The Clinical Role of Metabolic Imaging of the Heart by Positron Emission Tomography

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HISTORICAL BACKGROUND TO CARDIAC METABOLIC IMAGING

"Sometimes auscultation is impossible or of such doubtful value that it must be completely discounted and other methods relied on if they are available like the determination of the visible or palpable apex impulse or roentgenology."
(Paul Dudley White, MD 1931).

Only 60 years ago, the diagnostic work-up of patients with suspected or proven cardiac disease relied primarily upon clinical evaluation including use of the stethoscope, which was introduced in the early 19th century. Since then we have witnessed an impressive development of methods that allow the invasive and noninvasive characterization of cardiac disease. Cardiac imaging started with the discovery of x-rays at the end of the last century. Heart catheterization under fluoroscopic guidance was pioneered by Dr. Forssman in 1927. In the late 1940s, injection of contrast agents through catheters into the right ventricle provided visualization of the ventricular chambers (*1*). Approximately ten years later, elective coronary angiography became clinically available (*2*). Developments in invasive procedures were complemented by the introduction of the electrocardiogram in the 1930s and the application of ultrasound to the noninvasive assessment of cardiac function in 1954 (*3*). With the introduction of the Anger camera in 1964, visualization of the temporal and spatial distribution of radioactively labeled compounds in various organ systems including the heart became possible. Radiolabeled albumin was introduced for radionuclide angiography (*4,5*). Further development of radiopharmaceuticals led to new approaches for the assessment of myocardial mechanical function and perfusion and for the detection of acute myocardial necrosis. The role of planar imaging approaches was challenged over the next 15 years by advances in tomographic x-ray and scintigraphic data acquisition, which allowed the three-dimensional representation of cardiac structures. Positron emission tomography (PET) emerged in the seventies and, in combination with the improved radiochemical synthesis of multiple compounds labeled with positron-emitting radioisotopes such as carbon-11, oxygen-15, fluorine-18, and nitrogen-13, provided the ability to uniquely characterize regional myocardial tissue function. Most recently, nuclear magnetic resonance (NMR) has been introduced as a cardiac imaging modality, providing high spatial resolution and anatomical detail without ionizing radiation.

The Development of Physiologic Imaging

Together with the improved ability to define the structural changes associated with cardiac disease, it became apparent that functional characterization of the pathophysiologic consequences of disease was important to the study of the heart. Initial studies focused on definition of the hemodynamic consequences of cardiac disease employing pressure measurements in different chambers of the heart. Assessment of cardiac output provided an added dimension to the characterization of overall cardiac function. The ability to delineate anatomical changes in epicardial coronary arteries called for the need for measurements of myocardial perfusion. Among invasive and noninvasive techniques allowing the regional evaluation of myocardial perfusion, radionuclide approaches employing either single-photon techniques or PET have emerged as the methods of choice. PET currently represents the only technique allowing noninvasive quantification of regional myocardial blood flow in absolute terms (*6,7*).

Experimental data obtained in the sixties and seventies delineated the relationship between regional myocardial perfusion and function in ischemic heart disease. Noninvasive imaging procedures such as thallium-201 scintigraphy, radionuclide ventriculography, and echocardiography have been shown to provide highly accurate diagnosis and localization of coronary artery disease. However, neither functional parameters nor assessment of blood flow by imaging procedures specifically defines the effects of myo-

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cardial ischemia at a cellular level. Cardiac energy metabolism represents the link between oxygen delivery and contractile performance. Previous attempts to evaluate cardiac metabolism were limited to measurements of arteriovenous substrate differences across the heart (*8*). These measurements only provided estimates of global myocardial substrate extraction. The introduction of metabolic tracer techniques, as well as NMR spectroscopy, made the direct evaluation of regional cardiac metabolism possible. Although NMR spectroscopy yields high biochemical specificity, its application is limited by the poor spatial and temporal resolution of the data acquisition currently possible. At the present time, PET, in combination with various metabolic radiopharmaceuticals, allows unique evaluation of cardiac substrate metabolism in research as well as clinical practice (*9,10*).

This review will summarize available information on the clinical role of metabolic imaging by PET. We will briefly review the principles of cardiac substrate metabolism necessary for the understanding of radiopharmaceutical approaches currently used and describe commonly used positron-emitting metabolic tracers. We will focus on the application of metabolic imaging with PET in various cardiac disease states and discuss the findings in the context of clinical problems currently addressed in cardiology.

