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Integrated anatomy and viability assessment PET-CT

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The authors have no conflict of interest to declare.

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Abstract

Myocardial viability testing can identify patients with ischaemic heart disease and left ventricular dysfunction who can potentially benefit from both improved cardiac function and prognosis after revascularisation. Evaluation of myocardial glucose metabolism by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is considered the most sensitive tool to detect viability, and it predicts functional recovery as well as improved prognosis upon revascularisation. In parallel with the improved availability of PET, scanners have been changed into hybrid devices consisting of both multidetector computed tomography (CT) and PET (PET-CT). The immediate benefit for viability imaging is the ability to merge the coronary CT angiography images with FDG PET viability data. In addition, the possibility to utilise CT for myocardial viability imaging, such as delayed-enhancement imaging of myocardial infarction with acceptable radiation dose has been intensely investigated. This review will describe the principles of viability assessment by PET, and discuss the possibilities provided by hybrid PET-CT in this setting.

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Introduction

Ischaemic myocardium that is dysfunctional but viable has the potential for recovery of contractile function after revascularisation. The term myocardial "stunning" describes prolonged post-ischaemic contractile depression despite restoration of adequate perfusion after a brief ischaemic insult[1]. The term myocardial "hibernation" is used to describe a more persistent form of reversible contractile dysfunction due to coronary artery disease (CAD)[1,2]. The reversible myocardial dysfunction in a patient with chronic ischaemic heart disease is likely to present a mixture of stunned and hibernating tissue jeopardised by various degrees of ischaemia[1,2].

Ischaemic heart disease is the leading cause of heart failure, and the presence of ischaemic but viable tissue is common in patients with poor left ventricular function[3]. Non-invasive detection of viable myocardium in chronic heart failure associated with CAD has important clinical implications for treatment of patients. A meta-analysis of retrospective data summarised 10 studies in 1,046 patients, and found annualised mortality rates of 4% in those with viable myocardium who underwent revascularisation versus 17% for those with viability who did not undergo revascularisation[4]. In contrast to patients with viable myocardium, the mortality was 6% for those without viability undergoing revascularisation versus 8% for those without viability not undergoing revascularisation[4]. Thus, patients with ischaemic but viable myocardium are at a substantial risk of death, which can be effectively reduced by successful revascularisation[4]. Discrimination between viable dysfunctional myocardium and scar allows selection of patients who are most likely to benefit most from revascularisation, allowing others to avoid the risks associated with revascularisation when they are unlikely to benefit[3,4].

Positron emission tomography (PET) is a powerful imaging modality that has been increasingly used also in cardiology[5]. This has been largely due to the recent exponential growth in the number of hybrid scanners consisting of both multidetector computed tomography (CT) and PET (PET-CT). A hybrid PET-CT scanner allows immediate integration of cardiac anatomy in CT images with functional information provided by PET[5]. The state-of-the-art PET-CT hybrid scanners with a 64-slice CT offer the opportunity to make a comprehensive cardiac examination, including an assessment anatomic extent of CAD by non-invasive coronary angiography and its functional consequences on myocardial perfusion and metabolism in a single study[5,6]. One of the first clinical applications of PET was the assessment of myocardial viability, and it has been generally regarded as the gold standard technique for this indication[7,8]. We describe the PET methods for assessment of myocardial viability and review recent advances in delayed-enhancement CT imaging of myocardial infarction. We also show examples and discuss the possibilities that hybrid PET-CT imaging can provide in this setting.

Assessment of viability with PET

Evaluation of residual glucose metabolism, a hallmark of viable myocardium, by ^{18}F-2-fluoro-2-deoxyglucose (FDG) PET is considered as the most sensitive non-invasive tool to assess myocardial viability[7,8]. FDG is a glucose analogue that is taken up in the myocytes in proportion to the glucose transport and phosphorylation, whereas its uptake is only minimally influenced by blood flow[7,8]. After phosphorylation, FDG becomes trapped in the myocytes, its further metabolism is minimal, and thus it provides a strong signal for imaging[7,8]. Detailed descriptions of available methods of FDG imaging have been reviewed elsewhere[8,9]. A semi-quantitative analysis of the relative distribution of myocardial FDG uptake is the most commonly used[8]. However, it is also possible to quantify exogenous glucose utilisation in absolute terms with the use of FDG PET by applying a fitting procedure of myocardial kinetics and parametric display of the regional metabolic data[8]. The quantitative nature of PET allows assessment of the amount of viable tissue as a continuum from fully viable, through partially viable in the areas of partial infarction, to non-viable scar.

