) and HTN (−35%) g...

(1) IS group without coronary risk factors and normal insulin sensitivity;
(2) IR group without coronary risk factors and normal carbohydrate tolerance;
(3) IGT group, impaired glucose tolerance
(4) DM group without hypertension
(5) HTN; hypertensive group of diabetic individuals

Effect of ezetimibe–simvastatin over endothelial dysfunction in dyslipidemic patients: Assessment by 13N-ammonia positron emission tomography.

Endothelial-dependent vasodilation index (MBF after CPT)
Myocardial flow reserve

Endothelial Dysfunction in Hypertension

E Alexánderson y cols  Hypertension 2011
Endothelial Function in SLE

Alexanderson E. et al, Journal Of Nuclear Medicine, 2010/078212

N = 32
Global alteration in perfusion response to increasing oxygen consumption in patients with single vessel coronary artery disease.

Potential utility of Rubidium 82 PET quantification in pts with 3-vessel coronary artery disease.

Coronary vasoregulation in patients with various risk factors in response to cold pressor testing
Contrasting myocardial blood flow responses to short- and long-term vitamin C administration

Increased vascular production of reactive oxygen species markedly reduces the bioavailability of endothelium-derived nitric oxide, leading to impaired vasodilator function.
Tetrahydrobiopterin restores impaired coronary microvascular dysfunction in hypercholesterolaemia

Tetrahydrobiopterin is an essential co-factor for the synthesis of nitric oxide (NO)

Exercise Coronary Reserve recruitment

% MBF ADO

Controls

Hypercholesterol

Before Tx

After Tx by BH4 (10mg/kg ev)

p<0.01
Applications of PET / CT in Cardiology

- Myocardial Perfusion
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Myocardial viability: Why is it important?

It is the main point to decide between medical and revascularization treatment.
Outcome in Pts with Viability Evaluation

**With PET Mismatch**
- CABG: dotted line, survival probability
- Medicine: solid line, survival probability
  - P = 0.007

**Without PET Mismatch**
- CABG: dotted line, survival probability
- Medicine: solid line, survival probability
  - P = 0.12

Di Carli et al. JTCVS 1998
Viability

- Can be described as “living myocardium.”

- Myocardial ischemia, hibernation and stunning, may result in left ventricular dysfunction, but unlike scarred myocardium it represents a potentially reversible condition.

- Viable dysfunctional myocardium: potentially recoverable;
- Dead myocardium (necrosis or scar): not recoverable.

- Viable myocardium in the setting of myocardial contractile dysfunction represents hibernating or stunned myocardium.
Stunning

• Is a state of LV dysfunction persisting after an episode of ischemia and after recovery of normal coronary blood flow. It may last hours to minutes and it may follow a transient ischemia.

• The time of recovery depends on the duration, severity, and size of the ischemia.
Hibernation

1. Is a metabolic downregulation of myocardium caused by a reduced state of myocardial perfusion.

2. Physiologically there is a decreased coronary flow reserve.

3. Hibernation could be the result of repetitive stunning.
• Hibernating myocardium has depressed myocardial contractility at rest due to persistently impaired coronary blood flow.

• Function can be partially or completely restored by improving coronary blood flow, by providing inotropic stimulation or by reducing oxygen demand.
Myocardial Metabolism

• The heart is an aerobic organ.

• Under aerobic, fasting conditions, the primary substrate used by the heart is fatty acid because metabolism is mainly oxidative (glycolysis contributes only about 30% of substrate to the tricarboxylic acid cycle).

• When different circumstances prevail, the heart can use glucose, lactate, or ketones.
• In the fasting state, FFAs levels are high and glucose and insulin levels are low. Consequently, the rate of myocardial FFAs oxidation is high and inhibits glycolysis.

• After ingestion of carbohydrates, plasma concentrations of glucose and insulin rise. Glucose then becomes the dominant substrate for myocardial energy production.
• Myocardial ischaemia alters myocardial substrate metabolism.

• As blood flow and oxygen supply decline, oxidative metabolism decreases.

• Ischaemia is also associated with increased glycolysis.

• Residual glucose metabolism in dysfunctional myocardium indicates the presence of viable but functionally compromised myocardium.
F18-FDG

• FDG is taken up by the myocyte and phosphorylated by hexokinase to FDG-6-phosphate; it’s an indicator of myocardial viability.

• During fasting condition, increased FDG uptake can potentially be observed in ischemic tissue.

• Myocardial FDG uptake depends quantitatively on plasma concentrations of glucose and insulin.

• Myocardial glucose uptake also depends on myocardial work, plasma levels of FFAs and other competing substrates, insulin, catecholamines and oxygen supply.
The extreme variability of myocardial glucose pattern in fasting condition is documented by many different scenarios revealed in patients studied for oncologic purposes:

we can classify the FDG distribution patterns in the normal myocardium and in fasting conditions into three types:

• regional uptake;
• diffuse uptake.
• no to faint uptake;

But there are no specific meaning in the myocardial distribution patterns of FDG.

In addition, even in the same individual, the myocardial FDG uptake is neither stable nor reproducible unless under similar fasting conditions.

The transition from the intense FDG uptake of a dominantly glycolytic myocardial metabolism to the absent FDG uptake of a dominantly fatty acid metabolism is not entirely uniform either temporally or regionally.
To standardise the metabolic environment for myocardial FDG imaging different protocols have been proposed:

- fasting conditions;
- oral glucose loading;
- hyperinsulinaemic- euglycaemic clamping;
- nicotine acids derivates.
Under fasting conditions, the normal myocardium primarily utilises FFAs. In ischaemic myocardium, when glucose becomes an important energy substrate, FDG uptake will be enhanced.

Consequently, there should be a difference in FDG uptake between normal and ischaemic myocardium.

However, FDG distributes heterogeneously throughout the normal myocardium in the fasted state, limiting the specificity for detection of myocardial ischaemia.
Oral glucose loading

• Oral glucose loading (50–100gr) is commonly used to stimulate insulin secretion and regional glucose utilisation and thus myocardial FDG uptake.

• After a glucose load, plasma insulin concentrations rise, which enhances regional glucose utilisation.

• However, plasma concentrations of glucose also increase, so that the fraction of FDG sequestered metabolically into the myocardium and skeletal muscle declines, which in turn may offset the benefits of increased glucose utilisation for image quality.
• Diagnostically unsatisfactory images may still be obtained in 20%–25% of the patients with coronary artery disease.

• Type 2 diabetes account for the poor image quality in many of these patients.
### Glucose load - Insulin

**-Fasting condition**

**-Blood glucose levels:**

<table>
<thead>
<tr>
<th>Non-diabetic:</th>
<th>50gr oral glucose solution+ rapid insulin 3 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150mg/dl</td>
<td>50gr oral glucose solution+ rapid insulin 3 units</td>
</tr>
<tr>
<td>151-300mg/dl</td>
<td>25gr oral glucose solution+ rapid insulin 3 units</td>
</tr>
<tr>
<td>301-400mg/dl</td>
<td>25gr oral glucose solution+ rapid insulin 5 units</td>
</tr>
<tr>
<td>&gt;401mg/dl</td>
<td>25gr oral glucose solution+ rapid insulin 7 units</td>
</tr>
</tbody>
</table>

45’ after glucose loading and when glucose level <150mg/dl, inject F18-FDG (0.22mCi/Kg); imaging after 60’.

