Introduction

Myocardial ischemia and infarction cause abnormal myocardial metabolism, decreased left ventricular (LV) systolic function, diastolic dysfunction, congestive heart failure, and decreased survival. Consequently, revascularization techniques, either surgical or catheter based, have become integral to treatment of severe ischemic heart disease.

With revascularization, significant areas of dysfunctional myocardium can regain their function, resulting in improved LV performance and in increased survival. Current data suggests that 25–40% of patients with ischemic LV dysfunction are potential candidates for improvement following revascularization [1–5]. The challenge lies in correctly identifying this group of patients based on accurate detection of ischemic and viable myocardium.

Nuclear imaging techniques, like single photon emission tomography (SPECT) and positron emission tomography (PET), directly assess myocardial perfusion, cell membrane integrity, cellular metabolism, and the molecular mechanisms of ischemic viable or necrotic myocardium, thereby indicating revascularization procedures or not.

Historical Perspective and Definitions

Over the past 25 years, the basis for revascularization of dysfunctional injured myocardium has undergone major changes. In the initial years of quantifying LV function, its impairment at resting conditions was regarded as an irreversible process of myocardial necrosis and scarring. However, early observations from Heyndrickx GR et al. showed experimentally that regional myocardial dysfunction could persist for hours after coronary occlusion followed by recovery of function with reperfusion in the absence of myocardial infarction (MI) [6]. This delayed recovery of contractility was later called “stunned myocardium” [7]. The concept of stunned myocardium was then extended to repetitive short episodes of severe myocardial ischemia, followed by adequate myocardial perfusion after the transient ischemic period.

The concept of “hibernating myocardium” was later reported based on clinical observations rather than animal experiments [8, 9] as persistent, stable hypoperfusion, and ischemia leading to a chronic state of poor LV contractility that was reversible with revascularization or restoration of adequate coronary flow. Hibernating and stunned myocardium are both characterized by poorly contracting myocardium that is viable (alive) myocardium that recovers contractile function after revascularization, in contrast to permanently dysfunctional scar tissue. Finally, the concept of “ischemic preconditioning” was first described experimentally in dogs when short repetitive episodes of myocardial ischemia resulted in reduced infarction following a subsequent prolonged coronary artery occlusion [10].

Stunning, hibernation and ischemic preconditioning are all elements of acute or chronic heart
adaptation to severe temporary or persistent ischemia that contribute to the preservation of the myocyte structural and functional integrity [11] by reducing regional myocardial oxygen consumption in the face of limited blood supply. Ischemic tissue is viable with preserved contractility under resting conditions as opposed to stunned and hibernating myocardium that is viable with impaired contraction.

The term “myocardial viability” is defined functionally as the capacity of ischemically injured, non-contracting myocardium to recover contractile function after revascularization or reperfusion [12]. The term refers to both acute dysfunction (stunned myocardium) and a chronic state low resting perfusion (hibernating myocardium), both of which indicate revascularization and consequent improved cardiac contraction. This functional definition is based on the outcome of revascularization in retrospect and does not refer to specific biological processes or cell behavior that predicts recovery of LV function. Identifying any of several different cellular processes of viable or “live” but non-contractile myocardium by imaging or functional testing then becomes the basis for revascularization procedures expected to improve contractile function. Therefore, the term is defined by the specific imaging technology used to determine “viability”, such as by nuclear methods to image cell membrane integrity and metabolism or alternatively by low dose dobutamine echocardiography or magnetic resonance imaging of reserve contractility. Nuclear cardiology has evolved in parallel with our understanding of the myocardial response to severe ischemia from imaging markers of the myocyte potassium space by late redistribution imaging [13] to metabolic imaging for separating viable from necrotic or scarred myocardium to the concept of reverse redistribution as a marker of endothelial dysfunction in advanced or early coronary artery disease before significant ischemia develops [14] and finally to molecular imaging.

Physiologic Principles of Myocardial Perfusion Imaging

The well established phenomenon of “perfusion-contraction matching” [15] is an adaptive myocardial response to chronically diminished perfusion. Therefore, analyzing this adaptive process requires simultaneous study of myocardial perfusion, metabolism, and regional myocardial function. The physiologic principles of myocardial perfusion imaging (MPI) with SPECT and PET imaging for identifying or assessing severity of coronary artery stenosis and ischemia derive from the concepts of coronary flow reserve [16–23].

Flow through moderately severe coronary artery stenosis is commonly normal at rest but becomes inadequate for the increased metabolic requirements and blood flow during stress. Coronary blood flow normally increases to four times resting baseline flow rates after coronary artery vasodilators such as dipyridamole and adenosine. A stenosis restricts maximal blood flow capacity compared to normal coronary arteries, thereby causing a disparity in regional perfusion of areas supplied by a stenotic artery compared to normal coronary arteries. This disparity manifests as a relative perfusion defect during stress, corresponding to the ischemic myocardial territory supplied by a stenotic artery. Furthermore, the quantitative severity of the relative perfusion defect is proportional to the severity of the stenosis under conditions of maximal coronary flow after dipyridamole or adenosine stress [24].

Figure 2.1 illustrates normal myocardial perfusion by PET using $^{82}$Rubidium ($^{82}$Rb) at rest and after dipyridamole stress in 3D views. A coronary arterial map is overlaid on the perfusion image or alternatively an arterial distribution map as a precise perfusion atlas of the coronary artery tree and all its secondary and tertiary branches [25].

