

Clinical Applications of Positron Emission Tomography in Cardiology: A Review

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Abstract

Myocardial viability assessment is of utmost importance in the assessment of patients with poor left ventricular function undergoing revascularisation therapies or cardiac transplantation. Cardiac positron emission tomography (PET) is widely regarded as a “gold” standard in myocardial viability assessment. We review the current data on this subject with respect to tracers and techniques, and prognostic information. The newer cardiac PET techniques in perfusion, hypoxia and neuronal imaging are also discussed, with mention of possible new applications of cardiac PET.

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Introduction

Ischaemic heart disease associated with depressed left ventricular function is a common clinical management dilemma. There is overwhelming evidence that such patients have a poor prognosis when treated medically.¹ Although heart transplantation is a therapeutic alternative, the limited number of donor hearts restricts its use. On the other hand, it has been well documented that long-term benefits of myocardial revascularisation in this patient population are significantly better than medical therapy,^{2,3} provided there is evidence of myocardial viability. However, because of the high operative morbidity and mortality in these patients, the correct selection of patients who will benefit maximally from revascularisation is vital.

Dysfunctional myocardium in patients with poor left ventricular function can result from necrosis and scar formation (fibrosis), hibernating myocardium or myocardial stunning. The last 2 mechanisms represent viable myocardium. Identifying “viable myocardium” from non-viable scar tissue is crucial because it is well known that revascularisation in patients with substantial “viable myocardium” can improve left ventricular function, symptoms and survival.

Cardiac positron emission tomography (PET) using fluorine-18 2-fluoro-2-deoxyglucose (FDG) is a well-established modality of viability detection, and has been used as a “gold” standard for viability assessment. Although myocardial viability detection is the mainstay in cardiac

PET imaging, newer techniques for perfusion, atherosclerosis, hypoxia and neuronal imaging are fast gaining clinical importance. This review will deal mainly with viability detection, with additional short sections on the newer cardiac PET techniques.

Identification of Viable Myocardium

Different imaging modalities are available for assessing myocardial viability, such as single-photon emission computed tomography (SPECT), PET, magnetic resonance imaging (MRI), computed tomography (CT) and echocardiography.

PET is a technique that allows for both assessment of myocardial blood flow and metabolism. It has been shown that this modality has a very good sensitivity (87% to 90%) and specificity (78% to 100%) for detecting coronary artery disease and myocardial viability.

Identification of Myocardial Viability by Myocardial Blood Flow

Several PET tracers, such as ¹³N ammonia and ¹⁵O water, have been used in the non-invasive evaluation of blood flow in humans. Both tracers can be used to calculate absolute blood flow using a dynamic scanning protocol. Previous requirements for separate blood pool scan with ¹⁵O carbon monoxide for the evaluation of blood flow via ¹⁵O water have been overcome by a technique of generating myocardial factor images directly from dynamic scanning.⁴

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Assessment of regional blood flow has been used to identify the presence of viable myocardium within dysfunctional regions. While normal blood flow in a dysfunctional region likely represents myocardial stunning, a severe blood flow deficit below 0.25 mL/g/min would most likely represent non-viable tissue that is unlikely to improve function after revascularisation.⁵⁻⁷ Blood flow reduction of intermediate severity are, however, more difficult to interpret. They may represent a mixture of sub-endocardial necrosis with normal myocardial tissue, a condition unlikely to show improvement in function following revascularisation, or hibernating myocardium, whereby revascularisation would be strongly indicated. Some reports have shown that absolute measurements of blood flow alone is an unreliable measure of viability because of the considerable overlap in values between reversibly and irreversibly damaged dysfunctional myocardium.⁷⁻¹⁰ Others have suggested that late ¹³N-ammonia uptake provided useful information regarding functional recovery after revascularisation.⁷ Therefore, quantitation of myocardial blood flow alone appears to be of limited value for detecting viable myocardium. PET metabolic imaging adds significant information for distinguishing reversible from irreversibly dysfunctional myocardium.