<table>
<thead>
<tr>
<th>Diabetic</th>
<th>25gr oral glucose solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150mg/dl</td>
<td>25gr oral glucose solution</td>
</tr>
<tr>
<td>151-200mg/dl</td>
<td>rapid insulin 3 units</td>
</tr>
<tr>
<td>201-300mg/dl</td>
<td>rapid insulin 5 units</td>
</tr>
<tr>
<td>301-400mg/dl</td>
<td>rapid insulin 7 units</td>
</tr>
<tr>
<td>&gt;401mg/dl</td>
<td>rapid insulin 10 units</td>
</tr>
</tbody>
</table>

Glucose level every 15’ for 60’. If glucose level elevated, additional insulin per scale. 45’ after glucose loading and when glucose level <150mg/dl, inject F18-FDG (0.22mCi/Kg); imaging after 60’.
Why assessing Viability?

- **American College of Cardiology (ACC) guidelines on heart failure (update 2009 of 2005 guidelines)** assign a IIa recommendation to viability assessment in patients with heart failure, known CAD, and the absence of angina.

- **Canadian Cardiovascular Society (CCS guidelines 2006)** states as a class I indication that patients with large areas of viability should be evaluated for revascularization.

- **The joint appropriateness criteria published by the ACCF/ASNC/ACR/ASE/SCCT/SCMR/SNM in 2009** assign an appropriate use score of 9 (highest indication) for assessment of myocardial viability in ischemic cardiomyopathy patients with reduced LV function.

- **The CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive imaging** strongly supports (class I recommendation) the use of cardiac PET and CMR in the evaluation and prognostication of patients with ischemic cardiomyopathy and LV dysfunction.
The main value of non-invasive assessment of viability and hibernation is in the more severely and chronically disabled patient, in whom the outcome without intervention is poor but the risk of revascularisation is high.

The likelihood of recovery of function after revascularisation is related to the extent of myocyte injury and the amount of fibrosis.

Association between predicted 3-year mortality and the amount of compromised viable myocardium (ischemic and hibernating) determined by PET/FDG study according to performance of early intervention among all patients.

Revascularization

The potential benefits of revascularization include improvements in:

1) anginal or heart failure symptoms;
2) functional capacity;
3) left ventricular function;
4) electrical stability of the myocardium;
4) long-term prognosis.
Myocardial viability imaging has continually grown together with the concept of hibernation and stunning.

There is credible evidence that in patients with moderate to severe LV dysfunction, myocardial viability is best treated with revascularization for survival benefit.

However, many more issues remain unanswered that impact patient outcomes. Issues such as quality of life, arrhythmic benefit, CCS and NYHA class of symptoms, and health care costs are also important but remain under-investigated.
Figure 1. (a) Death rates for patients with and without myocardial viability treated by revascularization or medical therapy. There is 79.6% reduction in mortality for patients with viability treated by revascularization ($p < 0.0001$). In patients without myocardial viability, there was no significant difference in mortality with revascularization versus medical therapy. (b) Same data as (a) with comparisons based on treatment strategy in patients with and without viability. Annual mortality was lower in revascularized patients when viability was present versus absent (3.2% vs. 7.7%, $p < 0.0001$). Annual mortality was significantly higher in medically treated patients when viability was present versus absent (16% vs. 6.2%, $p = 0.001$). Revasc. = revascularization.
Implications. The results of this meta-analysis suggest that a search for preserved myocardial viability in patients with CAD and significant LV dysfunction using noninvasive imaging techniques identifies patients at substantial risk of death, a risk which may be reduced by successful revascularization. The magnitude of the potential reduction in mortality increases as the severity of LV dysfunction increases. Hence, noninvasive imaging of myocardial viability can be used to inform the often difficult clinical decision regarding revascularization in such patients, providing data on the potential benefit to balance against the known risks.
Optimal diagnostic test for viability assessment:

1. Non-invasive;
2. Accessible;
3. Fast and reproducible;
4. Inexpensive;
5. High diagnostic accuracy;
6. Safe;
7. Differentiate pts who would benefit from revascularization from those who would not.
Nuclear Medicine Study

SPECT (/CT) – PET (/CT)

Viability assessment relies on:

- intact cellular membranes for active uptake of radiotracers: 201-Tl;
- intact sarcolemmas function to maintain electochemical gradients across the cell membrane for radiotracer retention: 99Tc;
- intact glucose uptake: F18-FDG.

<table>
<thead>
<tr>
<th>Method</th>
<th>Major parameter</th>
<th>Assessment of:</th>
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<tbody>
<tr>
<td>Nuclear</td>
<td></td>
<td>Ischemia? Scar?</td>
</tr>
<tr>
<td>Myocardial perfusion imaging (SPECT)</td>
<td>Perfusion, cell membrane integrity</td>
<td>Y</td>
</tr>
<tr>
<td>PET FDG</td>
<td>Perfusion, glucose metabolism</td>
<td>Y</td>
</tr>
<tr>
<td>BMIPP SPECT</td>
<td>Fatty acid metabolism</td>
<td>Y</td>
</tr>
<tr>
<td>Echocardiography</td>
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<td></td>
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<tr>
<td>Dobutamine stress</td>
<td>Regional wall motion, “biphasic” response</td>
<td>Y</td>
</tr>
<tr>
<td>Myocardial contrast echocardiography</td>
<td>Perfusion, regional wall motion</td>
<td>Y</td>
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<tr>
<td>MRI</td>
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<td></td>
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<tr>
<td>Dobutamine stress</td>
<td>Regional wall motion</td>
<td>Y</td>
</tr>
<tr>
<td>Delayed-enhancement (with gadolinium)</td>
<td>Extent/morphology of scar (hyperenhancement)</td>
<td>N</td>
</tr>
<tr>
<td>CT</td>
<td>Perfusion, extent of scar (hyperenhancement)</td>
<td>N</td>
</tr>
</tbody>
</table>

BMIPP β-methyl-p-[123I]-iodophenyl-pentadecanoic acid, CT computed tomography, FDG fluorodeoxyglucose, MRI magnetic resonance imaging, PET positron emission tomography, SPECT single photon emission computed tomography
The mechanism used to assess viability is relevant for understanding the benefits and limitations of each modality:

- Modalities that depend on cell membrane function, a process that occurs early in the underperfused state, show a low likelihood of recovery following revascularization if viability is not present: **HIGH SENSITIVITY**

- Modalities that use contractile function, a change that occurs later in the underperfused state, show a high likelihood of functional recovery if viability is present: **HIGH SPECIFICITY**

Several studies have established that perfusion imaging with SPECT radiotracers is more sensitive and less specific compared to techniques using inotropic contractile reserve assessment in predicting myocardial viability (Bax et al. Curr Probl Cardiol 2001; 26:147–186).
<table>
<thead>
<tr>
<th>Technique</th>
<th>Imaging finding</th>
<th>Criteria for viability</th>
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</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td>Left ventricular wall thickness</td>
<td>&gt;6 mm [9]</td>
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<tr>
<td></td>
<td>Inotropic contractile reserve</td>
<td>Biphasic response better predictive accuracy versus monophasic response [14]</td>
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<tr>
<td></td>
<td>Contrast echocardiography perfusion imaging</td>
<td>No perfusion defect [16]</td>
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<tr>
<td></td>
<td>Strain and strain rate imaging</td>
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<tr>
<td><strong>Cardiac MRI</strong></td>
<td>Left ventricular wall thickness</td>
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<td>Inotropic contractile reserve</td>
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<td>LGE</td>
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<td><strong>Radionuclide techniques</strong></td>
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<td><strong>SPECT</strong></td>
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<td>Redistribution</td>
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<tr>
<td></td>
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<td>Technetium-99m</td>
<td>Perfusion</td>
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<tr>
<td>Nitrate-enhanced perfusion imaging</td>
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<tr>
<td>Low-dose dobutamine</td>
<td>Contractile reserve</td>
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<tr>
<td><strong>PET</strong></td>
<td>Glucose uptake</td>
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<tr>
<td>F-18 FDG</td>
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</table>