In Fig. 2.2, the PET perfusion images show severe stenosis or occlusion of the left circumflex (LCx) and right (RCA) coronary arteries with a moderately severe stenosis of the left anterior descending (LAD) coronary artery proximal to its second diagonal branch. The ejection fraction (EF) and regional LV contraction were normal. Therefore, this example illustrates purely ischemic myocardium without scar and without injured or poorly contracting myocardium.

With single photon emission computed tomography (SPECT), an average difference from normal to abnormal regions of 30–50% is necessary before the abnormality is visually identifiable [17], as opposed to PET where differences of only 5–10% can be visually detected. Moreover, PET has the unique ability to non-invasively quantify relative or absolute coronary blood flow and metabolism.
based on quantitative measurements of myocardial radionuclide uptake without attenuation artifacts that limit SPECT.

In contrast to imaging relative coronary reserve during stress for ischemia due to flow limiting stenosis, assessing viability requires imaging metabolic processes and perfusion at resting conditions. Both SPECT and PET can be used to evaluate direct measures of myocardial viability by imaging intermediary metabolism and/or the potassium space reflecting cell membrane function. However, PET is more accurate due to higher resolution and correction of attenuation defects. By comparison, dobutamine stress echocardiography and magnetic resonance imaging (MRI) evaluate the reserve contractile capacity of the heart during stress as an indirect measure of myocardial viability.

Non-contracting viable myocardium traps potassium analogues in the myocyte potassium space, such as $^{201}$Thallium ($^{201}$TI) for SPECT imaging and $^{82}$Rb for PET imaging, reflecting sufficient cell membrane integrity [4, 26–32] to maintain the intracellular potassium space. Therefore, residual trapping of these potassium analogue radiotracers identifies viable myocardium associated with recovery of contraction following revascularization.

For SPECT, $^{201}$TI is the most useful tracer for viability assessment, since it is a potassium analog pooling in the intracellular potassium space. After initial cellular uptake of $^{201}$TI in approximate proportion to perfusion, a continuous exchange of the tracer occurs between the blood pool, the extracellular space, and the intracellular space. This exchange is the basis for $^{201}$TI redistribution to underperfused regions with delayed trapping in the potassium space. In viable myocardium with persistent low coronary flow, $^{201}$TI slowly redistributes into the resting perfusion defect, thereby making it less severe or even normalizing on late 4–24 h resting images.

Redistribution imaging may be combined with stress. If a resting defect persists with late

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**Fig. 2.1** Normal myocardial perfusion by positron emission tomography using $^{82}$Rubidium ($^{82}$Rb) at rest and after dipyridamole stress in 3D views. Coronary arterial maps are superimposed. Perfusion is displayed on a color scale, representing fraction of normal perfusion.
redistribution imaging, a second dose of $^{201}$Tl may be injected with repeat imaging 6–24 h later. With this re-injection technique, up to 49% of the fixed defects on late redistribution imaging will show normal or improved uptake, suggesting viability [33].

While $^{201}$Tl is optimal for SPECT imaging of viable myocardium, Technetium-99m-sestamibi (MIBI) may also be used. MIBI distribution reflects regional blood flow and requires preserved cellular membrane and mitochondrial function for uptake and intracellular retention [34–36]. However, as compared to $^{201}$Tl, MIBI does not demonstrate redistribution and viability is based on initial uptake rather than on defect reversibility with delayed imaging. Since MIBI is more easily produced than $^{201}$Tl, it is more commonly used for stress perfusion imaging as well as viability. The use of ECG gated perfusion images of MIBI or $^{201}$Tl to assess LV wall motion (gated SPECT) may increase the accuracy of viability assessment [37]. The addition of nitrates to enhance resting perfusion may also increase diagnostic sensitivity [38].

Dual isotope SPECT protocols obtain resting images with $^{201}$Tl and stress images with MIBI followed by 24 h $^{201}$Tl late redistribution imaging [39, 40]. These protocols have demonstrated good prediction of contractile function recovery after revascularization comparable to simpler single tracer protocols [41].

While SPECT imaging with $^{201}$Tl and MIBI is commonly used to demonstrate viability, these technologies may provide incorrect information in approximately 20% of patients with large severe defects and low EF. PET is the gold standard for assessing viability due to its higher resolution, attenuation correction, and quantification of radionuclide uptake. Moreover, PET can demonstrate cell membrane integrity with the potassium analog $^{82}$Rb and uptake of metabolic tracers using radio-labeled glucose, fatty acids, and acetate or oxygen analogs.

With adequate blood flow and oxygen supply after fasting or a fatty meal, normal myocardium...
metabolizes primarily fatty acids while glucose metabolism is suppressed. Therefore, normally contracting, normally perfused myocardium does not take up glucose or its radio-labeled analogues like $^{18}$F-fluoro-2-deoxyglucose (FDG) under fasting conditions or after a fatty meal. Failure of myocardial FDG uptake due to preferential fatty acids metabolism may cause defects on an FDG image that look the same as a myocardial scar. Consequently, imaging with FDG is done after a high carbohydrate meal and oral glucose load that shifts normal myocardium from fatty acids to glucose metabolism such that normal and ischemic viable myocardium take up FDG but necrotic or scarred myocardium does not, appearing as a defect.

In ischemic viable myocytes, the lack of oxygen inhibits fatty acids oxidation and myocardial metabolism is shifted toward anaerobic glycolysis of glucose. Therefore, under fed conditions after a high carbohydrate meal or after an oral glucose load, areas of hibernating myocardium with low perfusion will preferentially take up FDG resulting in a metabolism–perfusion mismatch (high FDG uptake, low perfusion) as a marker of viable hypoperfused dysfunctional myocardium [42–44]. Surrounding normal myocardium will also take up FDG but will have normal perfusion and function. Regions of stunned myocardium also demonstrate normal or enhanced glucose uptake but the resting perfusion is normal in areas of poorly contracting myocardium [45]. However, with stunned myocardium, stress perfusion images have a severe stress induced perfusion defect as the cause of repetitive ischemia leading to contractile dysfunction.