Identification of Myocardial Viability by Assessment of Myocardial Metabolism

Evaluation of Glucose Uptake with FDG

The metabolic response of myocardium to acute ischaemia is to utilise more glucose than free fatty acids (FFA) for oxidative metabolism. Carbohydrate metabolism is also disturbed in acute myocardial infarct, with hyperglycaemia and failure to respond to insulin, secondary to underlying hormonal changes. The accumulation of FFA during ischaemia also inhibits the recovery of the myocardium after reperfusion by inhibiting myocardial glucose use after reperfusion. The change in glucose and FFA flux in chronic ischaemia is less certain. Some have suggested increased uptake of FDG (i.e. glucose utilisation) in both stunned and hibernating myocardium. Others have demonstrated a decreased capacity for FFA oxidation, compensated for by increased aerobic and in some cases anaerobic carbohydrate utilisation. Animal studies have showed certain myocyte glucose transporters (GLUT-1 and GLUT-4) are up-regulated during myocardial ischaemia, and the increase in glucose uptake and metabolism appeared to protect the myocardium from irreversible ischaemic injury.¹¹⁻¹³ Since glucose uptake and metabolism can only occur in living (viable) cells, the possibility of evaluation of glucose metabolism together with myocardial blood flow has very important clinical implications.

FDG is an analogue of glucose and is considered a

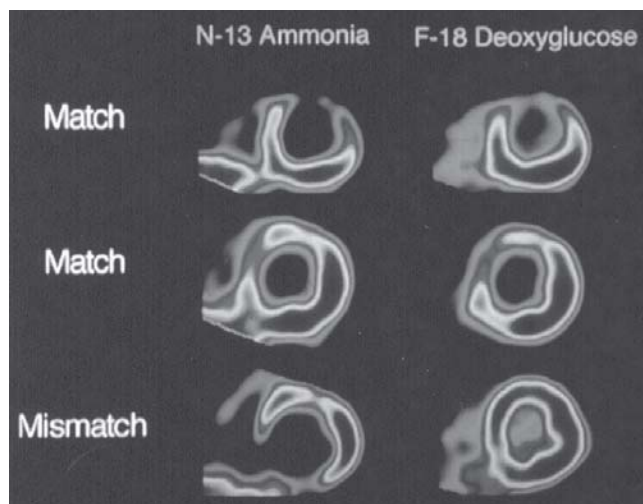


Fig. 1. PET Flow-Metabolism Patterns. Top and middle: Matched flow-metabolism patterns indicating non-viable tissue. Bottom: Flow-metabolism mismatch indicating viable myocardium in the anterior, septal and inferior walls of the left ventricle.

marker of external glucose utilisation. This tracer is transported into the myocyte by the same carrier as glucose and is phosphorylated to FDG-6-phosphate by the enzyme hexokinase.¹⁴ It subsequently undergoes little dephosphorylation in the myocardium. Thus, FDG activity only represents exogenous glucose uptake and membrane integrity.

The most widespread approach for detecting myocardial viability is the evaluation of myocardial blood flow in conjunction to myocardial glucose uptake. With this protocol, 3 patterns can be identified; normal blood flow with normal FDG uptake, reduced blood flow with normal FDG uptake (flow-metabolism mismatch) and reduced blood flow with reduced FDG uptake (flow-metabolism match) (Fig. 1). The pattern of mismatch or normal flow/metabolism detects reversibly dysfunctional myocardium (viable tissue) whereas the matched pattern represents irreversibly dysfunctional myocardium (non-viable tissue).

Technical Aspects of FDG Imaging

The plasma glucose level of the patient can influence myocardial glucose utilisation. In the fasting state, normal myocardium preferentially consumes fatty acids. In contrast, with increasing plasma glucose and insulin levels (for example, after oral glucose loading), glucose transiently becomes the main source of energy.¹⁵ Of note, ischaemic myocardium preferentially utilises glucose as the energy substrate. Thus, FDG imaging can be performed either after glucose administration or in the fasting state. However, studies performed in the fasting state often result in inadequate tracer accumulation in the myocardium and poor target to background ratio.^{15,16} Therefore, the glucose

loaded state is preferable for identifying viable myocardium. This can be achieved by oral glucose administration (50 g to 100 g) from 30 to 60 minutes prior to the tracer injection.