Viable myocardium shows preserved FDG uptake, whereas markedly reduced or absent uptake indicates scar formation. Most studies have related myocardial FDG uptake to myocardial perfusion[8]. With this approach, regional myocardial perfusion is evaluated prior to the FDG scan by single photon emission tomography imaging (SPECT) or PET following administration of ^{13}N-ammonia, ^{82}Rubidium or ^{15}O-water[9]. A preserved or increased uptake of FDG in the presence of reduced myocardial perfusion, known as flow-metabolism mismatch, is the most commonly used marker of hibernating myocardium that is capable of functional recovery after revascularisation[8] (Figure 1). However, in addition to dysfunctional segments with reduced resting perfusion, many studies have shown high frequency of functional improvement in the presence of near-normal or normal perfusion and preserved FDG uptake[8]. These segments most likely represent areas of myocardial stunning as a consequence of repetitive episodes of ischaemia. Areas with reduced perfusion and proportionally reduced FDG uptake known as matched defects are indicative of scar tissue with

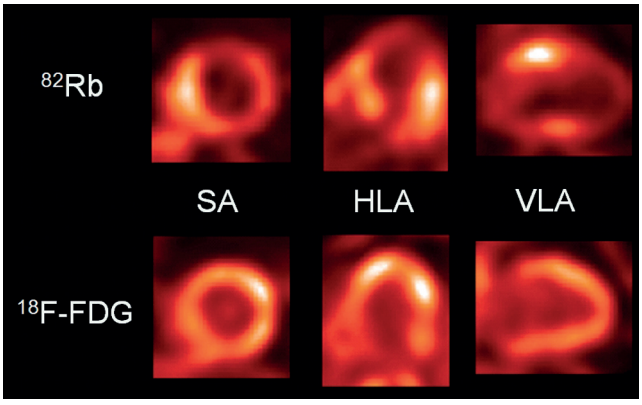

Figure 1. Assessment of myocardial viability by FDG PET: the flow-metabolism mismatch. The upper row shows the resting short axis (SA), horizontal long axis (HLA) and vertical long axis (VLA) images of myocardial perfusion using ^{82}Rb as the flow tracer. The corresponding FDG images are displayed in the lower row. A large anterior and apical region with reduced perfusion was detected. However, in the FDG images the corresponding region had normal or even enhanced uptake of FDG as a marker of myocardial viability. Reproduced with permission from reference 5.

irreversible functional defect[8]. Values of relative myocardial FDG uptake are used alone when FDG is employed without a perfusion tracer (Figure 2). Segments with relative FDG uptake of >50% of that in normal myocardium not affected by CAD have been typically considered viable, whereas segments with FDG uptake less than 50% recover only infrequently[8]. Compared to combined perfusion-FDG imaging FDG imaging alone has lower specificity for detection of viability. There is also data indicating that visual analysis of the severity of the reduction in the regional tracer uptake and semi-quantitative approach provide comparable accuracies for the detection of viable myocardium suggesting that visual analysis is acceptable and may be preferable in the clinical setting[8,9].