_LGE_ late gadolinium enhancement

The techniques of strain and strain rate imaging, 3D echocardiography, BMIPP SPECT, C-11 acetate and palmitate PET, and delayed contrast enhancement using MDCT are currently under investigation and criteria for viability are not well established.
<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Mechanism</th>
<th>Widely Available</th>
<th>Sensitivity (Improvement in regional function)</th>
<th>Specificity (Improvement in regional function)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>Viable myocardial membranes, uptake of tracers</td>
<td>Yes</td>
<td>83-87</td>
<td>54-68</td>
<td>Low cost, Well validated</td>
<td>Long acquisition protocols, Limited spatial resolution, Attenuation artefact, Radiation exposure, Expensive, Radiation exposure, Limited availability</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>Reflects K+ space</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Technitium-99</td>
<td>Reflects mitochondrial integrity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PET</td>
<td>Metabolic imaging–metabolism/perfusion mismatch</td>
<td>No</td>
<td>92</td>
<td>63</td>
<td>Less prone to artefact, Well validated, Excellent for perfusion and viability</td>
<td></td>
</tr>
<tr>
<td>DSE</td>
<td>Wall thickness/cavity size, Contractile reserve – low dose</td>
<td>Yes</td>
<td>74</td>
<td>82</td>
<td>No radiation, Greater spatial resolution than SPECT, Low cost, Can perform perfusion imaging with contrast agents</td>
<td>Inadequate images in up to 20% patients (poor acoustic windows), Attenuation artefact in basal images due to micro-bubbles</td>
</tr>
<tr>
<td>LGE-CMR</td>
<td>Percentage of scar</td>
<td>Yes</td>
<td>84</td>
<td>63</td>
<td>No radiation, Excellent spatial resolution, Reduced temporal resolution compared to DSE, Excellent for concurrent perfusion and viability assessment</td>
<td>Requires centre expertise, Cost, Requires patient co-operation with breath-holding (although new protocols available), Gadolinium risk in ESRF patients, Not possible in patients with intra-cardiac devices</td>
</tr>
<tr>
<td>DSMR</td>
<td>Using end-diastolic wall thickening and improvement in systolic wall thickening</td>
<td>Yes</td>
<td>88</td>
<td>87</td>
<td>Examines contractile recovery, Can be combined with LGE to provide additional information re viability</td>
<td>Same as above except renal CI</td>
</tr>
<tr>
<td>Technique</td>
<td>Author</td>
<td>Year</td>
<td>Imaging Technique</td>
<td>Viability Criterion</td>
<td>Patients Entered</td>
<td>Age (yrs)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>------</td>
<td>------------------------------------</td>
<td>------------------------------</td>
<td>-------------------</td>
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<tr>
<td>Thallium</td>
<td>Gioia (14)</td>
<td>1995</td>
<td>rest/redistribution TI SPECT</td>
<td>TI uptake score</td>
<td>85</td>
<td>65</td>
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<tr>
<td></td>
<td>Gioia (15)</td>
<td>1996</td>
<td>rest/redistribution TI SPECT</td>
<td>rest redistribution</td>
<td>89</td>
<td>69</td>
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<td></td>
<td>Pagley (18)</td>
<td>1997</td>
<td>rest/redistribution planar TI</td>
<td>Viability index 0.67</td>
<td>70</td>
<td>66</td>
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<tr>
<td></td>
<td>Petretta (19)</td>
<td>1997</td>
<td>rest/reinjection TI SPECT</td>
<td>TI uptake score</td>
<td>104</td>
<td>57</td>
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<td></td>
<td>Cuocolo (24)</td>
<td>1998</td>
<td>rest/redistribution TI SPECT</td>
<td>rest redistribution</td>
<td>84</td>
<td>55</td>
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<td></td>
<td>Pasquet (31)</td>
<td>1999</td>
<td>stress/rest/reinjection TI SPECT</td>
<td>TI reversibility</td>
<td>141</td>
<td>62</td>
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<tr>
<td>FDG</td>
<td>Eitzman (8)</td>
<td>1992</td>
<td>FDG PET</td>
<td>flow/FDG mismatch</td>
<td>110</td>
<td>59</td>
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<td></td>
<td>Tamaki (9)</td>
<td>1993</td>
<td>stress redistribution TI SPECT/</td>
<td>FDG uptake</td>
<td>158</td>
<td>60</td>
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<td></td>
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<td></td>
<td>FDG PET</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Yoshida (10)</td>
<td>1993</td>
<td>rubidium/FDG PET</td>
<td>Rubidium/FDG uptake</td>
<td>35</td>
<td>54</td>
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<td>Dreyfus (12)</td>
<td>1994</td>
<td>rest redistribution TI SPECT/</td>
<td>rest redistribution/FDG</td>
<td>50</td>
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<td>FDG PET</td>
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<td>Di Carli (11)</td>
<td>1994</td>
<td>FDG PET</td>
<td>flow/FDG mismatch</td>
<td>107</td>
<td>65</td>
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<td></td>
<td>Lee (13)</td>
<td>1994</td>
<td>FDG PET</td>
<td>flow/FDG mismatch</td>
<td>137</td>
<td>62</td>
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<tr>
<td></td>
<td>Haas (17)</td>
<td>1997</td>
<td>FDG PET</td>
<td>FDG uptake</td>
<td>34</td>
<td>62</td>
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<tr>
<td></td>
<td>Vom Dahl (20)</td>
<td>1997</td>
<td>mibi SPECT/FDG PET</td>
<td>flow/FDG mismatch</td>
<td>161</td>
<td>57</td>
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<tr>
<td></td>
<td>Di Carli (25)</td>
<td>1998</td>
<td>FDG PET</td>
<td>flow/FDG mismatch</td>
<td>93</td>
<td>68</td>
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<tr>
<td></td>
<td>Beanlands (23)</td>
<td>1998</td>
<td>mibi SPECT/FDG PET</td>
<td>viability score</td>
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<td>62</td>
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<td></td>
<td>Huitink (26)</td>
<td>1998</td>
<td>rest planar TI and FDG</td>
<td>flow/FDG mismatch</td>
<td>59</td>
<td>61</td>
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<td>Echocardiography</td>
<td>Williams (16)</td>
<td>1996</td>
<td>DASE</td>
<td>regional wall motion</td>
<td>136</td>
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<td>Afridi (21)</td>
<td>1998</td>
<td>DASE</td>
<td>“</td>
<td>353</td>
<td>64</td>
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<td>Anselmi (22)</td>
<td>1998</td>
<td>LDDE</td>
<td>“</td>
<td>210</td>
<td>59</td>
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<td>Meluzin (27)</td>
<td>1998</td>
<td>LDDE</td>
<td>“</td>
<td>274</td>
<td>58</td>
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<td></td>
<td>Smart (33)</td>
<td>1999</td>
<td>DASE</td>
<td>“</td>
<td>350</td>
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<td>1999</td>
<td>LDDE</td>
<td>“</td>
<td>87</td>
<td>62</td>
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<td>Bax (30)</td>
<td>1999</td>
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<td></td>
<td></td>
<td></td>
<td>3,088</td>
<td>61</td>
</tr>
</tbody>
</table>

DASE = dobutamine/atropine stress echocardiography; FDG = F-18 fluorodeoxyglucose; LDDE = low-dose dobutamine echocardiography; mibi = Tc-99m sestamibi; PET = positron emission tomography; SPECT = single photon emission computed tomography; TI = thallium.
Abstract

BACKGROUND—The assessment of myocardial viability has been used to identify patients with coronary artery disease and left ventricular dysfunction in whom coronary-artery bypass grafting (CABG) will provide a survival benefit. However, the efficacy of this approach is uncertain.

METHODS—In a substudy of patients with coronary artery disease and left ventricular dysfunction who were enrolled in a randomized trial of medical therapy with or without CABG, we used single-photon-emission computed tomography (SPECT), dobutamine echocardiography, or both to assess myocardial viability on the basis of pre-specified thresholds.