Patients with diabetes mellitus, many of whom have coronary artery disease, also present a challenging problem. Poorly controlled diabetics with high resting plasma glucose result in studies of poor quality. The need for blood glucose standardisation is a significant limitation for FDG imaging. Two alternatives have been used in this patient population to obtain high quality images: hyperinsulinaemic-euglycaemic glucose clamp technique^{17,18} or supplemental intravenous small doses of regular insulin.¹⁹ Because the former is a very demanding procedure, the latter is usually preferred in the clinical setting.

There has also been concern that the quantitation of glucose uptake by FDG may underestimate regional glucose metabolism *in vivo*. Hariharan et al²⁰ showed in rat hearts that the uptake and retention of FDG in the myocardium was linearly related to glucose utilisation only under steady state conditions. When the physiological milieu of the heart was altered, this linear relationship was altered. The authors thus cautioned that the quantitative analysis of regional rates of myocardial glucose metabolism may be of limited value.

Predicting Improvement in Regional and Global Left Ventricular Function

The predictive accuracy of blood flow and glucose metabolism for detecting “viable tissue” has been evaluated in many studies using PET, PET-SPECT hybrid techniques (SPECT perfusion with PET-FDG imaging) or FDG-SPECT imaging.^{19,21-32} The positive predictive value ranged from 72% to 95% and negative predictive value from 74% to 100%. The variability in predictive accuracies between studies could be due to patient selection, coronary anatomy, success of revascularisation, criteria for image analysis and the time from revascularisation to re-evaluation of regional myocardial wall motion. Many investigators have reported the beneficial effect of revascularisation of viable myocardium detected by FDG on left ventricular function. Average increases in ejection fraction ranged from 8% to 51% when PET had shown substantial amounts of viable dysfunctional myocardium.^{19,22,25-27,29,31,33-39}

Studies have shown that the magnitude of the functional improvement depended on the amount of viable myocardium assessed preoperatively.⁴⁰ There was a significant improvement in functional capacity in patients with large mismatches, compared with minimal functional improvement in those with minimal or no PET mismatch. More recent investigations provide additional support for such a relationship and described a linear correlation between the extent of a mismatch and the percent

improvement in LVEF following revascularisation.³⁸

Improvement in Congestive Heart Failure Symptoms and Exercise Capacity

With the exception of a few small studies with SPECT tracers, only PET imaging has addressed this important clinical endpoint. Several studies report significant post-revascularisation improvement in heart failure symptoms in patients with reversible dysfunctional myocardium.^{27,35,41,42} In one study of 23 patients with Class III and IV heart failure, Marwick et al showed a significant post-revascularisation increase in exercise capacity in patients with extensive blood flow metabolism mismatches who were successfully revascularised. There were no significant changes in exercise capacity and symptoms in patients exhibiting matched pattern. The same investigators further showed that the improvement in exercise capacity correlated ($r = 0.63$) with the extent of viable myocardium.⁴²

Prediction of Cardiac Events

Evaluation of blood flow and glucose utilisation offers important clinical information about future cardiac events.^{41,43-46} Several studies have examined the efficacy of revascularisation over medical therapy in patients with moderate or severe left ventricular dysfunction with and without evidence of viable myocardium.^{41,44} Although non-randomised, the data acquired from these studies are the main source of understanding of how to optimise treatment decisions in this patient population. The study population included patients with coronary artery disease and left ventricular ejection fraction less than 40%. Twenty per cent to 68% of them had severe heart failure and approximately one third presented with angina. Survival and recurrent ischaemic events (myocardial infarction, unstable angina and ventricular arrhythmia) were assessed for an average of 12 to 17 months. The patients were grouped based on the presence or absence of PET mismatch pattern. In patients with PET mismatch, 1-year event-free survival was poor with medical therapy. In contrast, 1-year event-free survival in these patients was significantly improved by revascularisation. In patients without PET mismatch, 1-year event-free survival was similar with either medical therapy or revascularisation. Thus, these studies show a clear benefit of revascularisation over medical therapy for patients exhibiting PET mismatch. Furthermore, the presence of blood flow-metabolism mismatch and lack of revascularisation were found to be the strongest predictors of cardiac death.⁴¹

