PET/CT in cardiac imaging

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Any combination of structural and functional information

Hybrid Imaging:

• 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).

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

- The current evidence for anatomic evaluation using CCTA remarks its:
  - 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 morphological measures delineating the physiologic implications of stenosis are well described.
- The 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?

- It 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.

- PET imaging with:
  1. 82R Rubidium
  2. 15O Water
  3. 13N ammonia
  4. [18F]-Flurpiridaz

- Opportunity to evaluate:
  1. LV myocardial perfusion
  2. Absolute quantification of myocardial blood flow ml/gram/min
  3. LVEF at rest and stress
WHERE do we stand?

- PET imaging with:
  1. 82 Rubidium
  2. 15O Water
  3. 13N ammonia
  4. 18F-Flurpiridaz

- Opportunity to evaluate:
  1. LV myocardial perfusion.
  2. Absolute quantification of myocardial blood flow
     - ml/gr/min
  3. LVEF at rest and stress

- K analogous, not linear
- Linear with flow, no
  Imaging possible, 20 min half time, on site cyclotron needed, post injection QA, 2 bombardment for 2 patients, no exercise stress test
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
- High quality imaging
- Adequate for gating
- Available as unit dose ($^{18}$F-labeled compound- 2h HT)
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

![Graph showing uptake vs coronary perfusion flow for BMS747158, 201Tl, and 99mTc-SESTAMibi.](image)

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
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.
Applications of PET / CT in Cardiology

- Myocardial Perfusion
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- Myocardial Blood Flow
- Molecular Imaging
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
MPI+CCTA

• 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]</th>
<th>relative</th>
<th>F[REST]</th>
<th>relative</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segment</td>
<td>ml/min/g</td>
<td>[% of Max]</td>
<td>ml/min/g</td>
<td>[% of Max]</td>
<td>S/R</td>
</tr>
<tr>
<td>LAD</td>
<td>1.3515</td>
<td>67.0</td>
<td>0.5796</td>
<td>56.8</td>
<td>2.332</td>
</tr>
<tr>
<td>1. basal anterior</td>
<td>1.6392</td>
<td>71.6</td>
<td>0.4329</td>
<td>79.4</td>
<td>3.787</td>
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<tr>
<td>2. basal anteroseptal</td>
<td>1.7516</td>
<td>63.0</td>
<td>0.6056</td>
<td>74.0</td>
<td>2.892</td>
</tr>
<tr>
<td>7. mid anterior</td>
<td>1.5417</td>
<td>39.3</td>
<td>0.5645</td>
<td>84.4</td>
<td>2.731</td>
</tr>
<tr>
<td>8. mid anteroseptal</td>
<td>0.9609</td>
<td>54.6</td>
<td>0.6441</td>
<td>79.3</td>
<td>1.492</td>
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<tr>
<td>13. apical anterior</td>
<td>1.3365</td>
<td>28.9</td>
<td>0.605</td>
<td>78.9</td>
<td>2.209</td>
</tr>
<tr>
<td>14. apical septal</td>
<td>0.7078</td>
<td>45.5</td>
<td>0.6019</td>
<td>85.3</td>
<td>1.176</td>
</tr>
<tr>
<td>17. apex</td>
<td>1.1116</td>
<td></td>
<td>0.6507</td>
<td></td>
<td>1.708</td>
</tr>
</tbody>
</table>

FLOW RESERVE [ Pathology < 2.0, Grey Zone 2.0 - 2.5, Normal > 2.5 ]

- LAD: 1. basal anterior, 2. basal anteroseptal, 7. mid anterior, 8. mid anteroseptal, 13. apical anterior, 14. apical septal, 17. apex
- RCA: 3. basal inferior, 4. mid inferior, 5. apical inferior
- LCX: 6. basal anterolateral, 11. mid inferolateral, 12. mid inferolateral, 16. apical lateral
- TOTAL
# Myocardial Blood Flow Quantification Software

<table>
<thead>
<tr>
<th>N=9 (normals)</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>

<table>
<thead>
<tr>
<th>N=18 (all)</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 Lk (>0.85)
  - High Diagnostic Value
  - Guide Management

Courtesy MF Di Carli
PET/CTA: A Sequential Approach

CT Scan

Normal

Mild/moderately abnormal

Suspect microvascular dysfunction

Ischemia evaluation

Medical Therapy

Severely abnormal

Invasive Angiogram ± revascularization
Atherosclerosis
Methodology

- **ENDEVI > 1.5**
- **CFR > 2.5**

Endothelial-dependent vasodilation index (MBF after CPT)
Myocardial flow reserve
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 dipyridamole 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–simvastatine 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, Hypertension
Endothelial Function in SLE

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

N = 32
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
Myocardial viability: Why is it important?