RESULTS—Among the 1212 patients enrolled in the randomized trial, 601 underwent assessment of myocardial viability. Of these patients, we randomly assigned 298 to receive medical therapy plus CABG and 303 to receive medical therapy alone. A total of 178 of 487 patients with viable myocardium (37%) and 58 of 114 patients without viable myocardium (51%) died (hazard ratio for death among patients with viable myocardium, 0.64; 95% confidence interval [CI], 0.48 to 0.86; P = 0.003). However, after adjustment for other baseline variables, this association with mortality was not significant (P = 0.21). There was no significant interaction between viability status and treatment assignment with respect to mortality (P = 0.53).

CONCLUSIONS—The presence of viable myocardium was associated with a greater likelihood of survival in patients with coronary artery disease and left ventricular dysfunction, but this relationship was not significant after adjustment for other baseline variables. The assessment of myocardial viability did not identify patients with a differential survival benefit from CABG, as compared with medical therapy alone. (Funded by the National Heart, Lung, and Blood Institute; STICH [ClinicalTrials.gov number, NCT00023595].)
Figure 1. Kaplan–Meier Analysis of the Probability of Death, According to Myocardial Viability Status

The comparison that is shown has not been adjusted for other prognostic baseline variables. After adjustment for such variables on multivariable analysis, the between-group difference was not significant (P = 0.21).

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>No. at Risk Without viability</th>
<th>No. at Risk With viability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>114</td>
<td>487</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>432</td>
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<tr>
<td></td>
<td>85</td>
<td>409</td>
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<td></td>
<td>80</td>
<td>371</td>
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<tr>
<td></td>
<td>63</td>
<td>294</td>
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<tr>
<td></td>
<td>36</td>
<td>188</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>102</td>
</tr>
</tbody>
</table>
Myocardial viability testing: Still viable after stich?

treat) or to the treatment actually received. The STICH data indicate that in patients with CAD and severe LV dysfunction, assessment of myocardial viability does not identify patients who will have the greatest survival benefit from adding CABG to aggressive medical therapy. The implications are that viability testing should not be considered a prerequisite for decisions regarding medical vs surgical management in such patients. Imaging should be reserved for those patients in whom management decisions are difficult in view of age, comorbidities, or complex coronary anatomy, and in whom additional information may be necessary to guide therapy recommendations.
Multimodality imaging in the assessment of myocardial viability

Sara L. Partington · Raymond Y. Kwong · Sharmila Dorbala

Table 2 Pooled analysis of different modalities of viability for predicting improvement in segmental LV function

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Weighted mean sensitivity (%)</th>
<th>Weighted mean specificity (%)</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine echocardiography(^a)</td>
<td>80</td>
<td>78</td>
<td>83</td>
<td>75</td>
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<tr>
<td>Thallium-201(^b)</td>
<td>87</td>
<td>54</td>
<td>79</td>
<td>67</td>
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<tr>
<td>Technetium-99m</td>
<td>83</td>
<td>65</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>FDG PET</td>
<td>92</td>
<td>63</td>
<td>87</td>
<td>74</td>
</tr>
<tr>
<td>CMR diastolic wall &lt;6 mm</td>
<td>95</td>
<td>41</td>
<td>92</td>
<td>56</td>
</tr>
<tr>
<td>CMR dobutamine stress</td>
<td>74</td>
<td>82</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>CMR LGE</td>
<td>84</td>
<td>63</td>
<td>78</td>
<td>72</td>
</tr>
</tbody>
</table>

Reproduced with permission from Schinkel et al. [15]

NPV negative predictive value, PPV positive predictive value

\(^a\) High-dose dobutamine has a higher sensitivity but similar specificity to low-dose dobutamine

\(^b\) Thallium rest distribution has a higher specificity but similar sensitivity compared to Thallium reinjection
Quantitative nature. Superior detection sensitivity and advantageous spatial and temporal resolution over conventional nuclear techniques; PET has been considered a “gold standard” for non-invasive assessment of myocardial perfusion and viability.
PET > SPECT

- The spatial resolution of PET is currently in the range of 3 to 5 mm, superior to conventional nuclear imaging techniques.

- PET has high temporal resolution, which allows for creation of dynamic imaging sequences to describe tracer kinetics.

- PET is a truly quantitative imaging tool that measures absolute concentrations of radioactivity in the body and allows for kinetic modeling of physiologic parameters such as absolute myocardial blood flow quantitation or glucose use.
• Despite its value as a high-end diagnostic tool, PET has struggled for many years to expand from its role as a reference standard to broader clinical applications.

• Impeding factors have been the complexity and limited availability of PET cameras, the complexity of production and delivery of short-lived positron-emitting radiotracers, and concerns related to the high cost.
Role of F-18 FDG Positron Emission Tomography (PET) in the Assessment of Myocardial Viability

Munir Ghesani, M.D.,* E. Gordon DePuey, M.D.,* and Alan Rozanski, M.D.†

Diagnostic Accuracy of Positron Emission Tomography Blood Flow-\(^{18}\)F-2-Deoxyglucose Studies for Recovery of Regional Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Number of segments</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tillisch(^{18})</td>
<td>17</td>
<td>67</td>
<td>95</td>
<td>80</td>
<td>85</td>
<td>93</td>
<td>88</td>
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<td>Tamaki(^{19})</td>
<td>22</td>
<td>48</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Tamaki(^{74})</td>
<td>11</td>
<td>58</td>
<td>100</td>
<td>38</td>
<td>80</td>
<td>100</td>
<td>82</td>
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<td>Marwick(^{75})</td>
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<td>85</td>
<td>71</td>
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<td>79</td>
<td>74</td>
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<td>Lucignani(^{41})</td>
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<td>54</td>
<td>82</td>
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<td>Carrel(^{76})</td>
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<td>23</td>
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<td>Gropier(^{51,52})</td>
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<td>118</td>
<td>83</td>
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<td>52</td>
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<td>63</td>
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<td>Knuuti(^{77})</td>
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<td>Tamaki(^{78})</td>
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<td>130</td>
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<td>82</td>
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<td>Maes(^{79})</td>
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<td>Gerber(^{80})</td>
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<td>75</td>
<td>67</td>
<td>78</td>
<td>67</td>
<td>71</td>
</tr>
</tbody>
</table>

WMA = wall motion abnormalities prior to coronary revascularization; PPV = positive predictive value; NPV = negative predictive value.
Reproduced with permission from Vasken Dilsizian, M.D.\(^{81}\)
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
But cardiac PET..... is cost-effective?
**Objectives**
We conducted a randomized trial to assess the effectiveness of F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET)-assisted management in patients with severe ventricular dysfunction and suspected coronary disease.

**Background**
Such patients may benefit from revascularization, but have significant perioperative morbidity and mortality. F-18-fluorodeoxyglucose PET can detect viable myocardium that might recover after revascularization.

**Methods**
Included were patients with severe left ventricular (LV) dysfunction and suspected coronary disease being considered for revascularization, heart failure, or transplantation work-ups or in whom PET was considered potentially useful. Patients were stratified according to recent angiography or not, then randomized to management assisted by FDG PET (n = 218) or standard care (n = 212). The primary outcome was the composite of cardiac death, myocardial infarction, or recurrent hospital stay for cardiac cause, within 1 year.

**Results**
At 1 year, the cumulative proportion of patients who had experienced the composite event was 30% (PET arm) versus 36% (standard arm) (relative risk 0.82, 95% confidence interval [CI] 0.59 to 1.14; p = 0.16). The hazard ratio (HR) for the composite outcome, PET versus standard care, was 0.78 (95% CI 0.58 to 1.1; p = 0.15); for patients that adhered to PET recommendations for revascularization, revascularization work-up, or neither, HR = 0.62 (95% CI 0.42 to 0.93; p = 0.019); in those without recent angiography, for cardiac death, HR = 0.4 (95% CI 0.17 to 0.96; p = 0.035).