Di Carli et al⁴⁶ also described the survival benefits of revascularisation in patients with viable myocardium irrespective of symptoms. In patients without PET mismatch, coronary revascularisation appeared to improve survival

and symptoms only in those patients with anginal symptoms. Furthermore, long-term survival in patients with ischaemic cardiomyopathy undergoing surgical revascularisation appears to be similar to that achieved with cardiac transplantation.

Most recently, Allman et al⁴⁷ published a meta-analysis of 18 viability assessment studies and showed the significance of accurate assessment of myocardial viability on the prognosis of patients followed up for a mean of 25 months. In that study, the authors also performed comparative studies of 3 modalities of viability assessment (i.e., thallium-201 SPECT imaging, PET metabolic-perfusion imaging and dobutamine stress echocardiography) and could not find any significant difference in accuracy in viability assessment by the 3 methods.

Impact of PET on Timing of Surgery

Recent observations have suggested that myocardial hibernation does not represent a steady state, but rather an incomplete adaptation to ischaemia. The precarious balance between perfusion and myocardial viability cannot be sustained indefinitely and necrosis, apoptosis or both might occur if flow is not restored.^{33,34,48-51}

Structural changes in the myocytes of dysfunctional but viable myocardium include peri-nuclear loss of contractile proteins and replacement by glycogen deposits. The severity of morphological degeneration appears to correlate with the timing and the degree of functional recovery after revascularisation.^{34,48} Patients with mild morphological alterations showed faster and more complete recovery of left ventricular function than those with more severe changes.⁴⁸ In support of this notion, a recent study investigated the role of PET imaging for identification of high-risk patients with depressed ventricular function.³⁹ PET identified viable myocardium in 35 of 46 patients who were scheduled for revascularisation. Operative mortality was significantly lower in patients undergoing early revascularisation (<35 days) compared to those that received late revascularisation (>35 days) (0% versus 24%). Furthermore, left ventricular ejection fraction only improved significantly among patients in the early revascularisation group ($24 \pm 7\%$ versus $31 \pm 11\%$) and not in those that underwent late revascularisation ($27 \pm 5\%$ versus $28 \pm 6\%$).

Other Cardiac PET Techniques

PET Imaging of Endothelial Dysfunction

Local vasoactive substances secreted by the endothelial cells strongly modulate coronary vascular smooth muscle contractility. Such substances include prostacyclin (PGI_2), thromboxane (TXA_2), endothelium-derived relaxing factor (EDRF, nitric oxide), endothelium-derived contracting

factor (EDCF, endothelin) and endothelium-derived hyperpolarising factor.

With denuded, dysfunctional, or regenerating endothelium, production of PGI_2 and EDRF are impaired, leading to greater propensity for vasoconstriction and platelet aggregation.

Risk factors for coronary artery disease (CAD), such as hyperlipidaemia and smoking, impair normal endothelial-mediated vasomotor function of both macro- and microcirculation, leading to vasoconstriction of epicardial vessels and arterioles, reduced flow reserve, impaired vasodilation and increased platelet thrombus formation. Chronic inhibition of endothelial nitric oxide production also leads to structural abnormalities of the microvasculature and peri-arteriolar fibrosis.

Endothelial dysfunction improves within weeks of medical interventions such as cholesterol lowering therapy, antioxidants, exercise training, low-fat diet, cessation of smoking and L-arginine administration.

Presently, only invasive coronary techniques, such as intravascular ultrasound measurement of arterial diameter and Doppler wire assessment of coronary flow velocity are able to provide data on coronary endothelial function.