PRINCIPLES OF CARDIAC METABOLISM AND PET TRACER METHODOLOGY

Compared with other organs, the mammalian heart has one of the highest energy demands per gram of tissue. The oxygen requirements of the heart average 6–8 ml/min/100 g at rest, compared with only 0.15 ml/min/100 g for resting skeletal muscle. Approximately 80% of myocardial oxygen consumption is related to mechanical work, with only 20% used to maintain cellular integrity. In line with these high energy demands, extraction of oxygen by myocardial tissue is high and can only be slightly increased in response to increased oxygen demand. Therefore, myocardial blood flow must be closely matched to energy demand in the normal heart. This explains the sensitivity of cardiac energy metabolism to limitations of myocardial perfusion reserve caused by coronary artery disease.

The major biochemical correlate of myocardial energy production is oxidative phosphorylation and synthesis of high-energy phosphates. The heart muscle possesses the remarkable ability to utilize a number of different energy-providing substrates. Depending on plasma substrate levels, hormonal factors, and myocardial oxygen supply and demand, the heart can metabolize such varied substrates as free-fatty acids, glucose, lactate, pyruvate, ketone bodies, and amino acids (*8,11–13*). In the normal heart, especially in the fasting state, fatty acid metabolism is the predominant source of myocardial energy production. Under these conditions, oxidation of long-chain fatty acids provides approximately 70% of cardiac energy requirements, while carbohydrates account for the majority of the remaining 30% of energy production (*8,11*). Following carbohydrate loading, plasma glucose and insulin levels increase and fatty acid plasma levels decrease. As a consequence of this change in metabolic environment, the heart primarily uses glucose as an energy source. During exercise, lactate plasma levels increase and provide an important energy source for cardiac metabolism (*13*). While this metabolic virtuosity may complicate the assessment of cardiac metabolism, it may also lead to unique patterns of substrate use which reflect cardiac pathophysiology. Identification of these patterns by PET in combination with metabolic tracers may allow characterization of the pathophysiologic consequences of various cardiac diseases (*14*).

Figure 1 represents a simplified scheme of cardiac substrate metabolism. Long-chain fatty acids enter the cell and are activated to long-chain acetyl-CoA. Activated fatty acids either contribute to triglyceride synthesis or are transferred by the carnitine shuttle into the mitochondria where beta-oxidation occurs. The end product of beta-oxidation, acetyl-CoA, enters the tricarboxylic acid cycle. Fatty acid metabolic tracers, such as ^{11}C-palmitate, follow these same pathways.

Glucose is transported into the cell and phosphorylated to glucose-6-phosphate. At this point, glucose metabolism branches into glycogen synthesis and glycolysis. Pyruvate, the end product of glycolysis, enters the mitochondria and is converted to acetyl-CoA, which then enters the tricarboxylic acid cycle. Glucose metabolism is regulated by the cytosolic concentrations of the intermediary products of energy metabolism, such as citrate and adenosine diphosphate. Flux through the glycolytic pathway is controlled by interaction of these substances with a few key enzymatic systems, including the hexokinase, phosphofructokinase, glyceraldehyde dehydrogenase, and pyruvate dehydrogenase reactions (*13*). The glucose analog, ^{18}F-fluorodeoxyglucose, traces this initial transmembranous transport and phosphorylation of glucose, but is not metabolized further.

Besides fatty acids and carbohydrates, lactate and ketone bodies may participate in myocardial substrate metabolism. Exogenous lactate is taken up by the myocardium and converted to pyruvate, which then has the same metabolic fate as pyruvate derived from glycolysis. Compared with the complexity of glucose and long-chain fatty acid metabolism, metabolism of ketone bodies requires only a few steps, none of which appear to be subject to any particular control. Amino acids are predominantly used for protein synthesis within the heart and play only a minor role in cardiac energy metabolism. However, during ischemia, phosphorylation of amino acids may provide nonoxidative energy production.