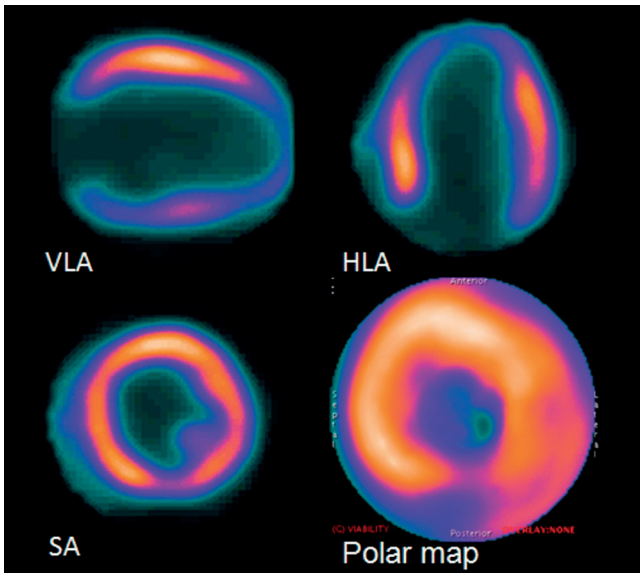

Figure 2. FDG PET images and polar map normalised to its own maximum in a patient presenting with recurrent syncope and non-sustained ventricular tachycardia in ECG monitoring. Coronary angiography showed two vessel CAD with subtotal stenosis in the mid LAD and chronic total occlusion in the proximal RCA. Echocardiography demonstrated severely reduced LV function (EF 35%). FDG PET shows preserved FDG uptake in the LAD region consistent with viable, but likely ischaemic myocardium. In the RCA region FDG uptake was reduced consistent with myocardial scarring. The patient had successful bypass surgery of both the LAD and RCA. After that tachycardia could not be induced in electrophysiological testing and EF improved to 44%. SA: short axis; HLA: horizontal long axis; VLA: vertical long axis

Like glucose uptake, cardiac FDG uptake is strongly influenced by metabolic circumstances, mainly plasma levels of insulin and free fatty acids[8,10]. Insulin stimulates myocardial uptake of glucose and FDG, but free fatty acids inhibit their accumulation. For successful application of FDG PET, appropriate patient preparation is mandatory to optimise diagnostic accuracy especially in patients with diabetes[8,9]. The majority of cardiac FDG viability studies have been performed after oral glucose loading, which is a simple and effective approach to stimulate glucose utilisation and thus, increase myocardial FDG uptake[8,9]. The main shortcoming is that image quality in some patients with impaired glucose tolerance or overt diabetes is poor. Hyperinsulinaemic euglycemic clamping can overcome this problem, but this approach is time-consuming and laborious[8,9,10]. It mimics the steady, post-absorptive metabolic state by means of continuous infusion of insulin and maintenance of euglycemia with a simultaneous infusion of glucose at a variable rate[8,10]. The use of oral nicotinic acid derivatives provides an easy, alternative approach to obtain adequate image quality even in patients with diabetes[8,9,11].

An improved contractile performance as a response to successful revascularisation is commonly considered as the gold standard for assessing myocardial viability. PET is an accurate method to predict improvement of the regional wall motion and the global LV EF after revascularisation. A recent pooled analysis of 24 studies in 756 patients demonstrated a weighed mean sensitivity and specificity of 92% and 63%, respectively for regional functional recovery, with PPV and NPVs of 74% and 87%, respectively[3]. Compared with other imaging methods, FDG PET has higher sensitivity for functional recovery, whereas inotropic response to dobutamine and techniques based on imaging of myocardial infarct scar have higher specificity[3]. Relatively low specificity of FDG PET indicates that a substantial percentage of segments that are classified as viable do not improve after revascularisation. Reasons for this may be multifactorial, including the absence of functional improvement in the presence of non-transmural infarct scar, advanced cellular alterations in the myocardium, delayed improvement observed in some patients with hibernating myocardium, incomplete revascularisation or perioperative myocardial damage[12].

It has been pointed out that the benefits of revascularisation do not appear to be limited to improved regional function[12]. Revascularisation may have beneficial effects also via prevention of progressive myocyte damage, adverse remodelling of the left ventricle and by treating potential substrate for ventricular arrhythmias in the infarct border zone (Figure 2). The prognostic value of FDG PET relies on the relative comparison of flow and glucose uptake (mismatch), which has been shown experimentally and clinically to reflect not only viable, but jeopardised myocardium. Several retrospective studies have indicated that there is an association between FDG PET mismatch and adverse clinical outcome[4]. These findings were supported in a recent randomised trial that assigned 430 heart failure patients to either management assisted by FDG PET imaging or standard care (including other imaging tests)[13]. Although there was no overall difference between FDG PET assisted imaging and standard care, the study observed survival benefits for FDG PET assisted management in the subgroup of patients whose treatment adhered to the recommendations based on the imaging[13]. The management of many patients deviated from the FDG-PET –recommended option, demonstrating the difficulty of designing such trials, because therapeutic decision making is difficult to control[13].

