^{18}F-FDG PET/CT in Myocardial Viability

H Verberne, Academic Medical Centre, Amsterdam
S van Eeckhoudt, Bravis ziekenhuis, Roosendaal

1. Introduction

Patients with multi-vessel coronary artery disease (CAD) in combination with complex coronary artery anatomy, and/or associated left ventricular (LV) impairment are at high risk of complications related to revascularization procedures. However, these high risk patients tend to benefit the most from revascularisation. Therefore appropriate patient selection is crucial and should be based on an accurate assessment of both possible risks and benefits. An important parameter in this setting is the presence of myocardial viability i.e. dysfunctional but potentially viable myocardium ('stunned or hibernating myocardium'). Stunning is defined as reversible contractile dysfunction in the presence of restored coronary blood supply, following a brief period of coronary occlusion. Contractile recovery in this acute "stunned" state may occur spontaneously many weeks to months after restoration of normal blood supply to the previously ischaemic myocardium.
In contrast, hibernating myocardium has been defined as a state of down-regulated contractile function in non-infarcted myocardium in the setting of severe coronary stenosis that improves after revascularisation. Next to dobutamine stress echography (DSE) and cardiac magnetic resonance (CMR), ^{18}F-Fluorodeoxyglucose (FDG) imaging is one of the techniques to evaluate and distinguish viable, stunned, hibernating or scarred myocardial tissue.
The myocardium can quickly adapt to changing environments by switching its energy source to the most efficient one. Under fasting and aerobic conditions fatty acids are preferred. As fatty acid metabolism is highly oxygen dependent however, the myocardium will quickly switch to glucose metabolism in ischaemic conditions. Stunned and hibernating myocardial tissue still have intact cells and even in low blood flow, ischaemic conditions, these cells will take up FDG in comparable or even greater amount than healthy, normal myocardial tissue.
The assessment of myocardial viability has been an important prerequisite in the decision-making regarding revascularisation. This central role of myocardial viability assessment was supported by observational studies and meta-analyses showing that after revascularization patients with myocardial viability had a better outcome compared to those without myocardial viability. However with the publication of the STICH (Surgical Treatment for Ischemic Heart Failure) trial and especially the viability sub-study, questions have arisen regarding the benefit of viability testing in patients with left ventricular systolic dysfunction and CAD prior to revascularization decisions.
The main criticism is that the STICH-study was not designed for the assessment of the benefit of viability testing in a randomised way. Therefore the findings that suggest that viability testing may not be the only or most important independent determinant of outcome should be viewed with some caution.
Acknowledging that prospective outcome data are limited, viability testing still has a role

in complex patients who are at the highest risk of adverse events from revascularization. In this scenario an objective measurement of viability can tip the balance in favour of medical therapy or revascularization. Myocardial viability testing will continue to play a role in revascularisation decision making, although larger randomised trials with clinical outcome end-points are needed to further define its role.
Based on these data the recent guidelines for myocardial revascularization state that myocardial revascularization should be considered in presence of viable myocardium (Class IIa, level B).

2. Methodology
This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications
Assessment of myocardial viability in patients considered for revascularization in order to predict outcome benefit, for correct stratification and to guide further treatment.
Contraindications
Pregnancy is a relative contraindication.

4. Relation to other diagnostic procedures
^{201}Tl
^{201}Tl rest/redistribution SPECT has been shown to be effective in the assessment of myocardial viability. However due to the relatively high radiation burden and the suboptimal photon energy spectrum ^{201}Tl is not advocated for the assessment of myocardial viability.

Dobutamine stress echography
The ability to assess viability using dobutamine stress echography relies on the concept of contractile reserve. As a result of an increased workload, normal myocardial tissue will display an increase in wall motion and thickening whereas scarred tissue will show marked motion abnormalities. If viable, areas with reduced wall motion and thickening at rest will show a biphasic reaction to dobutamine. Low dose infusion (2,5 µg/kg/min) will result in an improvement of contractility. At increased dobutamine dosage (up to 40 µg/kg/min) workload increases and as the tissue becomes ischaemic, contractility worsens.
The main advantage of this technique is the wide availability and the absence of ionizing radiation. It may be more specific than other techniques for the recovery of regional function after revascularization.
Disadvantages include the high inter-observer variability and operator dependency. Also image quality can be limited in obese patients and patients with chronic obstructive pulmonary disease because of poor acoustic windows.