The final common pathway of oxidative metabolism within the myocyte is the tricarboxylic acid cycle. Free-fatty acids, glycolytic metabolic intermediates, and lactate all enter this cycle. Carbon-11-acetate has recently been introduced as a tracer of oxidative metabolism (*15*) owing

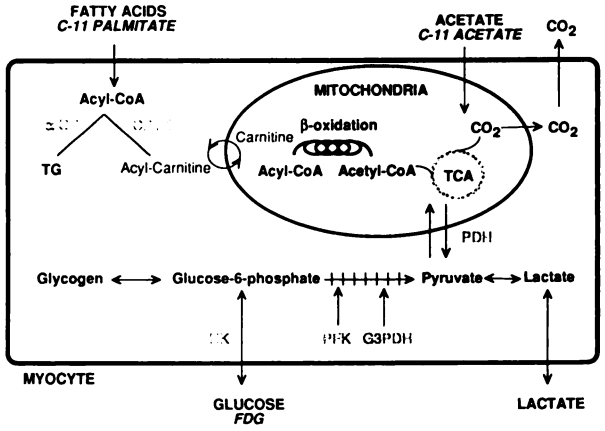

FIGURE 1. Schematized representation of metabolic pathways of myocardial substrate metabolism. Positron-emitting radiopharmaceuticals such as ^{11}C-palmitate, ^{11}C-acetate, and [^{18}F]FDG act as tracers of the metabolic fate of important energy substrates such as free-fatty acids and glucose. The tricarboxylic acid cycle (TCA) is the final common pathway of oxidative metabolism. The rate of glycolysis is controlled by several enzymatic systems including hexokinase (HK), phosphofructokinase (PFK), glyceraldehyde-3-phosphate dehydrogenase (G3PDH), and pyruvate dehydrogenase (PDH). Similarly, free-fatty acid metabolism is controlled by the availability of α-glyceryl phosphate (αGP) and the activity of the carnitine-palmitoyl-transferase (CPT 1).

to its preferred status as a direct substrate of the tricarboxylic acid cycle (*16*).

Although the basic patterns of substrate interaction in cardiac metabolism are known, the more detailed knowledge of the regulating steps in this complex interaction is limited. Several detailed reviews of cardiac metabolism are available (*8,11,13,17,18*).

RADIOPHARMACEUTICALS USED AS METABOLIC TRACERS

Carbon-11-palmitate

Carbon-11-palmitate has been widely employed for the experimental and clinical studies of cardiac fatty acid metabolism (*19–23*). Since the extraction fraction of ^{11}C-palmitate by the heart is over 50%, initial uptake of this tracer primarily reflects blood flow. Clearance of ^{11}C activity from the myocardium is bi-exponential, reflecting the metabolic fate of the tracer (*22*). The early rapid clearance phase corresponds to the release of ^{11}C-carbon-dioxide as the end product of beta-oxidation. The size and rate of this clearance phase has been shown to sensitively reflect changes in cardiac workload and substrate utilization (*23*). In contrast, the late slow phase most likely relates to the deposition of tracer in endogenous lipid pools in the form of triglycerides or phospholipids. The complexity of fatty acid metabolism limits quantitative evaluation of fatty acid oxidation based on PET-derived ^{11}C-palmitate kinetics. A major limitation is contamination of the early tissue kinetics by back diffusion of unmetabolized tracer into the vascular space (*24*). In addition, the relative amount of tracer entering the endogenous lipid pool varies depending on the intracellular availability of α-glycerol phosphate and the activity of carnitine palmitoyl transferase (*13,23*). Nevertheless, the evaluation of ^{11}C-palmitate kinetics has rendered valuable qualitative information about fatty acid metabolism in the normal and diseased heart.

Fluorine-18-fluoro-2-deoxyglucose

Fluorine-18-fluoro-2-deoxyglucose (FDG) is widely used for the noninvasive assessment of exogenous glucose utilization. FDG traces the initial metabolic steps of glucose metabolism, specifically its uptake and subsequent phosphorylation by the hexokinase reaction. The phosphorylated product, FDG-6 phosphate, is not further metabolized by glycolysis, glycogen synthesis, or the pentose phosphate shunt pathways. Dephosphorylation of FDG-6-phosphate is slow in the heart, and since the sarcolemma is largely impermeable for charged species, FDG-6-phosphate remains essentially trapped in the cytosol and accumulates proportionately to exogenous glucose utilization (*25,26*). Figure 2 demonstrates the progressive accumulation of FDG in the heart over time. In contrast to the brain, where glycogen synthesis is negligible, FDG uptake in the heart reflects the sum of glycolysis and glycogen synthesis. However, under steady-state conditions, the rates of glycogen formation and breakdown are in equilibrium and consequently the net accumulation of myocardial FDG-6-phosphate reflects the steady-state extraction and phosphorylation rate of exogenous glucose (*26–28*).