**Conclusions**
This study did not demonstrate a significant reduction in cardiac events in patients with LV dysfunction and suspected coronary disease for FDG PET-assisted management versus standard care. In those who adhered to PET recommendations and in patients without recent angiography, significant benefits were observed. The utility of FDG PET is best realized in this subpopulation and when adherence to recommendations can be achieved.

(J Am Coll Cardiol 2007;50:2002–12) © 2007 by the American College of Cardiology Foundation
In conclusion, the data suggest that many patients with severe LV dysfunction and suspected CAD might not always benefit from FDG PET imaging. However, there is potential value for FDG PET, particularly in a high-risk patient population where decisions for therapy are most difficult. When patients adhere to FDG PET recommendations, a reduction in events might be realized.

This subsequently led to a sub-study (Ottawa-Five) published recently which was a post hoc analysis in centres with clinical expertise, readily available FDG-PET and integration with clinical teams [13]. Indeed this post hoc analysis showed significant reduction in cardiac events in the FDG-PET arm, suggesting (although not proving) that viability testing may yet have a key role in decisions regarding revascularisation.
Conclusions

One of the main management decisions in CAD concerns which patients and lesions should be revascularised. Complex revascularisation can potentially carry a high risk to patients, and so it seems intuitive that in complex patients with coronary artery disease and akinetic LV segments or more generalised LV impairment, information from imaging techniques which accurately define LV function, viability and ischaemia might be incrementally important in informing clinical decision making. However, whether or not decision making supported by viability assessment improves clinical outcomes compared with decision making based upon the history and the coronary angiogram alone remains to be clarified. Larger randomised trials (where the use or non-use of imaging itself is randomised), with ‘hard’ clinical outcome end-points, are needed to answer this question. Furthermore, with increasing pressure on the health care dollar, comparative imaging studies, tailored to clinical outcome, cost-effectiveness and comparative effectiveness end-points are need to be performed in the assessment of myocardial viability.
Conclusions

The most common techniques used for the assessment of myocardial viability are SPECT myocardial perfusion imaging, FDG PET, dobutamine echocardiography, and DE-MRI. Each of these techniques has been validated for prediction of functional ventricular recovery after revascularization in patients with ischemic cardiomyopathies. Data on clinical outcomes are strongest for the nuclear and echocardiographic techniques, and are emerging for MRI. In particular, PET is arguably the most established technique, with the greatest amount of data on functional recovery and clinical outcomes. Most of the outcomes data are primarily observation studies, and randomized studies comparing the various imaging modalities with regard to clinical outcomes are lacking. The preponderance of data strongly suggests that viability testing has a significant role in the assessment of patients with ischemic cardiomyopathy, potentially guiding therapeutic decisions and assessing prognosis.
Hybrid Imaging is possible.

The most accurate non invasive way to evaluate CHD.

Provides anatomic and functional information.

Great Improvement in diagnostic Accuracy.
Dilated cardiomyopathy (DCM)
Hypertrophic cardiomyopathy (HCM)
Restrictive cardiomyopathy (RCM)
Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
Unclassified cardiomyopathies
99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc DPD) scintigraphy
(1) acquired monoclonal immunoglobulin light chain amyloidosis (AL), characterized by clonal plasma cells in the bone marrow which produce the immunoglobulin light chains of the fibrillar deposits;
(2) the hereditary, transthyretin-related form (ATTR), which can be caused by over 100 mutations of transthyretin (TTR), a transport protein mainly synthesized by the liver;
(3) wild-type (non-mutant) transthyretin-related amyloidosis (systemic “senile” amyloidosis, SSA), which mainly affects the hearts of elderly men.

AL cardiac amyloidosis is twofold: treatment of the heart failure and treatment of the underlying plasma cell dyscrasia. This requires chemotherapy TTR is primarily formed in the liver, orthotopic liver transplantation is a rational and effective treatment for ATTR Treatment of SSA is normally restricted to symptom relief with conventional heart failure therapy. However, some younger SSA patients may be eligible for heart transplantation
(99mTc DPD) Retention

Innervation Autonomica

- Sympathetic nervous system
  - Mesencephalus
  - Pons
  - Medulla obl.
  - Superior cervical ganglion
  - Stellate ganglion
  - Celiac ganglion
  - Superior mesenteric ganglion
  - Inferior mesenteric ganglion
  - Sympathetic trunk

- Parasympathetic nervous system
  - Tear and salivary gland
  - Lung
  - Stomach
  - Pancreas
  - Small intestine
  - Large intestine, rectum
  - Bladder
  - Reproductive organs

- Vagus n. (X)
neurotransmitters

Active on recettori adrenergic & muscarinic receptor with stimulating or inhibiting effects

ACH

NORADRENALINE (sympathetic)

ACETILCHOLINE (sistema parasimpasthetic)
Imaging of cardiaca neurotransmission

- picomolar NA concentration in synaptic cleft

Pect and PET are the only imaging modalities
<table>
<thead>
<tr>
<th>Tracer</th>
<th>SPECT/ PET</th>
<th>Metabolized by MAO</th>
<th>Development Stage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-123 metaiodobenzylguanidine (MIBG)</td>
<td>SPECT</td>
<td>No</td>
<td>Clinical</td>
<td>Most extensively studied, wide potential clinical applications. Limitations from normal variants and attenuation as a SPECT agent</td>
</tr>
<tr>
<td>C-11 metahydroxyephedrine (HED)</td>
<td>PET</td>
<td>No</td>
<td>Clinical</td>
<td>Most widely used PET tracer. More homogenous uptake than MIBG, with fewer inferior defects in normal patients</td>
</tr>
<tr>
<td>C-11 epinephrine</td>
<td>PET</td>
<td>Yes</td>
<td>Clinical</td>
<td>A more physiologic tracer for evaluation of presynaptic function with respect to uptake, vesicular storage, and metabolism</td>
</tr>
<tr>
<td>C-11 phenylephrine</td>
<td>PET</td>
<td>Yes</td>
<td>Clinical</td>
<td>Vesicular storage necessary to protect from rapid metabolism by neuronal MAO. Potential use to assess function/impairment of vesicular storage function</td>
</tr>
<tr>
<td>F-18 6-fluorodopamine</td>
<td>PET</td>
<td>Yes</td>
<td>Clinical</td>
<td>Had been used mainly to identify cardiac involvement from neurologic diseases. Allows assessment of uptake and washout of NE. Difficult to produce</td>
</tr>
<tr>
<td>F-18 6-fluormetaraminol</td>
<td>PET</td>
<td>Yes</td>
<td>Experimental</td>
<td>Low specific activity. Potent vasoactive properties</td>
</tr>
<tr>
<td>F-18 (-)-6-fluoronorepinephrine</td>
<td>PET</td>
<td>Yes</td>
<td>Experimental</td>
<td>High cardiac uptake and retention shown in baboons</td>
</tr>
<tr>
<td>F-18 para-fluorobenzylguanidine (PFBG)</td>
<td>PET</td>
<td>No</td>
<td>Experimental</td>
<td>PET analog of $^{123}$I-MIBG, with potential for quantitation. Considerable nonneuronal retention by uptake-2 mechanism. May depend less on flow for uptake</td>
</tr>
<tr>
<td>F-18 fluoriodobenzylguanidine</td>
<td>PET</td>
<td>No</td>
<td>Experimental</td>
<td>Greater lipophilicity than PFBG—more similar to MIBG</td>
</tr>
<tr>
<td>Br-76 metabolomobenzylguanidine</td>
<td>PET</td>
<td>No</td>
<td>Experimental</td>
<td>Low uptake-1 selectivity</td>
</tr>
</tbody>
</table>
Metaiodobenzylguanidina (\(^{123}\)I-MIBG)
(Wieland, University Michigan Medical Center 1980)

- False neurotransmitter
- Iodinated Analogue of guanetidine and of NA
- Share with NA same reuptake mechanisms (uptake-1, anche uptake-2)

After i.v. MIBG injection diffuses in the synaptic cleft, than accumulates in vesiculae (uptake 1) with a higher concentration than NA.