Cardiac magnetic resonance
Distinguishing viable from non-viable tissue with CMR depends on the concept of delayed gadolinium enhancement. Normal myocardium consists of healthy cells and a tight interstitial space that does not allow much gadolinium based contrast to leak into it. Non-enhancing myocardium is in general considered viable. After infarction myocardial necrosis

results in a more open interstitial space leading to a greater accumulation of contrast.
The extent of viable myocardium can be graded according to the transmural extent of enhancement. As the extent of transmural enhancement increases, the likelihood of improvement after revascularization decreases.
Patterns of delayed enhancement cannot only evaluate ischaemic heart disease, but can also diagnose cardiomyopathies of other aetiologies.
Also cine CMR can provide information on global and regional wall motion and thickening and left ventricular function.
A key difference is that CMR distinguishes scar from viable tissue, where nuclear imaging can evaluate normal, stunned, hibernating and scarred tissue.
In recent years MRI techniques have evolved and now dobutamine stress CMR is feasible offering information on both scarring and contractile reserve. It does remain costly and it requires considerable local expertise.

5. Medical information necessary for planning

- Indication to perform the study
- Full cardiac history (e.g. previous infarction or revascularization)
- Results of previous imaging tests (myocardial perfusion imaging, echography, CMR, coronary angiography)
- Medication
- Diabetic status

6. Radiopharmaceutical

Tracer:	^{18}F-FDG (FDG)
Nuclide:	Fluorine 18
Activity:	Appropriate dosage should be determined considering several factors mostly depending on the available PET camera (e.g. crystal type, 2D or 3D scan mode, time of flight capabilities). Currently used doses range from 185 to 400 MBq
Administration:	Intravenous injection

7. Radiation safety

Intravenously administered ^{18}F-FDG results in an effective dose of 0,019 mSv/MBq in adults.
Pregnancy is a relative contra indication.
Discontinuation of breast-feeding is not required. Close and prolonged contact with an infant however should be avoided during the first hours after injection.

8. Patient preparation/essentials for procedure

To ensure that the myocardium will preferentially use glucose instead of fatty acids, a strict preparation is needed.
The evening preceding the investigation a low fat meal should be consumed. In the morning a low fat/no fat breakfast is allowed, patients should be advised not to use milk or creamer in their coffee or tea. In contrast to FDG imaging in oncology or inflammation sugar is allowed.
Several options exist to further reduce the amount of free fatty acids and to promote myocardial glucose metabolism.

Acipimox

Acipimox, a nicotinic acid derivative, is used to lower free circulating fatty acid levels. By adding a low fat/high carbohydrate meal insulin levels will rise promoting the use of glucose by the myocardium. With this method myocardial FDG uptake can reach similar levels compared to the more cumbersome euglycemic clamping method. The acipimox method is commonly used in the Netherlands. However, acipimox is not available for clinical use in all countries. For example acipimox cannot be obtained in the United States. A protocol can consist of the administration of 2 tablets of 250 mg acipimox 30 min apart, followed by a carbohydrate rich meal (e.g. white bread with jam, without butter, coffee with sugar, juice) 30 min later. One hour after the second acipimox tablet, FDG can be administered. Imaging is started 45 min after FDG injection.
Flushing is a common side effect of acipimox, which can be prevented by the administration of 500 mg acetylsalicylic acid (aspirin). In diabetic patients a short acting insulin can be added shortly before FDG administration.

Euglycemic hyperinsulinemic clamping

This method consists of a continuous (preceding, during and after FDG administration) and simultaneous infusion of both glucose and insulin to maximize glucose, and thus FDG, uptake in the myocardium. To prevent hypopotassaemia KCl is added to the infusion. During infusion monitoring of blood glucose levels is required to adjust infusion speed accordingly. This method results in high insulin levels and consequently excellent image quality in both diabetic and non-diabetic patients, it is however labour intensive and time consuming. A less extensive version of this method, using a 30 min glucose-insulin-potassium infusion, has also been reported to result in excellent image quality.

Oral glucose loading

Promoting cardiac glucose uptake can be achieved by administering 25-100 g glucose orally, sometimes with the addition of intravenous insulin. This method will often result in suboptimal images and up to 10% uninterpretable scans. Certainly in diabetic patients this method will not lead to sufficient cardiac FDG uptake.