In combination with a three-compartment tracer kinetic model, FDG kinetics derived from dynamic PET imaging can be used to quantify the rate of exogenous glucose utilization (*29*). This approach has been successfully applied to the human heart (*30,31*). Although FDG represents an analog of glucose and has similar metabolic handling by the heart, differences exist in the affinity for transport and phosphorylation of FDG and glucose. Quantification of glucose utilization based on FDG kinetics requires a correction factor called the "lumped constant," which describes these differences (*32*). Experimental studies have demonstrated the stability of this constant under various physiologic conditions (*33*), but further studies defining the relationship between FDG and glucose kinetics under pathophysiologic conditions are required.

Carbon-11-acetate

Carbon-11-acetate is avidly extracted by the myocyte. Within mitochondria, ^{11}C-acetate is converted to ^{11}C-acetyl-CoA, which enters the tricarboxylic acid cycle. Carbon-11 activity is cleared from the heart in the form of ^{11}C-carbon-dioxide and as a function of tricarboxylic acid cycle flux. Since the tricarboxylic acid cycle represents the final common metabolic pathway of oxidative metabolism, ^{11}C-acetate can be used to assess cardiac metabolism independent of overall substrate utilization (*16*). The use of this tracer offers several advantages over other metabolic

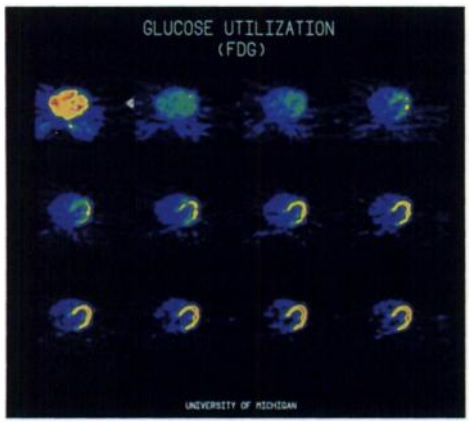

FIGURE 2. Accumulation of FDG within the heart is determined by the net rate of glucose extraction and phosphorylation by the heart. In this dynamic series of images of a single, mid-ventricular transaxial slice, progressive accumulation of FDG in the heart occurs during the 1-hr imaging period. The PET images in this and the following figures were acquired using a whole-body Siemens 931 PET instrument.

tracers and especially over ^{11}C-palmitate. First, ^{11}C-acetate undergoes immediate metabolism and only minimal activity is retained in the myocardium as tricarboxylic acid cycle intermediates. Second, animal studies have demonstrated a close relationship of ^{11}C clearance rate constants and myocardial oxygen consumption over a wide physiologic range (*16,34,35*). Although no studies have been performed to directly compare ^{11}C clearance rate constants with myocardial oxygen consumption in man, clinical studies have demonstrated a close relationship between ^{11}C clearance kinetics and independent parameters of myocardial oxygen demand including the rate-pressure product (*36,37*). Third, ^{11}C-acetate is a preferred substrate of the tricarboxylic acid cycle and its metabolism is little affected by substrate availability (*16*). This is in marked contrast to the metabolism of ^{11}C-palmitate and FDG, which are highly dependent on metabolic conditions.

In initial studies, evaluation of myocardial ^{11}C-acetate clearance kinetics employed mono- or bi-exponential curve-fitting approaches (*16,34,35,37–39*). However, accurate characterization of the tissue kinetics of ^{11}C-acetate requires correction for the effects of recirculating ^{11}C activity in the form of ^{11}C-acetate early after intravenous injection and subsequently as ^{11}C-carbon-dioxide or bicarbonate. Thus, recent approaches have involved tracer kinetic modeling, which takes recirculation of ^{11}C activity and contamination of the input function into account (*40*). Such approaches offer promise for absolute quantification of myocardial oxygen consumption using PET in combination with ^{11}C-acetate.

New Metabolic Tracers

Radiolabeled amino acids have been introduced for the noninvasive characterization of myocardial amino acid metabolism. Glutamate has been shown to contribute to nonoxidative phosphorylation in ischemic myocardium. Therefore, ^{13}N-glutamate has been proposed as a marker of ischemic myocardium (*41*). However, since this radiopharmaceutical is avidly taken up by the myocardium, its tissue retention has been shown to primarily reflect myocardial perfusion (*42*).