PET can now provide a non-invasive, easily interpretable view of endothelial dysfunction by utilising quantitative perfusion imaging, and this may become applicable for routine clinical use in future. This view of endothelial dysfunction integrates the effects of endothelial dysfunction along the entire length of all coronary arteries throughout the vascular tree.

The abnormal vasomotor tone associated with endothelial dysfunction of coronary atherosclerosis is seen as heterogeneous areas of lower resting perfusion by PET.

In the absence of flow limiting stenoses, the heterogeneous resting perfusion improves after administration of direct arteriolar vasodilators such as dipyridamole or adenosine, reflecting heterogeneous endothelial dysfunction that may improve after risk factor modification.

Haemodynamically significant epicardial coronary stenoses cause perfusion images to worsen after vasodilator infusion, indicating reduced coronary flow reserve.

Coronary Flow Reserve (CFR)

Under resting conditions, coronary blood flow remains normal during progressive coronary artery narrowing until the coronary arterial lumen is severely reduced, to approximately 70% to 80% diameter stenosis, reflecting advanced disease. Consequently, resting coronary flow or myocardial perfusion imaging at rest does not sensitively reflect the presence or severity of coronary disease, and the

disease remain clinically silent until thrombosis, spasm or further narrowing lead to unstable angina, myocardial infarction or sudden death.

However, maximal coronary flow and coronary flow reserve (capacity to increase flow to high levels in response to exercise or pharmacologic stress) becomes impaired with even mild coronary stenosis. This technique can be applied clinically as a means of identifying and quantifying the functional and haemodynamic significance of coronary stenosis.

The value of CFR, as a measure of stenosis severity, depends on the effectiveness of the vasodilator stimulus for maximally increasing coronary flow, in order to maximise regional differences in maximal perfusion caused by flow limiting stenoses. As exercise is not an optimal stimulus for maximal flow, a potent arteriolar vasodilator, such as dipyridamole or adenosine, which can stimulate a 4-fold increase in blood flow, is used instead. Abnormalities in coronary flow reserve can thus be used to reflect the presence and severity of coronary stenoses.

Base-to-Apex Longitudinal Perfusion Gradient

The coronary arteries arise at the base of the heart and distribute obliquely towards the apex. The distribution of blood is, therefore, longitudinal from the base to apex along the long axis of the heart. With mild to moderate diffuse coronary narrowing, cumulative branch steal along the arterial lengths causes a gradual longitudinal base to apex perfusion gradient.

Elderly individuals and subjects with no coronary disease do not show significant perfusion gradient. In contrast, many patients without flow-limiting stenosis demonstrate this type of perfusion abnormalities, indicating diffuse atherosclerosis. Subjects with risk factors for CAD also demonstrate this perfusion gradient, indicating the development of early atherosclerosis.⁵² Thus, one could postulate that this gradient can be used as a very early indicator of CAD.

This concept can also be utilised in selection of patients for percutaneous transluminal coronary angioplasty (PTCA), especially if there are multiple lesions in the target vessel. In some patients, the flow reserve fails to improve after revascularisation, probably from unrecognised diffuse coronary narrowing.

Myocardial Ischaemia Imaging

Myocardial ischaemia results from an imbalance of demand and supply. There is a whole cascade of changes occurring, starting with reduced perfusion, metabolic changes including decreased oxygen tension, increased glucose utilisation, reduced free fatty acid utilisation and reduced lactate uptake, finally resulting in wall motion

abnormalities, ECG changes and ultimately symptoms.

An agent that can show up areas of ischaemia directly would be ideal in the detection of ischaemic heart disease, negating the need for both stress and rest perfusion imaging, with its accompanying problems. New tracers for hypoxia imaging are in development and have completed animal studies, and are now awaiting large-scale human trials. Such tracers include both technetium-based agents and positron emitters. These tracers all have the properties of being lipophilic, with high membrane permeability, have electron affinity with low redox potential, have a trapping mechanism dependent on oxygen concentration, and the positron emitters are typically nitro-heterocyclic compounds.