Essentials for procedure

- A glucose monitoring device
- Depending on preparation protocol: acipimox, acetylsalicylic acid, short acting insulin, glucose, KCl, glucagon (in case of hypoglycaemia), infusion systems

9. Acquisition and processing

Nowadays PET/CT camera systems are widely available and accessible for routine clinical use. Usually myocardial viability imaging is done in combination with a form of perfusion imaging, which may even be done the same day using ^{99m}Tc, ^{82}Rb or other perfusion tracers.
Acquisition can be started 45 min after tracer injection.
Images are acquired in supine position preferably with both arms above the head. The heart will usually fit in a single bed position. Acquisition time depends on the injected dose and camera parameters; scan times vary between 10 and 30 min. Optionally ECG gated images can be acquired; however perfusion images will usually already provide

information on left ventricular function.
In the hybrid PET/CT systems a CT scan should be obtained to provide attenuation correction. Depending on the CT these images can be used for anatomical reference. In advanced systems capable of 64 or more slice CT's, even a CT coronary angiography can be added to the investigation providing information on the presence and extent of coronary artery stenosis. This anatomical information might be helpful in the overall interpretation of the images.
Images should be reviewed prior to the patient leaving the department. In case of high blood pool activity images should be reacquired after administration of additional insulin. Artefacts may be caused by patient motion during acquisition or in between PET and CT imaging. Reacquiring may be necessary.
The acquired data is reoriented into the standard cardiac views (short axis, horizontal long axis, vertical long axis) in a similar fashion to perfusion images. Several software packages are available to analyse and segment these images and provide quantified data on the extent of metabolic defects, also in comparison to perfusion images.

10. Interpretation

Four image patterns emerge when metabolic images are compared to perfusion images:

- Normal perfusion + normal metabolism: Normal, stunned or remodelled myocardium. All three represent viable tissue. On ECG gated images normal tissue will have normal wall motion and thickening. Stunned and remodelled tissue will both have wall motion abnormalities and cannot be distinguished by gated imaging. If stress imaging is added, regions showing reversible ischaemia will represent stunned myocardium. This distinction is important to predict possible improvement for remodelled tissue may not regain function as much as stunned tissue will.
- Reduced perfusion + preserved or increased metabolism (mismatch): Hibernating myocardium
- Normal perfusion + reduced metabolism (reversed mismatch): This pattern can be observed in a few settings, including left bundle branch block, following revascularization early after myocardial infarction, non-ischaemic cardiomyopathy and diabetes. The significance of this pattern remains unclear, however as perfusion is preserved it needs to be interpreted as viable myocardial tissue.
- Reduced perfusion + reduced metabolism: Scarred myocardium. The extent of scarred tissue has been reported to predict LV function improvement after revascularization. The larger the scar, the less improvement can be expected.

Caution is advised when SPECT perfusion images are compared to PET metabolic images as these different techniques might display different artefacts (typical breast or diaphragm attenuation artefacts in SPECT).

11. Report

The report should include patient information and identification, a brief description of cardiac history and the indication to perform the study. Preparation and acquisition protocols should be stated concisely. Image quality should be noted.
The report should describe the regional distribution of FDG in the left ventricle in comparison to perfusion images. The extent and severity of metabolic defects should be described and interpreted as regions of normal, stunned, hibernating and scarred

myocardial tissue. These regions can be represented as a percentage of total left ventricular volume. It may be useful to allocate these findings to coronary territories, especially if coronary angioography data is available.
A statement can be made about predicted benefit after revascularization.

12. Literature

- Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatnerm SF. Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 1978;234:H653-9.
- Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146-9.
- Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002;39:1151-8.
- Velazquez EJ, Lee KL, Deja MA, STICH Investigators et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011;364:1607-16.
- Bonow RO, Maurer G, Lee KI, STICH Investigators et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med 2011;364:1617-25.
- Grover S, Srinivasan G, Selvanayagam JB. Myocardial viability imaging: Does it still have a role in patient selection prior to coronary revascularisation? Heart, Lung and Circulation 2012;21:468-79.
- Mc Ardle BA, and Beanlands RS. Myocardial Viability: Whom, what, why, which, and how? Can J Cardiol 2013;29:399-402.
- Chareonthaitawee P, Gersh BJ, Panza JA. Is viability imaging still relevant in 2012? J Am Coll Cardiol 2012;5:550-8.
- Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35:2541-619.
- Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC), 2010.
- SNMMI/ASNC/SCCT Guideline for Cardiac SPECT/CT and PET/CT 1.0, 2012.
- ASNC imaging guidelines for nuclear cardiology procedures – PET myocardial perfusion and metabolism clinical imaging, 2009.
- EANM/ESC guidelines for radionuclide imaging of cardiac function, 2008.
- Aanbevelingen NVNG, Myocardperfusiescintigrafie in rust en na inspanning, 2007.
- Aanbevelingen NVNG, F-18-FDG-SPECT / PET van het myocard, 2007.
- Myocardial viability: it is still alive. Semin Nucl Med 44:358-74.
- Contemporary Reviews in Cardiovascular Medicine - Stunning, Hibernation, and Assessment of Myocardial Viability. Circulation. 2008;117:103-14.
- Feasibility and image quality of dual-isotope SPECT using 18F-FDG and (99m)Tc-tetrofosmin after acipimox administration. J Nucl Med. 2003;44(2):140-5.