Fluorine-18-misonidazole represents a very promising approach for the identification of ischemically compromised myocardium. This nitro-compound preferentially accumulates in hypoxic tissue by forming reactive species that become covalently bound with macromolecules such as proteins and nucleic acids. Experimental data have shown increased retention of this radiopharmaceutical in acutely ischemic myocardium (*43–45*). Preliminary clinical data demonstrate the feasibility of this imaging approach in patients with coronary artery disease, although correction for persisting high blood-pool activity is required.

CLINICAL APPLICATIONS OF METABOLIC IMAGING

In Vivo Study of Normal Myocardial Metabolism

Before metabolic imaging can be used rationally for the detection and characterization of cardiac disease, an in-depth understanding of the tracer kinetics in normal myocardium is required. Several clinical investigations have concentrated on the definition of ^{11}C-palmitate, ^{11}C-acetate, and FDG tissue kinetics in the normal heart. With the advent of multi-slice PET instrumentation, regional kinetics of these tracers can be defined with high spatial and temporal resolution. Early studies with ^{11}C-palmitate demonstrated that myocardial kinetics of this tracer are sensitive to changes in cardiac work and metabolic environment (*23,46*). Similarly, ^{11}C-acetate clearance kinetics in the normal human heart are closely linked to myocardial oxygen consumption as estimated by independent indices of myocardial oxygen demand, such as the heart rate-pressure product (*36,37*). Pharmacologic stimulation of the heart with intravenous infusion of dobutamine has been used to define the metabolic oxidative reserve in the normal heart and should provide a reference for subsequent studies in patients with cardiac disease (*36*).

More recently, clinical studies in normal volunteers have focused on the homogeneity of myocardial substrate metabolism. A knowledge of the normal variation in metabolism within the heart, and of the factors that may effect it, is crucial for the accurate recognition of pathologic derangements of regional metabolism in cardiac disease. Relatively decreased FDG accumulation within the normally perfused septum has been observed in several studies (*33,47,48*). Gropler et al. demonstrated that FDG retention was significantly lower in the interventricular septum compared with the lateral wall of the left ventricle when normal subjects were studied in the fasting state (*48*). This study employed semi-quantitative analysis of regional FDG retention. Hicks et al. quantitatively evaluated regional glucose utilization in the normal heart using the

Patlak approach (*49*). Glucose utilization was compared with ^{11}C-acetate kinetics under tightly controlled conditions of glucose and insulin loading obtained by use of the hyperinsulinemic-euglycemic clamp technique. Although this study demonstrated significantly lower glucose utilization in the septum than in the free lateral wall of the left ventricle (Fig. 3), the relative difference was less than that described by Gropler et al. in individuals studied in the fasting state. The relatively decreased glucose utilization in the septum was not accounted for by decreased metabolic demand since ^{11}C clearance rate constants were, in fact, slightly higher in the septum compared with the lateral wall, suggesting higher oxygen consumption in this region. The authors concluded that regional differences in substrate utilization may be responsible for the observed findings. Since the myocardial handling of FDG is similar but not identical to glucose, it is possible that this heterogeneity of FDG tissue retention may reflect regional differences in the lumped constant or in the rate of dephosphorylation of FDG-6-phosphate. Further research is required to elucidate the mechanism of these observations. Nevertheless, these studies have important clinical implications since they emphasize that FDG uptake in the septum may be subject to larger variation when compared with the lateral wall of the left ventricle. This normal variation has to be taken into account when clinical studies are evaluated (Fig. 4). Furthermore, these results suggest that metabolic standardization is of the utmost importance for the interpretation of the metabolic status of the heart.