Residual trapping of metabolic analogues by hibernating myocardium, such as FDG [46–48], $^{11}$Carbon ($^{11}$C) acetate [49–52], and $^{11}$C palmitate [53–55] reflects sufficient integrity of myocytes and their metabolism to allow recovery of myocardial contractile function after revascularization.

Of these metabolic analogues, FDG has been the most extensively studied and is the most widely used PET marker of myocardial viability [56]. FDG is transported across the myocyte cell membrane and is phosphorylated by hexokinase. The phosphorylated compound cannot be metabolized or transported out of the cell and is therefore trapped in the myocyte. However, under some conditions, FDG studies may not accurately predict contractility recovery, since FDG uptake also depends on fasting or fed state, insulin and serum fatty acids levels, insulin resistance, cardiac work, catecholamines, and pH [57–60]. Good FDG PET images of the heart can be routinely obtained by having patients eat a carbohydrate meal, giving a glucose load, with insulin in diabetics, and avoiding catecholamine stimulus such as aminophylline after pharmacologic stress.

Concomitant with PET imaging of FDG, myocardial perfusion is imaged with $^{13}$N-ammonia [61–63] or with $^{82}$Rb [64]. The combined perfusion FDG images demonstrate several patterns:

(i) matched normal flow and metabolism in normal myocardium with normal perfusion and normal function;
(ii) matched normal flow and metabolism in normal myocardium with reduced regional contractile function characteristic of stunned myocardium or, if global, typical of cardiomyopathy;
(iii) matched defects on both perfusion and metabolic images showing diminished flow and diminished metabolism consistent with scar tissue;
(iv) the perfusion-metabolism mismatch pattern, with reduced coronary flow and normal/increased FDG uptake, characteristic of viable hibernating myocardium;
(v) reversed perfusion metabolism mismatch with normal perfusion, reduced FDG uptake and normal function that is due to preferential fatty acids metabolism in non-ischemic myocardium. However, if contractile function is reduced, this reverse mismatch may also indicate stunned myocardium with normal fatty acids metabolism that recovers quickly after restored perfusion, whereas recovery of contractile function may require weeks to months [65].

Figure 2.3 illustrates PET images of resting perfusion and metabolism using FDG showing a large myocardial scar in the LAD proximal to the first septal perforator that wraps around the apex and up the infero-apical wall. The scar is characterized by low perfusion and low metabolism or low FDG uptake (perfusion–metabolism match with low uptake of both radionuclides). The distribution of the LCx is mildly hypoperfused at rest but active metabolically with FDG uptake, thereby indicating
Fig. 2.3 Positron emission tomography (PET) images of resting perfusion and metabolism using FDG showing a large myocardial scar in the LAD proximal to the first septal perforator.

Fig. 2.4 PET images showing hibernating myocardium with low resting perfusion but active metabolism with normal FDG uptake in the distribution of the LCx and the diagonal branches off the LAD (perfusion-metabolism mismatch). There is also a septal scar.
that it is viable. The ramus intermedius (RI) and the RCA are normally perfused at resting conditions with normal metabolic uptake of FDG (perfusion–metabolism match—normal perfusion and metabolism).

Figure 2.4 illustrates hibernating myocardium with low resting perfusion but active metabolism with normal FDG uptake in the distribution of the LCx and the diagonal branches of the LAD (perfusion–metabolism mismatch). There is scar with low perfusion and low FDG uptake in septum (perfusion–metabolism match—low perfusion and low metabolism) indicating scar.

Figure 2.5 illustrates still another combination of metabolic states of clinical importance. There is hibernating myocardium (mismatch with low perfusion and normal metabolic FDG uptake) in the distribution of the mid LAD wrapping around the apex with scar (matched low perfusion and low metabolism—low FDG uptake) in the RCA distribution. In the distribution of the LCx and proximal LAD including the first septal perforator, the perfusion is high and FDG uptake is low due to such good blood perfusion that the myocardium burns free fatty acids rather than taking up the glucose analog FDG.

Figure 2.6 illustrates stunned myocardium with normal resting perfusion but a severe stress induced perfusion defect that indicates severe ischemia in the distribution of the RCA and the LAD proximal to the first septal perforator. Metabolic imaging with FDG is not necessary, since resting perfusion is normal without scar with a left ventricular ejection fraction (LVEF) of 30% thereby indicating stunned myocardium that normalized after bypass surgery. This patient with severe stress induced ischemia and reduced LV function characteristic of stunned myocardium contrasts with the patient of Fig. 2.2 with severe ischemia but normal LV function and no stunning.

Figure 2.7 also illustrates stunned myocardium with resting perfusion and resting metabolic uptake of FDG in a patient with congestive heart failure, diabetes, and a LVEF of 10% where stress was not

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![Fig. 2.5 Positron emission tomography (PET) scan showing hibernating myocardium (mismatch with low perfusion and normal metabolic FDG uptake) in the distribution of the mid LAD with scar (matched low perfusion and low metabolism—low FDG uptake) in the RCA distribution](image)
done due to known severe three-vessel disease by prior coronary arteriography. Resting perfusion is mildly reduced in the distribution of the LCx and second diagonal branch of the LAD with normal resting perfusion throughout the rest of the LV. Such mild hypoperfusion of a relatively modestly sized area would not reduce the LVEF to 10% leaving the conclusion that the low LVEF was due to stunning associated with severe three-vessel disease. After 6 vessel bypass surgery the CHF resolved and LVEF improved to 40%, suggesting an element of cardiomyopathy that accounted for the remaining mildly impaired contractility.