Although direct “hot-spot” imaging of hypoxia has great potential, such as a single imaging technique, it also faces certain difficulties. Duration of ischaemia is usually short and variable, which allows for only a short window period for imaging. Variable physiological circumstance, such as myocardial infarction, reperfusion following myocardial injury, hibernation and stunning also complicate the imaging.

Both Lewis et al⁵³ and Fujibayashi et al^{54,55} have demonstrated the possibility of using a positron emitter, Cu-64-diacetyl-bis, for hypoxic imaging in experimental rats and dogs. In these studies, the authors showed that the tracer only accumulated in hypoxic mitochondria and not in reperfused or normal myocardium, and that hypoxia imaging was inversely correlated with perfusion imaging. Recent studies have suggested the possibility of imaging hypoxic myocardium during stress with ¹⁸F-DG,⁵⁶ and using ¹¹C lactate imaging as indirect evidence of myocardial hypoxia.

The advent of hypoxia imaging certainly appears promising, but more clinical studies will have to be carried out before the clinical potential can be fully realised.

Non-invasive Imaging in the Management of Coronary Artery Disease

In clinical application, treatment regimens to partially reverse or stop progression of atherosclerosis involves substantial commitment to diet, exercise, weight reduction, blood pressure, sugar and cholesterol control. Of patients with risk factors for CAD, only about half will have significant coronary disease. Thus, a firm diagnosis of CAD is essential as the basis for undertaking a vigorous lifelong cardiac reversal regimen.

For non-invasive diagnosis, cardiac PET detects localised and diffuse CAD and assesses its severity with a high degree of diagnostic accuracy, providing reliable basis for treatment. PET identifies which coronary arteries are involved and the quantitative severity of disease, and it is

accurate in asymptomatic and symptomatic subjects.^{57,58}

For following changes in disease severity, PET measures small changes in myocardial perfusion more reliably, compared to quantitative coronary angiography.

Although symptom dictated reactive treatment remains important in cardiovascular medicine, advanced diagnostic and therapeutic technology now provides an alternative approach for management of clinically silent disease. PET has sufficient accuracy for the diagnosis of CAD in asymptomatic and symptomatic individuals that permits testing for dietary and pharmacologic stabilisation and reversal of either silent or clinical manifest CAD.

Cost Effectiveness of Cardiac PET

Although there is no doubt of the clinical utility of PET, the cost of this modality is significantly higher compared to other modalities such as SPECT and echocardiography. Cost effectiveness and containment studies have not shown conclusive evidence for its widespread use in all patient population groups. It would thus be prudent to reserve this investigative modality for certain groups of patients in whom other testing methods have shown equivocal or inconclusive results. This is supported by the fact that some authors have shown that sestamibi SPECT is clinically as useful as ¹⁸F-DG PET in determining management and outcome in patients with significant coronary disease.⁵⁹

The Future

Because of the inherent improved spatial resolution of PET imaging, the future appears bright. Several important aspects that will appear in future are that of apoptosis imaging and coronary plaque imaging via molecular cardiac imaging, with targets that can include genes and cardiac cell receptors. PET neuronal imaging with C-11 labelled analogues of epinephrine and nor-epinephrine also appear promising, akin to I-123-meta-iodo-benzyl-guanidine (MIBG) imaging for cardiac receptors in SPECT. Preliminary studies have shown that PET cardiac neuronal imaging have the same prognostic significance as MIBG cardiac imaging.

Conclusions

This review emphasises the vast clinical evidence of the benefits of PET assessment of myocardial viability prior to coronary revascularisation. Proper viability assessment will lead to the correct use of resources for patients who would benefit from intervention the most, thus saving health costs. Perfusion imaging has now come to the forefront of PET imaging. The ability to measure absolute blood flow opens the possibility of very early detection of coronary artery disease. Its high spatial resolution lends itself to the ability to detect minute changes in flow, and thus it can be used to follow patients with CAD after risk

factor modification. The future appears bright for cardiac PET, with the development of various other imaging modalities for hypoxia, apoptosis and in future cardiac receptors and genes.

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