Evaluation of Diabetic Heart Disease

Coronary artery disease and impaired cardiac function are prevalent in patients with diabetes mellitus (*50*). These patients may thus benefit from assessment of myocardial metabolism. However, qualitatively poor FDG images are frequently obtained in patients with diabetes, potentially limiting application of this modality in this important population. Few studies have focused on the effect of this endocrinologic disease on myocardial FDG uptake. Preliminary results indicate that myocardial FDG uptake can be normalized by pretreatment of these patients with intravenous insulin (*51*). These observations are in keeping with experimental data from animal studies, which suggest that insulin significantly augments myocardial uptake of exogenous glucose even though it is not required for myocardial glucose uptake (*52,53*). While the absolute or relative lack of insulin in patients with diabetes mellitus may decrease myocardial glucose utilization and therefore FDG uptake, it is likely that the poor FDG image quality in these patients reflects additional factors. The presence of elevated free-fatty acids may also play a role in inhibiting FDG uptake by the heart since myocardial glucose utilization rates in the fasting state have been shown to be inversely correlated with free-fatty acid levels (*54,55*). Insulin acts to decrease free-fatty acid levels in the blood. Furthermore, insulin not only stimulates myocardial uptake of glucose but also clearance of circulating glucose by the liver and skeletal muscle in particular. Lack of clearance of FDG activity from the blood of patients with diabetes mellitus may result in poor FDG image quality, which may not necessarily reflect decreased myocardial glucose utilization, but rather poor myocardial-to-blood pool activity ratios. In summary, administration of insulin to patients with diabetes mellitus may enhance the quality of FDG images through direct augmentation of myocardial glucose metabolism by decreasing circulating free-fatty

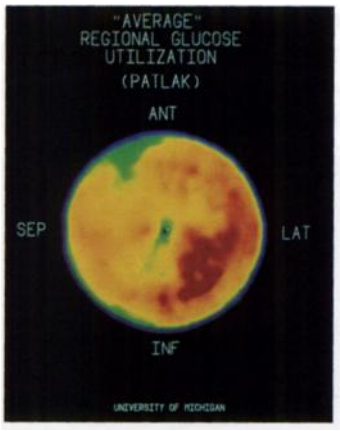

FIGURE 3. Polar representation of regional myocardial glucose utilization in the normal heart as determined by Patlak analysis of nine healthy subjects. Relatively decreased FDG retention in the normal septum, reflecting slightly decreased glucose utilization, has been described by several groups, in the fasting state. These findings suggest that caution should be used in interpreting relatively reduced FDG retention in the septum, particularly when perfusion to this region is normal (See Fig. 4).

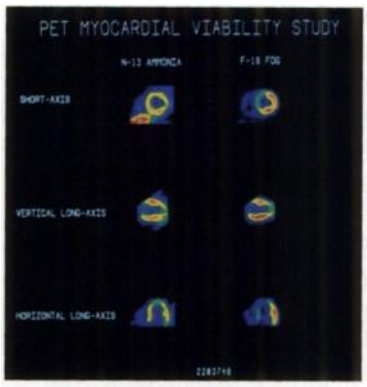

FIGURE 4. PET myocardial viability study demonstrates the potential difficulties in interpretation of relatively decreased FDG retention in the septum. Selected short-axis (above), vertical long-axis (middle), and horizontal long-axis (below) images are displayed. In this patient, resting myocardial perfusion to the septum is normal while septal FDG retention is obviously reduced compared to that in the lateral wall. Whether this represents normal regional variation or pathologically augmented glucose use by the lateral wall is unclear. In such settings, correlation with clinical information including coronary angiographic findings and quantitative evaluation of myocardial glucose utilization may be helpful in defining the significance of such changes.

acid and glucose levels and by enhancing clearance of FDG activity from the blood. Clearly, further studies are required to define the optimal preparation regime in patients with diabetes mellitus before metabolic imaging with FDG, and also to determine the significance of altered FDG uptake patterns in the diabetic heart.

Evaluation of Coronary Artery Disease

The largest clinical experience with PET metabolic imaging exists in the area of ischemic heart disease. The metabolic changes associated with myocardial ischemia have been well defined using animal experimental models. In brief, metabolism in ischemic myocardium is characterized by impaired oxidation of fatty acids, accelerated glycogen breakdown, and increased glycolytic flux (*13*). Oxidative fatty acid metabolism is particularly sensitive to decreased delivery of oxygen. Ischemic inhibition of beta-oxidation leads to activation of glycogen breakdown and to increased exogenous glucose uptake and glycolytic flux. Because of the inhibitory action of protons, lactate, and NADH-2 produced during nonoxidative glucose utilization, the glycolytic rate critically depends on the washout of detrimental metabolites from ischemic tissue. Therefore, in severe low-flow ischemia, accumulation of lactate leads to cessation of glycolysis and subsequently to cell death. These metabolic changes provide the basis for detection of ischemically compromised myocardium using metabolic imaging with PET.