Non viene metabolizzata dal Not metabolized by MAO system and Cathecolamine transferases.

Correlation with cardiac density of cardiac innervation.
Patient preparation

- fasting from midnight

Pharmacological interferences with:

**Anti ipertensivi**
- Reserpina
- Guanetidina
- Labetalolo

**Opioids**
- Cocaine

**Tricyclic antidepressant**

**Anti psycotics**
- Fenothiazines, thioxantines
- Butirrofenoni
- Sympathomimetic inhalators: anphetamine, dopamine
Tracer injection

- Thyroid uptake block 30 min before injection (KCl) (ADMIRE-HF clinical trial optional)

- Patient at rest for 15'

-slow injection (1-2 min). 185-370 Mbq (±10%) $^{123}$I-MIBG (ADMIRE-HF = 370±10% MBq). Flush with 10 ml saline
Planar acquisition:

- 15-20 min and 4 hours planar acquisition (10 min)
- SPECT (20 min) after planar
- Tra lefastinf and resting between the two acquisition.
Which parameter are useful?

**4h CARDIAC GLOBAL UPTAKE (planar ant)**
Distributor of cardiac sympathetic nervous fibers and uptake-1 function

H/M ratio 1.9-2.8 (<1.6 negative prognostic impact)

**4h CARDIAC GLOBAL WASHOUT (planar ant)**
Measure of myocardium capacity to retain MIBG (10%±9%)
(>27% poor prognosis)

**REGIONAL CARDIAC (UPTAKE SPECT)**
Heterogeneous uptake may indicate arrhythmia risk (no norma limits available)
different methods, similar results

Valori normal values (1.9-2.8)
media di circa 2.2

heart ROI – ROI mediastinum / ROI mediastinum)
<table>
<thead>
<tr>
<th>administered activity</th>
<th>370 MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>early acquisition time</td>
<td>28-11-06 10:51</td>
</tr>
<tr>
<td>late acquisition time</td>
<td>28-11-06 14:47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>method 1</th>
<th>early heart</th>
<th>mediastinum</th>
<th>late heart</th>
<th>mediastinum</th>
<th>method 3</th>
<th>early heart</th>
<th>mediastinum</th>
<th>late heart</th>
<th>mediastinum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>107306</td>
<td>71225</td>
<td>58279</td>
<td>49346</td>
<td>Totale</td>
<td>715328</td>
<td>71225</td>
<td>419205</td>
<td>49346</td>
</tr>
<tr>
<td>min</td>
<td>527</td>
<td>298</td>
<td>268</td>
<td>202</td>
<td>min</td>
<td>363</td>
<td>298</td>
<td>215</td>
<td>202</td>
</tr>
<tr>
<td>max</td>
<td>768</td>
<td>446</td>
<td>420</td>
<td>322</td>
<td>max</td>
<td>768</td>
<td>446</td>
<td>420</td>
<td>322</td>
</tr>
<tr>
<td>Area</td>
<td>167</td>
<td>192</td>
<td>168</td>
<td>193</td>
<td>Area</td>
<td>1330</td>
<td>192</td>
<td>1347</td>
<td>193</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>decay corrected counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>method 1</td>
</tr>
<tr>
<td>CD/MBq</td>
</tr>
</tbody>
</table>

Cardiac I-123 MIBG

<table>
<thead>
<tr>
<th>parameter</th>
<th>method 1</th>
<th>Media ± SD</th>
<th>method 3</th>
<th>Media ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washout</td>
<td>33,6%</td>
<td>23,0 ± 6,4</td>
<td>28,9%</td>
<td>22,3 ± 8,1</td>
</tr>
<tr>
<td>H</td>
<td>early</td>
<td>1,74 ± 0,29</td>
<td>1,45 ± 0,43</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>late</td>
<td>1,15 ± 0,22</td>
<td>1,03 ± 0,30</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>early</td>
<td>1,00 ± 0,12</td>
<td>1,00 ± 0,15</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>late</td>
<td>0,85 ± 0,10</td>
<td>0,85 ± 0,10</td>
<td></td>
</tr>
<tr>
<td>H/M</td>
<td>early</td>
<td>1,73 ± 0,14</td>
<td>1,45 ± 0,30</td>
<td></td>
</tr>
<tr>
<td>H/M</td>
<td>late</td>
<td>1,36 ± 0,16</td>
<td>1,22 ± 0,17</td>
<td></td>
</tr>
</tbody>
</table>
$^{123}$I-MIBG planar

NORMAL

H/M = 2.47

CHF

H/M = 1.56

(4h imaging)
$^{123}$I-MIBG SPECT

NORMAL

CHF

Imaging a 4h
123I-MIBG e scompenso cardiaco utilità prognostica?
Cardiac function impairment

SAS Activation

RAS Activation

release of vasoactive mediators: Endothelin, vasopressin, cytokine

Downregulation Remodelling Fibrosis Apoptosis Necrosis
At cellular level?

- **Early phases:** NA release in the synaptic cleft and increased NET1 uptake

- **Late:** Down-regulation of NET1, further increase of NA synaptic concentration

- **End stage:** Reduction of synaptic function (intact presynaptic fibers, dysfunctional) Low MIBG uptake di (low H/M ratio and increased washout rate)

*Chen et al; J Nucl Cardiol 2005*
A) Late H/M rate = 2.2  
WR = 15%  

Normale

B) Late H/M rate = 1.7  
WR = 25%  

NYHA II

C) Late H/M rate = 1.1  
WR = 40%  

NYHA IV

*Carrio, I. et al. J Am Coll Cardiol Img 2010;3:92-100*
Valore prognostico H/M ratio

- 90 pazienti (HF moderato e severo)
- LVEF < 45% (media 22%)
- H/M < 1.2
(sopravvivenza a 6 e 12 mesi del 60 e 40% rispettivamente paragonati al 100% di sopravvivenza a 12 mesi per i pazienti che avevano H/M superiori)

Merlet et al; J Nucl Med 1992
Merlet et al; J Nucl Med 1999
Ogita et al; Heart 2001

20 NC  WR 9.6±8.5  2SD=27%

79 pts CHF  LVEF < 40%

Gruppo 1 (WR ≥ 27%)
Gruppo 2 (WR < 27%)

123I-MIBG washout rate prognostic value
I-123-mIBG myocardial imaging for assessment of risk for a major cardiac event in heart failure patients: insights from a retrospective European multicenter study.