Delayed-enhancement CT of myocardial infarction

Wide-detector CT design along with prospective ECG triggered protocols has made it possible to obtain high resolution images of myocardial morphology during a coronary CT angiography (CTA) exam with acceptable radiation and contrast exposure[6,14]. It is

possible to evaluate cardiac regional function and calculate ejection fraction from coronary CTA images[6,14]. Furthermore, similar to magnetic resonance imaging (MRI), CT delayed-enhancement imaging several minutes after contrast agent injection can be used to detect myocardial infarct scar[6,14]. The presence of myocardial necrosis or scar alters kinetics of iodinated CT contrast agents that diffuse passively into the increased extracellular matrix space in the necrotic tissue or between collagen fibres resulting in enhancement of these areas (Figure 3). Delayed-enhancement CT images of myocardial infarction show good agreement with histological methods and the extent of MRI delayed-enhancement in experimental studies and patients with recent or old myocardial infarction[14-17]. CT delayed-enhancement appears promising method for detection of infarction. However, it remains at a preliminary state compared with delayed-enhancement MRI and more experience is needed to confirm its clinical value. Moreover, a reduction in radiation dose for a complementary scan is essential for routine clinical application.

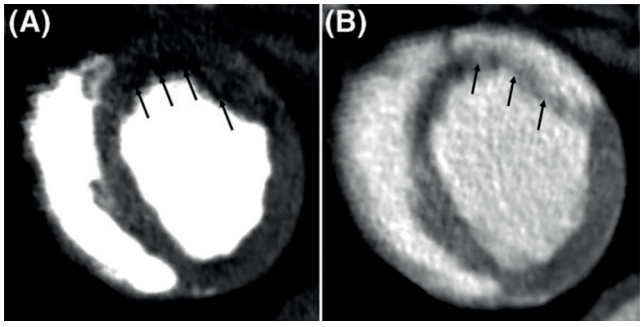

Figure 3. Example of delayed-enhancement CT of myocardial infarction. In a porcine model of subacute anterior myocardial infarction, there is a hyper-enhanced area (arrows, b) in the anterior wall when imaged 10 minutes after injection of a contrast agent bolus when compared with the image obtained during the first-pass of the contrast bolus (a) and the remote, non-infarcted myocardium. Reproduced with permission from reference 5.

Hybrid PET–CTA

A few years ago hybrid imaging systems with multidetector CT and PET were introduced and are rapidly becoming the dominant scanner type[5]. Although their use is primarily driven by oncological applications, the interest in cardiac studies is increasing. Hybrid PET-CT scanners allow immediate integration of PET signals with detailed anatomical CT images of coronary and cardiac morphology. Furthermore, CT could be used for attenuation correction and calcium score measurement. New prospective gated CT acquisition techniques, which lower radiation exposure for CT angiography to 1-3 mSv will contribute to its more wide-spread use in hybrid PET-CT protocols[6,18].

Coronary computed tomography angiography (CTA) has emerged as a promising method for anatomic detection of coronary atherosclerotic plaques. Numerous single centre studies, as well as recent multicentre studies, have demonstrated its high diagnostic accuracy for the identification of >50% coronary artery stenosis in a patient population with an intermediate likelihood of CAD[6]. Importantly, these studies indicate that a normal coronary CTA can reliably rule out the presence of significant CAD (negative predictive value >95%). Evaluation of coronary arteries in patients with new onset heart failure is a common indication of coronary CTA in order to evaluate the aetiology of left ventricular dysfunction[6]. However, the presence of advanced CAD in these patients as well as concomitant conditions, such as kidney disease may cause problems. A hybrid PET-CT scanner permits evaluation of viability with FDG-PET immediately in combination with coronary anatomy by CTA and automatic fusion of FDG images with coronary images as demonstrated in Figure 4. Functional mapping of the myocardium is typically based on a standard template of the coronary artery system to indicate the supplied myocardial segments of the left ventricle. However, the standard template may not reflect the true coronary anatomy in a large number of patients and thus, a mismatch between dysfunctional myocardium and significant coronary lesions is not uncommon[19]. Therefore, hybrid PET-CT providing integration of coronary CTA with FDG PET images could possibly improve the accuracy of viability imaging.