Despite addressing different cellular functions, imaging the potassium space by $^{82}$Rb or by cellular metabolic trapping of FDG, the size and severity of the defects obtained with both radionuclides by PET are virtually identical [66, 67], indicating equivalent preservation of these two measures of viability.

**Radionuclide Imaging of Chronic Ischemic Heart Disease**

For patients with chronic CAD, nuclear imaging is essential for addressing the following major clinical issues: (i) detection of ischemic myocardium, (ii) differentiation between viable hibernating or stunned myocardium and scar tissue in mechanically dysfunctional regions, and (iii) risk stratification for future major adverse events. Such information provides the basis for percutaneous coronary intervention (PCI) or coronary artery bypass (CAB) surgery and assessing their outcomes based on detection of residual ischemia and recovery of contractile function.

Indications for radionuclide imaging in these patients are detailed in current ACC/AHA guidelines [68] and ACCF/ASNC appropriateness criteria for SPECT myocardial perfusion imaging [69]. While a detailed discussion of these indications is beyond the purpose of this text, for patients with advanced...
ischemic heart disease and LV dysfunction, these guidelines emphasize the following:

(i) Detection of ischemic myocardium: for symptomatic patients at risk for or with known CAD an MPI study is warranted, either by SPECT or by PET, if the patient can tolerate a form of stress and if cardiac catheterization is not the most appropriate initial test as for acute unstable coronary syndromes. For asymptomatic patients, radionuclide imaging with stress to detect ischemia is appropriate for the following categories: (a) new onset or known heart failure or LV systolic dysfunction if there is no prior CAD evaluation and no cardiac catheterization is planned for other reasons and (b) in patients at greater than or equal to 5 years after CAB and at 2 years after PCI [69].

(ii) Viability assessment: SPECT or PET imaging are indicated in patients with known CAD after myocardial infarction or by cardiac catheterization with dysfunctional myocardial segments by echocardiography, radionuclide angiography or gated SPECT. Any viability imaging protocol should address the presence of coexistent ischemia as well as of regional wall motion abnormalities and LV global systolic performance.

(iii) Evaluation of risk for future events: the combined assessment of myocardial ischemia and of the amount of scar and viable tissue represents a powerful tool in predicting outcomes of patients with ischemic heart disease.

Size and severity of ischemic areas correlate well with mortality in both stable CAD populations [70] and after myocardial infarction [71]. Moreover, the presence of ischemia in a dysfunctional segment of myocardium is a powerful predictor of functional recovery. Up to 83% of regions with reversible defects (ischemia) will improve with revascularization compared to only 33% for regions where no reversibility was demonstrated [72]. In patients with heart failure, viable poorly contracting myocardium correlates with recovery.
of regional [73] and global LV function [74] after revascularization with improvement of functional heart failure class [75]. For post MI patients, the presence of viable tissue is a powerful predictor of future adverse cardiac events [76, 77] that warrants radionuclide imaging as a guide to revascularization.

(iv) After revascularization, appropriate indications for MPI include patients who present with a chest pain syndrome, or are asymptomatic but at greater than 5 years after CAB or 2 years after PCI [69]. Radionuclide ventriculography or gated perfusion imaging is useful to evaluate LV functional recovery in these patients.

**Myocardial Viability, Size of Myocardial Scar, LV Function, and Outcomes**

Positron emission tomography provides the optimal basis for clinical decisions on revascularization of patients with impaired LV function and for reducing the number of unnecessary procedures. Overall, PET positive and negative accuracy for predicting improved LV function is 85–90% [78].

In post myocardial infarction patients, LVEF is closely related to the infarct size by PET, as illustrated in Fig. 2.8 [79]. In such patients, the presence of viable myocardium is associated with good survival post revascularization, whereas the absence of viable myocardium predicts a higher mortality rate that is not improved by revascularization. Thus, appropriate evaluation for presence of viable myocardium can exclude patients from unnecessary revascularization procedures.

Almost half (46%) of all post MI patients will have completed necrosis without remaining areas of viable myocardium; of the remaining 54%, some will benefit from revascularization or from vigorous reversal treatment of atherosclerosis [79, 80], summarized by Fig. 2.9. The benefit of revascularization has been well established only in patients with moderate LV dysfunction (LVEF < 35%), whereas the survival benefit for those with regional LV dysfunction without reduced LVEF is suggested only by non-randomized or uncontrolled studies [81].

The challenge consists of identifying those at high enough risk, with a substantial amount of viable myocardium, who would benefit from revascularization. The criteria for selecting such patients include symptoms, collaterals, LV function, ischemic burden, associated indications for cardiovascular surgery or co-morbidities, and the amount of viable myocardium.

Much of the research on myocardial viability has focused on measuring pathological changes, cellular metabolism, or myocardial contractility without defining how much of the myocardium is involved, its relation to LV systolic function, and clinical outcomes. PET currently provides the best answer to the following questions: (a) How much myocardium is scarred or viable as a percent of the zone at risk distal to a stenosis and as a percent of the whole heart? (b) What amount of viable tissue justifies revascularization?

The zone at risk is defined differently from the infarct area and from viability as the area of reduced flow reserve by dipyridamole stress perfusion imaging rather than by rest perfusion imaging. The physiologic basis for this approach is the well documented observation that resting coronary flow may be normal with up to 85% stenosis; consequently, rest imaging may not define the correct size of zone at risk, as illustrated by the example below.