It is the main point to decide between medical and revascularization treatment
CARDIOVASCULAR IMAGING

• ECHO
• MRI
• CT
• SPECT
• SPECT/CT
• PET
• PET/CT
Outcome in with Viability Evaluation

Di Carli et al. JTCVS 1998
Viability

- Can be described as dysfunctional “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; potentially arrhythmic focus

- 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

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

• Physiologically there is a decreased coronary flow reserve.

• 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.
Sensitivity, specificity, and predictive accuracies of non-invasive tests, singly and in combination, for diagnosis of hibernating myocardium

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:

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.
(Fasting)

• 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.
• 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>Insulin and Glucose Solution</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>Insulin and 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.
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.
Change in global LV ejection fraction after revascularization in patients with ≥4 and in those with <4 viable segments

Thallium
p < 0.0001

Sestamibi
p < 0.0001

(30% of the total LV)

Cuocolo et al J Nucl Cardiol 2000
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>Table 1 Imaging methods used for assessment of myocardial viability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Nuclear</td>
</tr>
<tr>
<td>Myocardial perfusion imaging (SPECT)</td>
</tr>
<tr>
<td>PET FDG</td>
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<tr>
<td>BMIPP SPECT</td>
</tr>
<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>Dobutamine stress</td>
</tr>
<tr>
<td>Myocardial contrast echocardiography</td>
</tr>
<tr>
<td>MRI</td>
</tr>
<tr>
<td>Dobutamine stress</td>
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<tr>
<td>Delayed-enhancement (with gadolinium)</td>
</tr>
<tr>
<td>CT</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

Several studies have established that perfusion imaging with SPECT radiotracers is more sensitive compared to techniques using contractile reserve assessment in predicting myocardial viability (Bax et al. Curr Probl Cardiol 2001; 26:147–186).

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
Table 1  Techniques to study myocardial viability

<table>
<thead>
<tr>
<th>Technique</th>
<th>Imaging finding</th>
<th>Criteria for viability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular wall thickness</td>
<td>&gt;6 mm [9]</td>
</tr>
<tr>
<td></td>
<td>Inotropic contractile reserve</td>
<td>Biphasic response better predictive accuracy versus monophasic response [14]</td>
</tr>
<tr>
<td></td>
<td>Contrast echocardiography perfusion imaging</td>
<td>No perfusion defect [16]</td>
</tr>
<tr>
<td></td>
<td>Strain and strain rate imaging</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular wall thickness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inotropic contractile reserve</td>
<td></td>
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<tr>
<td></td>
<td>LGE</td>
<td></td>
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<tr>
<td><strong>Radionuclide techniques</strong></td>
<td></td>
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<tr>
<td><strong>SPECT</strong></td>
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<tr>
<td>Thallium-201</td>
<td>Perfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Redistribution</td>
<td></td>
</tr>
<tr>
<td>Technetium-99m</td>
<td>Perfusion</td>
<td></td>
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<tr>
<td>Nitrate-enhanced perfusion imaging</td>
<td>Perfusion</td>
<td></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>
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<td></td>
</tr>
<tr>
<td>F-18 FDG</td>
<td>Glucose uptake</td>
<td></td>
</tr>
</tbody>
</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 Thallium-201 Technitium-99</td>
<td>Viable myocardial membranes uptake of tracers Reflects K+ space Reflects mitochondrial integrity</td>
<td>Yes 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</td>
</tr>
<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>
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<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>
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<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>
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<td>Year</td>
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<td>Viability Criterion</td>
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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).
Myocardial viability testing: Still viable after 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>
<thead>
<tr>
<th>Imaging modality</th>
<th>Weighted mean sensitivity (%)</th>
<th>Weighted mean specificity (%)</th>
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<th>PPV</th>
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</table>

Reproduced with permission from Schinkel et al. [15]

NPV negative predictive value, PPV positive predictive value

<sup>a</sup> High-dose dobutamine has a higher sensitivity but similar specificity to low-dose dobutamine

<sup>b</sup> 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-¹⁸F-2-Deoxyglucose Studies for Recovery of Regional Left Ventricular Dysfunction

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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.
Applications of PET / CT in Cardiology

CONCLUSION

Hybrid Imaging is possible.

The most accurate non invasive way to evaluate CHD.

Provides anatomic and functional information.

Great Improvement in diagnostic Accuracy.