It still remains to be studied whether the combination of FDG-PET, evaluation of cardiac function in CT images, and delayed-enhancement CT could improve detection of viability clinically. A recent study compared delayed-enhancement CT with FDG PET in 17 patients with myocardial infarction and found that both methods were concordant in localising the myocardial infarction in most segments, but there were some segments with subendocardial delayed-enhancement, but viable by FDG PET[20]. It is important to realise that delayed-enhancement detects myocardial scar, whereas FDG PET is the only method capable of detecting the mismatch of perfusion and metabolism, which has been shown experimentally and clinically to reflect viable, but jeopardised myocardium. There is a need for trials comparing delayed-enhancement of infarction and viability PET to better understand whether they provide complementary clinical value. A recent experimental study using hybrid PET-CT scanner compared directly FDG PET and delayed-enhancement CT in an experimental myocardial infarction demonstrating that FDG PET in the acute phase of myocardial infarction was related to inflammation rather than viability in the infarcted area[21]. This study provided an example of how hybrid imaging of CT delayed-enhancement and PET could help to localise PET-derived signals and thus, clarify the complex pathogenesis underlying the left ventricular dysfunction in ischaemic heart failure.

Conclusions

Myocardial viability testing can identify patients with ischaemic heart disease and left ventricular dysfunction who can potentially benefit from the improved cardiac function and prognosis after revascularisation. FDG PET is the most sensitive tool to detect viability and it predicts functional recovery as well as improved prognosis upon revascularisation. Hybrid PET-CT system allows immediate combination of cardiac and coronary anatomy with detection of myocardial viability by FDG in a single imaging session. The potential benefits of hybrid PET-CT imaging protocols, such as combination of FDG PET and delayed-enhancement imaging of

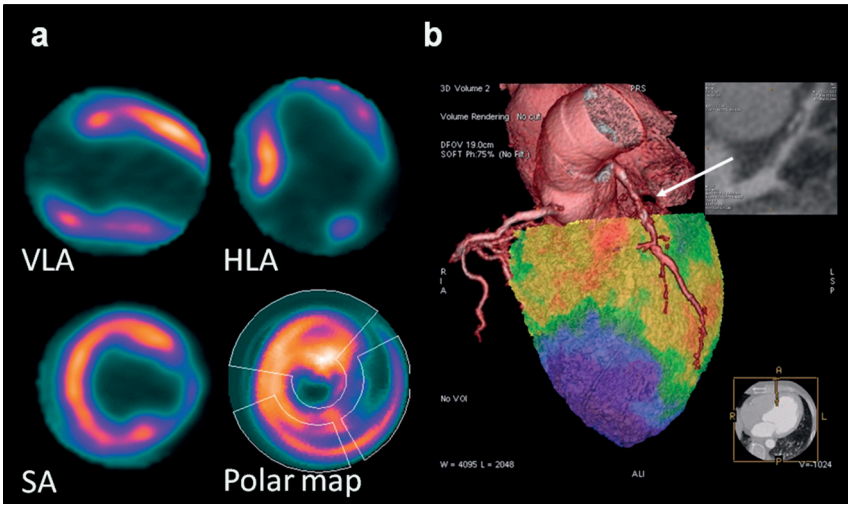

Figure 4. A hybrid PET-CT study of coronary angiography and myocardial viability. The patient presented with new onset heart failure. Echocardiography demonstrated severe left ventricular dysfunction with akinesia or hypokinesia in the apex, anterior septum, and anterior free wall as well as posterolateral wall. Due to the presence of left ventricular apical thrombus, coronary CTA was performed initially instead of invasive coronary angiography. Coronary CTA showed chronic occlusion in the proximal LCX, severe stenosis in the proximal LAD (arrow and the insert in b), and chronic total occlusion in the mid LAD. Then, FDG PET was performed to assess viability. FDG PET images (a) demonstrated local defects in FDG uptake in the apex and lateral wall consistent with infarct scars. However, there was preserved FDG uptake in the septum and most of the anterior wall as well as in the inferior wall consistent with large areas of viable myocardium. Panel b demonstrates 3-D reconstruction of coronary CTA and FDG PET. Co-registration clearly demonstrates viable myocardium (green and red colours) in the septum and anterior wall (supplied by a large diagonal branch) excluding the apical scar (blue colour). The patient had successful bypass surgery with venous grafts implanted in the distal LAD, diagonal branch and LCX. Heart failure symptoms were relieved by surgery. SA: short axis; HLA: horizontal long axis; VLA: vertical long axis

myocardial infarction still remain largely to be studied in this setting. Such approaches could potentially improve the accuracy of viability detection as well as help to understand the complex pathogenesis of myocardial damage and left ventricular dysfunction associated with chronic ischaemic heart disease.

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