There is a conceptual difference between myocardial viability in a resting perfusion defect versus a stress induced defect. A rest perfusion defect may enlarge peripherally with stress due to reduced flow reserve secondary to a flow limiting stenosis,
defining a border zone at risk that is by definition viable myocardium. However, in this situation there is no information on viability of the central area of the resting defect that may be either scar or partial scar mixed with viable (hibernating or stunned) myocardium. Incorrect definition of the size of the zone at risk, scar, and amount of viable myocardium leads to unnecessary revascularization in 31–39% of the patients undergoing such procedures [77, 79, 82, 83].

Figure 2.10 illustrates a zone at risk by PET perfusion imaging. In this example, there is a moderate resting perfusion defect indicating a small non-transmural scar in the distribution of the LAD. After dipyridamole stress, the perfusion defect becomes larger and more severe, indicating a large border zone of ischemic myocardium around the small scar supplied by a severe stenosis. The border zone area is large enough to justify revascularization without metabolic imaging in this instance.

The different stages of ischemic dysfunctional myocardium are a continuum of regional rest or stress-induced hypoperfusion, cell membrane integrity ($^{201}$TI and $^{82}$Rb uptake), metabolic changes (FDG uptake), preserved, absent, or inducible contractility (dobutamine echocardiography or MRI), variable degrees of myocyte dedifferentiation [84], and tissue fibrosis. The degree to which each of these elements is impaired defines the specific conditions of ischemic, stunned, and hibernating myocardium (all viable tissue states) and scar (non-viable tissue) for a particular myocardial region. Moreover, for a particular region of the myocardium, two or more of these conditions usually coexist, such as scar mixed with ischemia

**Fig. 2.9** Effect of revascularization on myocardial viability in post myocardial infarction (MI) patients. Almost half of all post MI patients will have completed necrosis without remaining areas of viable myocardium.
or ischemic tissue mixed with non-contractile but viable myocardium or a mix of all three.

Therefore, various methods used for viability testing may provide somewhat discordant predictions of the recovery of contractile function after revascularization, as demonstrated by Bax JJ et al. [85, 86]. In an early comparative study, FDG PET and $^{201}$Tl had the highest weighted mean sensitivity (88% and 90%, respectively) in predicting myocardial functional recovery, whereas FDG PET and low dose dobutamine echocardiography had the highest specificity (73% and 81%, respectively) [86]. The overall accuracy of different viability methods in predicting recovery with revascularization ranges between 66% and 81% [87]. However, another large meta-analysis study found no difference between different viability testing methods for predicting survival after revascularization, suggesting that decisions driven by viability studies are clinically equivalent and have similar outcomes, irrespective of the technique used [88]. While improved LV function is a major factor affecting survival, reduced risk of arrhythmia and reduced rate of acute coronary syndromes and/or heart failure symptoms may contribute to the overall benefit.

While this chapter focuses on myocardium that will benefit from revascularization procedure, vigorous treatment of risk factors is essential for stopping progression of the atherosclerosis in native or coronary bypasses. The patient in Fig. 2.11 is a physician who had a myocardial infarction leading to coronary bypass surgery. The PET scan in Fig. 2.11 was obtained a year after bypass surgery, showing a severe resting (top row) defect of the apex in the distribution of the initial LAD occlusion. Dipyridamole stress causes more severe larger perfusion defects (middle row) in the distribution of the LAD and a large LCX, indicating severe residual diffuse coronary artery disease. The lower row of Fig. 2.11 shows the rest and dipyridamole stress perfusion images after 10 years of vigorous lifestyle and pharmacologic management including food with 10% of calories as fat, maintenance of lean...
body weight, daily workouts, Zocor 20 mg and Niaspan 1,500 mg daily to maintain total cholesterol 136 mg/dl, triglycerides 65 mg/dl, LDL 58 mg/dl, and HDL 65 mg/dl. Interim PET scans showed steady improvement up to this 10-year follow-up scan with progressively marked improvement of the diffuse disease that initially caused severe defects despite open bypass grafts.

Not all severe perfusion defects require revascularization procedures for patients with stable, even severe, angina who prefer vigorous medical treatment. In Fig. 2.12, the rest perfusion image (upper row) shows a small transmural scar in the distribution of the distal LCx that is more severe and larger after dipyridamole stress (middle row). Quantitative analysis showed myocardial steal in the region of the defect, indicating collateralization to the LCx beyond an occlusion, confirmed by coronary arteriography. After reviewing the options and risks, the patient undertook a strict
lifestyle regimen maintaining 10% fat food, lean weight, regular exercise, Lipitor 5 mg, and Niaspan 1,000 mg daily achieving total cholesterol of 154 mg/dl, triglycerides 81 mg/dl, LDL 75 mg/dl, and HDL 63 mg/dl for the next 10 years. On the follow-up PET at 10 years, the stress induced perfusion defect is markedly smaller, essentially the same size as the small transmural scar on the baseline resting image and the patient had no exertional angina. With a documented LCX occlusion, this improvement is due to extensive collateral development with flow capacity that approaches that of the native artery under dipyridamole stress.