**Table:**

<table>
<thead>
<tr>
<th>H/M Ratio</th>
<th>Number of Patients</th>
<th>Transplants (row %)</th>
<th>SCD and arrhythmic events (row %)</th>
<th>HF and other cardiac deaths (row %)</th>
<th>Total MCEs (row %)</th>
<th>2-year event-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.45</td>
<td>71</td>
<td>25 (35)</td>
<td>1 (1)</td>
<td>8 (11)</td>
<td>34 (48)</td>
<td>52</td>
</tr>
<tr>
<td>1.46–1.74</td>
<td>74</td>
<td>12 (16)</td>
<td>7 (9)</td>
<td>2 (3)</td>
<td>21 (28)</td>
<td>72</td>
</tr>
<tr>
<td>1.75–2.17</td>
<td>72</td>
<td>6 (8)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>11 (15)</td>
<td>85</td>
</tr>
<tr>
<td>≥2.18</td>
<td>73</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>99</td>
</tr>
<tr>
<td>Total</td>
<td>290</td>
<td>44 (15)</td>
<td>10 (3)</td>
<td>13 (8)</td>
<td>67 (23)</td>
<td>99</td>
</tr>
</tbody>
</table>

**Figure:**

- LVEF ≤35%
  - NYHA II-III
  - N=182

13% of ICD candidates

**Graphs:**

- Studio multicentrico (6 centri)
  - 290 pts HF; NYHA II-IV

**Text:**

**Agostini et al; EJNM 2008**
New risk stratification evidence from the ADMIRE-HF study\textsuperscript{18}

Adreview Myocardial Imaging for Risk Evaluation in Heart Failure
ADMIRE-HF objective

Primary objective

• To demonstrate the prognostic value of the H/M ratio of 123I-MIBG for identifying subjects at higher risk of an adverse cardiac event

Secondary objectives

• To quantify the risks for adverse cardiac events due to heart failure and arrhythmias
• To assess myocardial sympathetic innervation H/M ratio as a continuous variable
ADMIRE-HF endpoints\textsuperscript{18}

Composite primary endpoint

- Occurrence of any of the following 3 categories of adverse cardiac events
  - Heart failure progression,
  - arrhythmia and
  - cardiac death

Defined by the time to first event in relation to the H/M ratio

Secondary endpoint

- Any secondary event following a first event of heart failure progression or arrhythmia
- Defined by the time to secondary event for all unique events in relation to H/M ratio
ADMIRE-HF adverse cardiac events\textsuperscript{18}

**Heart failure progression**

- Progression of heart failure stage from one NYHA class to the other
- NYHA II to III or IV – NYHA III to IV

**Life threatening arrhythmia**

- Sustained ventricular tachyarrhythmia
- Appropriate ICD discharge
- Aborted cardiac arrest

**Terminal cardiac death**

- Sudden Cardiac Death
- Progressive heart failure death
- Myocardial Infarction
- Cardiac surgery complication
### ADMIRE-HF patients characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yr)</td>
<td>62.4</td>
<td>20-90</td>
</tr>
<tr>
<td>Gender (M/F) (%)</td>
<td>80/20</td>
<td>-</td>
</tr>
<tr>
<td>Race (White/Black/Other) (%)</td>
<td>75/14/11</td>
<td>-</td>
</tr>
<tr>
<td>NYHA II/III (%)</td>
<td>83/17</td>
<td>-</td>
</tr>
<tr>
<td>HF Etiology (I/NI) (%)</td>
<td>66/34</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>I=Ischemic; NI=Non-ischemic</td>
<td></td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>27</td>
<td>5-35</td>
</tr>
<tr>
<td>Median Follow-up (mo)</td>
<td>17</td>
<td>0.1-27</td>
</tr>
<tr>
<td>ACE Inhibitor*/ARB** (%)</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Beta Blocker (%)</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>ARA*** (%)</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>2-year mortality rate (%)</td>
<td>12.8</td>
<td>-</td>
</tr>
</tbody>
</table>

*ACE inhibitors: Angiotensin Converting Enzyme Inhibitors  
**ARB: Angiotensin Receptor Blockers  
***ARA: Aldosterone Receptor Antagonist
ADMIRE-HF supports a cut-off value for stratifying the risk of an adverse cardiac event

H/M ratio $\geq 1.6$ – low risk
H/M ratio $< 1.6$ – high risk
Kaplan-Meier estimates of ACE free probability

H/M ratio

237 subjects had an adverse cardiac event on primary analysis

Separation from groups is evident within the first two months

35\%^{21} greater probability of not experiencing an adverse cardiac event for patients with an H/M ratio ≥1.6 vs. those with H/M ratio <1.6

*\textit{p}=0.0001 vs H/M ratio≥1.60

ACE free probability (%)

H/M ratio ≥1.60; ACE free probability = 85%

H/M ratio <1.60; ACE free probability = 63%

Time (months)

\begin{tabular}{|c|c|}
\hline
H/M ratio & ACE free probability (%) \\
\hline
≥1.60 & 85\% \\
<1.60 & 63\% \\
\hline
\end{tabular}
Greater arrhythmia-free survival at 2 years for patients with H/M ratio ≥1.60 vs. those with H/M ratio of <1.60

Kaplan-Meier estimates of arrhythmia free probability

H/M ratio

64 patients had an arrhythmia on secondary analysis

*P = 0.002 vs H/M ratio ≥1.60

H/M ratio ≥1.60: 2-year event-free survival 96%

H/M ratio <1.60: 2-year event-free survival 85%*

Negative Predictive Value of arrhythmia likelihood is 96%
NPV 96% for arrhythmias

201 subjects 6 arrhythmias

760 subjects 58 arrhythmias

Greater arrhythmia-free survival at 2 years for patients with H/M ratio ≥1.60 vs. those with H/M ratio of <1.60
Kaplan-Meier estimates of ACE incidence\textsuperscript{21}

LVEF

LVEF 30% MADIT II threshold on ACE

LVEF 30% threshold does risk-stratify…as known and expected\textsuperscript{21}

\textbf{LVEF 30% threshold does risk-stratify…as known and expected}\textsuperscript{21}
Kaplan-Meier estimates of ACE incidence
H/M ratio vs. LVEF

H/M ratio 1.6 ADMIRE-HF threshold vs. LVEF 30% MADIT II threshold on ACE

H/M ratio 1.6 threshold provides additional prognostic information over EF 30% threshold

DoF
Kaplan-Meier estimates of ACE incidence
H/M ratio vs. BNP
H/M ratio 1.6 ADMIRE-HF threshold vs. BNP 140 ng/l threshold on ACE

H/M ratio 1.6 threshold provides additional prognostic information over BNP 140 ng/l threshold21

ACE Cumulative incidence (%) vs. Months

BNP>140 ng/l, H/M<1.60*

BNP≤140 ng/l, H/M<1.60†

BNP>140 ng/l, H/M≥1.60*

BNP≤140 ng/l, H/M≥1.60†

*p=0.004  †p=0.041

406 subjects  146 events
326 subjects  60 events
57 subjects  9 events
137 subjects  15 events

Months
The main findings of the study can be summarized as follows. Late 123-I MIBG SPECT defect score was an independent predictor for ventricular arrhythmias causing appropriate ICD therapy (primary end point) as well as the composite of appropriate ICD therapy or cardiac death (secondary end point). In addition, cumulative event rates for appropriate ICD therapy (52% vs. 5%, p < 0.01) and appropriate ICD therapy or cardiac death (57% vs. 10%, p < 0.01) were significantly higher in patients with a large late 123-I MIBG SPECT defect (summed score >26) as compared with patients with a small late 123-I MIBG SPECT defect (summed score ≤26) at 3-year follow-up. Importantly, only 2 (3%) patients with a small late 123-I MIBG SPECT defect received appropriate ICD therapy during follow-up.
Increase in the Use of Implantable Cardioverter-Defibrillators (ICDs) in the United States

Age and sex standardised ratios of implantable cardioverter defibrillator (ICD) use and standardised mortality ratios for ischaemic heart disease (IHD SMR) in English health regions, 1998-2000

The crude rate of implantation of new ICD in UK rose from 12.4 per million in 1998 to 30 per million in 2002.

Significant regional differences in standardized rates of implantation (p=0.005).

Differences between implantation and need in five out of eight Regions suggested inequity.
Cardiac autonomic neuropathy in patients with diabetes and no symptoms of coronary artery disease: comparison of $^{123}$I-metiodobenzylguanidine myocardial scintigraphy and heart rate variability

Arthur J. H. A. Scholte, Joanne D. Schrijff, Victoria Delgado, Jurriaan A. Kok, Mieke T. J. Bus, Arie C. Maan, Marcel P. Stokkel, Antje V. Kharagitsingh, Petra Dibbets-Schneider, Ernst E. van der Wall, Jeroen J. Bax

A composite endpoint (HMR <1.8, WR >25%, or TDS >13) was used to define an abnormal $^{123}$I-mIBG study.