Since the first concept of viability, FDG imaging by PET has been the gold standard for myocardial viability assessment due to its proven value in predicting functional outcomes after revascularization [61, 64, 89, 90] and in risk assessment for those patients with viable myocardium who are treated conservatively [76, 82, 91]. This leading role for PET in assessing viability has continued into current literature with further advances in PET imaging in

**Fig. 2.12** Effect of intense medical therapy on progression of non-revascularized CAD. Rest perfusion image (*upper row*) shows a small transmural scar in the distribution of the distal LCX that is more severe and larger after dipyridamole stress (*middle row*). Follow-up PET (*lower row*) after 10 years of intense medical therapy shows that the stress induced perfusion defect is markedly smaller.
comparison to other advanced imaging technologies. In a recent study, FDG PET had positive predictive value of 86%, negative predictive value of 100%, and diagnostic accuracy of 90% for recovery of LV function after revascularization [92]. Studies assessing viability with dobutamine MRI studies have reported comparable diagnostic accuracy but may have used a more selected study population [92]. The clinical value of FDG viability imaging can be further increased by gated FDG studies. The presence of LVEF < 25%, an end-diastolic LV volume > 260 ml, and of perfusion-mismatch pattern on gated FDG PET reliably identifies a patient population at highest risk with incremental value over viability information alone [93].

**Essential Conditions for FDG PET Imaging**

Clinical interpretation of FDG PET images depends on whether the patient is in a fasting or fed condition. Under fasting conditions, normal myocardium will metabolize fatty acids and will not uptake FDG; ischemic viable myocardium will take up FDG and create a positive image of the ischemic viable area. However, with fasting, areas of no FDG uptake can represent either normal myocardium or scar, thereby preventing a definitive clinical interpretation. After a carbohydrate meal or following a glucose load, both normal and ischemic viable myocardium will take up FDG and create a positive image of normal and ischemic viable myocardium; areas of scar will not take up FDG and therefore produce an image defect. Accordingly, PET protocols may vary depending upon the clinical or research question [94]. However, the standard clinical protocol now is to perform FDG PET imaging after a carbohydrate meal, with glucose loading before the scan and for diabetics a low fixed intravenous dose of insulin to reduce fatty acids levels and to assure myocardial uptake of FDG in all areas of viable myocardium except scar. Additional protocol details can be obtained from the American Society for Nuclear Cardiology and Society of Nuclear Medicine guidelines [95].

For assessing viability of a non-contractile myocardial region, the non-fasting, fed patient is given an oral glucose load and resting perfusion images are obtained with $^{13}$N-ammonia or $^{82}$Rb prior to FDG in order to identify hypoperfused areas. FDG is then injected intravenously and 45 min later, resting images are again obtained. Normal and ischemic viable myocardium will take up FDG but scar tissue will not. A perfusion–metabolism mismatch (low perfusion, FDG uptake) in poorly contracting segments identifies hibernating myocardium. Normal resting perfusion and FDG uptake with poor contraction identifies stunned myocardium. Areas with severe defects of both perfusion and FDG images (low or no FDG uptake) represent scarred or necrotic myocardium. Areas of normal perfusion and no FDG uptake with normal contraction indicate normal preferential uptake of fatty acids rather than FDG in the presence of adequate oxygen supply. A common variation of this protocol determines both flow limiting stenoses and viability by sequential rest perfusion imaging followed by dipyridamole or adenosine stress perfusion imaging followed by resting FDG imaging.

If the clinical question is whether the viable myocardium is normally oxygenated or metabolically ischemic due to a coronary artery stenosis, imaging is done with the patient in fasting state and with exercise stress. Under such circumstances, ischemic myocardium will take up FDG, whereas normal or scarred myocardium will not. A resting perfusion scan (with $^{13}$N-ammonia or $^{82}$Rb) is obtained first, followed by exercise carried out on a treadmill with reinjection of the perfusion tracer at peak stress, which is maintained for another 45–60 s, followed by stress imaging. While the patient is recovering after exercise, FDG is injected and 45 min later, FDG imaging is started. Transiently ischemic myocardium during stress will continue to take up FDG for hours after the stress induced ischemia has resolved due to the induction of metabolic pathways for FDG uptake by transient ischemia. An area with normal perfusion at rest, but with a stress induced perfusion defect and FDG uptake is metabolically ischemic due to a severe flow-limiting coronary stenosis. An area with normal perfusion at rest, a stress induced perfusion defect, and no FDG uptake has a mild/moderate flow-limiting stenosis that is not severe enough to cause metabolic ischemia. An area with severe rest and stress perfusion defects and no FDG uptake represents myocardial scar. However, this fasting protocol for assessing
metabolic ischemia is seldom used clinically, since a flow-limiting stenosis causing a significant stress induced perfusion abnormality is commonly considered adequate grounds for revascularization. There are limitations in the use of FDG for viability assessment. Normal myocardium (normal perfusion and normal metabolism) in diabetics may not take up FDG due to insulin resistance associated with elevated free fatty acids in blood. Consequently, there is no FDG uptake anywhere in the heart and the study is uninterpretable. However, giving insulin intravenously at the time of glucose loading enhances myocardial uptake, reduces free fatty acids in blood, and provides diagnostic images. With appropriate attention to patient preparation, FDG PET in diabetics for assessing viability reportedly has high sensitivity (92%) and specificity (85%) [96]. A perfusion FDG mismatch on PET in diabetic patients reliably identifies high risk for cardiac death with medical treatment compared to revascularization [97].

**Limitations of FDG Imaging**

$^{18}$F-fluoro-2-deoxyglucose imaging in fasting, resting state should not be performed in the early stages of evolving or recovery from an acute myocardial infarction. In such circumstances, FDG uptake is highly variable, sufficient to preclude interpretation, with intense uptake in necrotic areas due to uptake of FDG by inflammatory cells giving a false positive diagnosis of viable tissue. Moreover, FDG uptake may not parallel glucose metabolism [98, 99], with regional heterogeneity of uptake related to blood concentrations of glucose, insulin, fatty acids, catecholamines, and beta-blockers. Lastly, FDG studies with perfusion and metabolic imaging usually require up to 3 h, thereby limiting the patient volume and revenues.

Alternatives to FDG for detecting viable myocardium are based on myocardial leak of creatine phosphokinase, inosine, inorganic phosphate [100–103] due to impaired cell membrane function induced by ischemia and/or necrosis. Therefore, the use of a potassium analogue reflecting myocardial cellular membrane function and the myocardial potassium space represents an alternative for a quantitative assessment of viability and infarction size. $^{201}$Tl is a potassium analogue for SPECT assessment of perfusion and myocardial viability that has well-documented value both experimentally and clinically. However, SPECT is limited by attenuation artifacts and depth-dependent poor resolution compared to PET.

$^{82}$Rb is a potassium analogue from commercially available $^{82}$Strontium generators. After intravenous injection, $^{82}$Rb is rapidly extracted and trapped in the potassium space of normal/viable myocardium but leaks out of necrotic cells as determined by histochemical methods leaving a perfusion defect [104]. The size of myocardial infarction determined by the size of the defect in $^{82}$Rb uptake on rest images equals the size of myocardial infarction as detected by FDG imaging [67, 79]. In contrast to FDG, one $^{82}$Rb viability study will take 1 h to complete, allowing higher volume per unit of time. Thus, viable or necrotic myocardium can be identified by either by measures of glucose metabolism (FDG) with PET imaging or cell membrane integrity using potassium analogs such as $^{201}$Tl with SPECT imaging or $^{82}$Rb with PET imaging. However, the ability of $^{82}$Rb washout between early and late resting imaging to reliably predict presence of viable myocardium as compared to identification of a perfusion–metabolism mismatch by FDG has been challenged in a recent study [105]. The authors reported poor specificity of $^{82}$Rb washout for identifying areas of viable myocardium. On the other hand, their methodology for quantifying $^{82}$Rb washout is open to question, since loss of the potassium space with corresponding defects on myocardial images of potassium analogs has been documented experimentally and clinically as a marker of necrotic or scarred myocardium.

The value of SPECT viability imaging with $^{201}$Tl is well established clinically with overall 70–75% accuracy for predicting recovery of LV function compared to PET [28, 29, 61, 89]. For MIBI, predictive accuracy decreases to 64% compared to PET [106, 107]. Some of these discrepancies are explained by frequent inferior wall attenuation artifacts encountered with SPECT [4, 108]. The randomized trial CHRISTMAS (Carvedilol Hibernating Reversible Ischemia) demonstrated that SPECT MIBI predicted LV functional recovery in patients receiving carvedilol [109] with LVEF improving by 3.8%, more in those patients with
hibernating myocardium by SPECT compared to those with no viable tissue. Whether such a small change is relevant for improved quality of life and prolonged survival was not determined. Larger controlled clinical trials are necessary to evaluate the role of revascularization in managing patients with heart failure due to ischemic heart disease [5]. The ongoing STITCH trial (Surgical Treatment for Ischemic Heart Failure) may provide an answer by randomizing patients with ischemic cardiomyopathy to medical therapy or CAB surgery based on SPECT imaging.

The value of PET for predicting clinical outcomes is complex, since the relevant end points include LV function, symptoms, reduced hospitalizations, and mortality. The utility of PET for assessing viability will vary for each of these endpoints. Most studies on changes in LV function as related to myocardial viability imaging have been performed in patients with moderately impaired systolic performance without quantifying the size of the viable myocardium or scar. In these studies the positive predictive accuracy decreases significantly in patients with more severe LV dysfunction (LVEF < 30–35%) [110]. In patients with severe LV dysfunction, quantification of the amount of viable myocardium as more than 31% of the left ventricle accurately predicts improvement in LVEF after revascularization [111, 112].

Clinically significant improvement of symptoms and reduction of repeat hospitalizations are also more accurately predicted in those patients with hibernating myocardium comprising more than 18% of the whole heart, particularly in the LAD coronary artery territory [75, 113]. Patients with large areas of hibernating myocardium will have a poor outcome if treated conservatively with medical therapy compared to revascularization [79, 113]. For these patients with large zones at risk, revascularization is associated with improved outcomes, irrespective of the method used for assessing viability, including SPECT, PET, or dobutamine echocardiography as reported by meta-analysis [88].

The value of PET for predicting contractile function after revascularization depends on whether perfusion or metabolic imaging is performed, or both. For perfusion imaging alone, if regional blood flow is preserved to more than 50% of normal, contractile dysfunction will likely recover with an average positive and negative predictive value of 63% (range 45–78% and 45–100%, respectively) [114]. Compared to perfusion imaging alone, PET metabolic imaging of 11C-acetate predicts functional recovery with a higher average positive predictive value of 72% and average negative predictive value of 76% (range 62–88% and 65–89%, respectively) [114].

Meta-analysis of perfusion—metabolism PET imaging for viability may not take into account the essential variables outlined above, differences in patient selection, or potential technical problems causing imaging artifacts [115]. Consequently, even when both measures of perfusion and metabolism are evaluated, the average positive predictive accuracy in predicting myocardial functional recovery after revascularization has a wide range of 52–100% with an average of 76%. The average negative predictive accuracy has an equally wide range of 67–100% with an average of 82% [114]. However, with optimal choice of patients, attention to medical and technical details with quantitative extent of viable myocardium, the accuracy of selecting patients for revascularization procedures approaches the upper end of these ranges—over 90%.

FDG PET and 201TI SPECT may be particularly useful in the future for following replacement of infarcted myocardium using intracoronary injections of progenitor cells. In a small series of patients, this approach demonstrated a significant increase in myocardial viability and perfusion [116].