Results The prevalence of CAN in patients asymptomatic for CAD with type 2 diabetes and normal myocardial perfusion assessed by HRV and $^{123}$I-mIBG scintigraphy was respectively, 27% and 58%. Furthermore, in almost half of

Fig. 6 Agreement and disagreement between HRV and $^{123}$I-mIBG scintigraphy for the assessment of CAN

Fig. 1 Pie chart showing the location of the innervation defects on $^{123}$I-mIBG myocardial scintigraphy
$^{123}\text{I-MIBG}$

e

monitoraggio della risposta

alla terapia

nei pazienti con

insufficienza cardiaca
Efficacy of Beta-blockers on Cardiac Function and Cardiac Sympathetic Nerve Activity in Patients with Dilated Cardiomyopathy

Effects of carvedilol on myocardial sympathetic innervation in patients with chronic heart failure

multicenter study
- 64 CHF pts
- before and after 6 month therapy with carvedilol v.s. placebo

Results: $^{123}\text{I-MIBG}}$ uptake (planar & SPECT) $<$ EDV $>$ LVEF

Effect of Carvedilol on Cardiac 123I-MIBG Uptake in Patients with Dilated CM

22 patients Class II, III, IV CHF

Gerson et al. J Nucl Cardiol 2002

Nessuna chiara relazione con miglioramento della LVEF

Gerson et al. J Nucl Cardiol 2002
Altri farmaci che migliorano i parametri MIBG

- ACE-I
- ARB
- Spironolattone
- Amiodarone
Farmaci che influenzano il sistema RAS

- **Takeishi et al (J Nucl Med 1997)**
  19 pazienti; classe NYHA II-III; trattati con enalapril
  incremento H/M r; riduzione WR

- **Toyama et al (J Nucl Med 1999)**
  - 24 pazienti con cardiomiopatia dilatativa trattati con ACE-I
  - incremento H/M r

  aggiungendo un sartanico all’ACE-I
  miglioramento della captazione di 123I-mIBG (H/Mr; WR)
  incremento della LVEF
  miglioramento NYHA
Lo studio dell’innervazione cardiaca con $^{123}$I-MIBG potrebbe essere utile ad identificare i soggetti che non rispondono in modo soddisfacente alla terapia medica e quindi guidare l’utilizzo di interventi terapeutici più invasivi e costosi. Migliorando la prognosi?
- 85 pazienti con cardiomiopatia dilatativa
- LVEF<45%

tra 19 parametri (clinici, sierici e di imaging) il peggioramento del H/M r dopo 6 mesi di terapia medica era il maggiore fattore predittivo di morte

sensibilità 92%
specificità 73%
Cardiac sympathetic activity pre and post resynchronization therapy evaluated by 123I-MIBG myocardial scintigraphy

- 30 pazienti CHF
- NYHA III-IV
- in terapia medica
- candidabili a CRT

H/M r > 1.36

Fattore predittivo di risposta alla CRT

sensitivity 75%
specificity 71%

D’Orio Nishioka et al; J Nucl Cardiol 2007
Identificazione dei pazienti a rischio di morte improvvisa che necessitano di un ICD
Nel 50 % dei pazienti con CHF la morte è improvvisa per TV o FV

Meccanismi complessi, multifattoriali e non completamente conosciuti

Difficile identificare i pazienti a rischio, ma il SAS gioca un ruolo importante (il miocardio denervato, ma vitale può essere a rischio)

La $^{123}$I-MIBG potrebbe identificare i pazienti a rischio di aritmia e SCD e quindi selezionare quelli che potrebbero trarre maggior beneficio dall’impianto di un ICD
- 17 pazienti CHF;
- ICD
- NYHA IV

- H/M r < 1.54
- VPP 71%
- VPN 17%

Fig. 3. \(^{123}\)I-MIBG results in relation to the occurrence of ICD discharges in 17 patients who had ICDs and 2 control patients who did not have heart disease. Compared with patients who did not have ICD discharge (ICD -), patients with a discharge (ICD +) had a lower mean HMR, a higher mean neuronal tracer defect score, and a higher mean neuronal tracer uptake/perfusion tracer mismatch score. (Data from Arora R, Ferrick KJ, Nakata T, et al. I-123 MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator. J Nucl Cardiol 2003;10:121–31.)
123-MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator

Denervazione in aree di miocardio vitale

$^{123}$I-MIBG

e

CARDIOPATIA ISCHEMICA
La cardiopatia ischemica determina alterazioni dell’innervazione simpatica che possono essere evidenziate con la $^{123}$I-MIBG
Qual è l’effetto dell’ischemia/infarto sulla trasmissione nervosa attraverso i tronchi nervosi simpatici che corrono lungo le coronarie prima di penetrare nel miocardio?

L’ischemia/infarto interrompono la trasmissione simpatica ed il miocadio distale rispetto alla sede dell’infarto, non coinvolto nel processo ischemico può essere interessato risultando In un tessuto perfuso e vitale, ma denervato.

Mismatch perfusione/innervazione

Le aree di miocardio denervato, ma vitale sono aree a rischio predisponenti alle aritmie ventricolari

Fallavollita J et al; J Nucl Cardiol 2010
Presence of sympathetically denervated but viable myocardium and its electrophysiologic correlates after early revascularised, acute myocardial infarction.

67 pazienti (14 giorni dopo l’infarto)

- 123I-MIBG
- $^{201}$Tl

**RISULTATI**

- 90% dei pazienti MIBG/Tl mismatch
- intervallo QTc prolungato

**TUTTAVIA**

scarso significato prognostico
follow-up > 4aa (2 morti)

Simoes et al; Eur Heart J 2004
$^{123}$I-MIBG

e
ARITMIE PRIMITIVIE
Nel 5% dei casi le aritmie ventricolari letali o potenzialmente letali sono primitive ed a volte non evidenti all’ECG

- **Mitrani et al (J Am Coll Cardiol 1993)**
  5/9 (55%) pazienti con TV (coronarie indenni) denervazione simpatica rispetto ai 9 soggetti di controllo

- **Gill et al (Br Heart J 1993)**
  7/15 (47%) pazienti con TV (coronarie indenni) uptake asimmetrico della 123I-MIBG (minore uptake nel setto)
Cardiac autonomic dysfunction in Brugada syndrome

- 17 pazienti (sindrome di Brugada) + 10 NC

  - MIBG-SPECT  (analisi mappe polari a 33 segmenti)

RISULTATI

- Riduzione regionale della captazione della MIBG in 8/17 (47%) dei pazienti con sindrome di Brugada, ma in nessun soggetto di controllo

- Riduzione regionale nelle pareti inferiore ed infero-settale se paragonati con il gruppo di controllo (p<0.05)

Wichter T et al; Circulation 2002
Cardiac autonomic dysfunction in Brugada syndrome
La compromissione del sistema nervoso simpatico cardiaco gioca un ruolo cruciale nella fisiopatologia della CHF
CONCLUSIONI

- La scintigrafia con $^{123}$I-MIBG
  - ha un valore prognostico elevato superiore a quello di altri parametri (LVEF; BPN) (elevato VPN)
  - può guidare la terapia medica
  - indirizzare verso altre terapie (CRT, trapianto)
  - identificare pazienti ad elevato rischio di aritmia cardiaca fatale che potrebbero trarre beneficio dalla terapia con ICD

- Necessità di linee guida standardizzate
- Ulteriori studi per il consolidamento delle conoscenze fino ad ora acquisite