**Molecular Imaging**

From the original applications in coronary perfusion, cell membrane integrity, and cellular metabolism, nuclear medicine is evolving toward in vivo imaging of vasoreceptor functions and gene expression in early and advanced coronary artery disease [117, 118] including end stages such as heart failure. A major development of cardiac molecular biology involves transfer of genetic information from DNA to RNA by transcription and subsequent protein synthesis based on RNA template by translation. Various molecular biology techniques allow manipulation of both DNA and RNA, identification of therapeutic and reporter genes, molecular probes, and target peptides.
Gene therapy represents an area of great research interest due to potential expression of local therapeutic factors specific for the disease process with a parallel need for clinical methods of imaging these localized processes [119] using SPECT, PET, and MRI. Such targeted imaging requires several fundamental interacting elements: (i) a specific molecular probe, (ii) a target peptide for either a direct or indirect imaging strategy [120], and (iii) adequate imaging characteristics such as target size, stability and specificity of radionuclide localization, signal to noise, blood pool clearance, and radionuclides availability.

Direct methods use radiolabeled monoclonal antibodies (molecular probes) directed against cell surface antigens and receptors, or specific enzymes [120]. Cardiac applications of these techniques have been primarily designed to image alpha and beta adrenergic or muscarinic receptors [121] and drug pharmacokinetics including receptor binding [122].

Single photon emission tomography of 123I-meta-iodobenzylguanidine (MIBG) images presynaptic sympathetic innervation of the heart. MIBG has a molecular structure similar to norepinephrine and is therefore taken up and stored in nerve presynaptic sympathetic endings [123]. In heart failure patients, low myocardial MIBG uptake combined with poor LV systolic performance (LVEF < 40%) [124, 125] and an accelerated MIBG washout rate [126] are independent predictors of mortality. For these patients, effects of drug therapy can be monitored using MIBG SPECT, including prediction of response to beta blockers [127, 128]. MIBG uptake is significantly reduced in areas of myocardial ischemia or infarction [129, 130], with the area of post infarct denervation being larger than the infarct related size of perfusion defects obtained with 201Tl. Denervation of the viable area of myocardium around a scar contributes to increased vulnerability to ventricular arrhythmias [131].

Of particular interest for early detection of coronary artery disease is the observation that MIBG washout rate correlates inversely with the severity of coronary stenoses, suggesting that adrenergic function may be impaired prior to developing flow limiting stenoses [132]. Imaging the sympathetic system may be important for transplanted hearts. While the cardiac allograft is initially completely denervated, MIBG SPECT studies have demonstrated reinnervation as early as 1 year after transplantation, a process that may be impaired by graft vasculopathy [133].

Positron emission tomography offers substantial advantages over SPECT in imaging cardiac neurotransmission, primarily due to absolute quantification of radionuclide uptake as the basis for calculating receptor density, or drug-receptor interaction for specific myocardial regions of interest. Multiple tracers are available for PET imaging of the sympathetic system, using either radiolabeled catecholamines or catecholamine analogues [134]. Most frequently used PET tracers are 11Carbon-meta-hydroxyephedrine (HED) and 18Fluorine-flurodopamine for studying ischemic heart disease [135, 136].

A reduction of HED uptake in patients with moderate heart failure is a predictor of poor outcome, a finding consistent with SPECT MIBG studies [137]. HED PET imaging demonstrates reinnervation of the transplanted heart [138] paralleling recovery of primarily fatty acids metabolism after an initial metabolic shift from fatty acids to glucose utilization associated with myocardial denervation [139].

Indirect imaging strategies such as reporter gene imaging [120] are more complex. This method involves delivery of a reporter gene to the target tissue via a viral or non-viral vector. The DNA of the reporter gene is transcribed to RNA with a reporter gene product generated via translation. The reporter gene product interacts with a reporter probe, leading to amplification of probe signal that may be imaged by PET, thereby localizing the reporter gene expression site and potentially the strength of expression [120].

Positron emission tomography reporter gene imaging may be particularly important for assessing angiogenic gene therapy in ischemic heart disease [140]. Hypoxia resulting from ischemia is the main stimulus for naturally occurring angiogenesis and collateral formation that provides blood flow to ischemic tissue [141]. Angiogenesis is mediated by a variety of factors, one of which is the vascular endothelial growth factor (VEGF), with 111Indium labeled VEGF having high uptake in ischemic tissue [142]. Several clinical trials of coronary angiogenesis have been reported, some of which used MPI as an endpoint [143, 144]. Other trials used reporter gene
imaging by linking a therapeutic gene to a reporter gene that is imaged by PET. Initial results of this approach have been reported using VEGF genes [145], recombinant human immunosuppressive cytokine interleukin-10 with intracoronary delivery [146], or other vectors with direct intramyocardial injection [147, 148].

Another approach images the expression of survival genes in hibernating myocardium with upregulation of anti-apoptosis and cytoprotective proteins as well as of growth factors—including VEGF [149]. The findings suggest a gene program for preventing cell death under conditions of prolonged ischemia. This study demonstrates the potential of PET gene imaging to evaluate hibernating or stunned viable myocardium or to monitor the effects of therapy aimed to enhance genetic survival mechanisms.

Molecular imaging may potentially address not only the pathophysiology of ischemia but also vascular inflammation causing rupture of atherosclerotic plaques before major ischemic events. Initial approaches have used imaging of $^{111}$Indium radiolabeled monocytes [150], upregulated metalloproteinases [151], and imaging of apoptosis in atherosclerotic lesions [152]. However, none have evolved into clinically useful tests.

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