Based on extensive experimental data in animals, markedly decreased FDG uptake in ventricular segments with reduced myocardial perfusion has been proposed as a marker for irreversible myocardial damage, while maintained FDG uptake has been proposed as a marker of tissue viability in segments with reduced perfusion (*56*). These postulates form the framework for PET myocardial viability studies using perfusion tracers, such as ^{13}N-ammonia and FDG (Figs. 5 and 6). While ^{11}C-acetate and ^{11}C-palmitate quantitatively describe the impairment of regional oxidative metabolism occurring during ischemia, the clinical role of these measurements is yet to be clearly defined.

Detection of Demand-Induced Ischemia. Noninvasive characterization of flow and function are currently used for the detection of regional coronary artery disease. However, with the advances in therapeutic interventions such as angioplasty, the functional significance of a given coronary artery stenosis has gained increasing clinical importance. It has been hypothesized that metabolic markers of ischemia may provide specific evidence of myocardial ischemia at a cellular level. Clinical studies have demonstrated the feasibility of PET imaging with ^{11}C-palmitate or FDG for the definition of regional metabolic abnormalities during stress-induced ischemia. Grover-McKay et al. studied ^{11}C-palmitate kinetics at baseline and during moderately increased workload imposed by atrial pacing in patients with proven coronary artery disease (*57*). Regional ^{11}C-palmitate tissue kinetics suggested increased fatty acid oxidation in normal and post-stenotic myocardium. However, the increase was attenuated in post-stenotic segments of the left ventricle. Left ventricular segments with altered ^{11}C-palmitate kinetics developed echocardiographic wall motion abnormalities in approximately half of the patients studied.

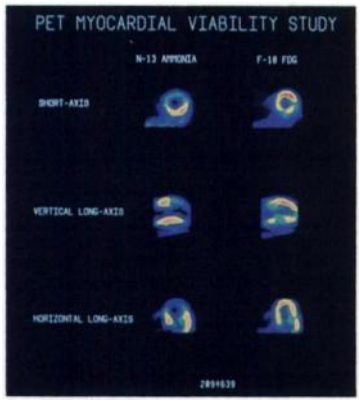

FIGURE 5. The presence of reduced resting perfusion as determined by ^{13}N-ammonia (left panels) accompanied by relatively increased FDG retention (right panels) in the anterior wall of this patient with prior infarction suggests the presence of ischemically jeopardized, but viable myocardium in the territory of an occluded left anterior descending artery.

Since the FDG uptake by the myocardium requires about 40 min after injection, this tracer is not suitable for imaging during exercise. However, Camici et al. administered FDG soon after exercise and demonstrated that myocardial glucose utilization was increased in segments that demonstrated exercise-induced ^{82}Rb perfusion defects (*47*). The increased FDG uptake in the post-exercise period has been suggested to reflect either prolonged recovery of metabolic function after transient ischemic stress or sustained restoration of glycogen stores depleted during ischemia. These initial studies suggest that metabolic imaging may be useful in the definition of regional myocardial ischemia, but no direct comparison with conventional

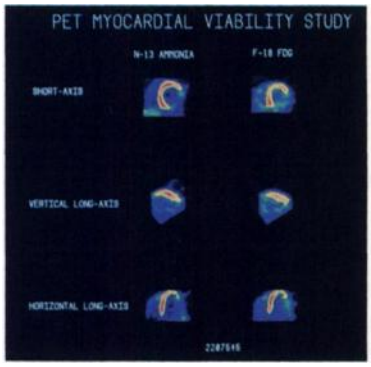

FIGURE 6. "Matched" areas of reduced resting perfusion and FDG retention as seen in the posterolateral wall of this patient with previous inferior myocardial infarction represent scar or nonviable myocardium.

techniques such as ^{201}Tl scintigraphy or dobutamine echocardiography has been performed. Thus, the diagnostic and prognostic value of metabolic imaging during or following stress for the detection of functionally significant coronary artery disease has not yet been defined.

Evaluation of Acute Myocardial Infarction. The use of intravenous thrombolytic agents is a widely accepted treatment for patients with acute myocardial infarction (MI). For optimal results, this therapy should be initiated as early as possible after the onset of symptoms (*58,59*). Any delay in instituting thrombolytic therapy occasioned by time-consuming imaging procedures is unwarranted. Thus, sophisticated imaging procedures such as PET appear to have little application in the very early phase of acute MI. However, there are several observations that suggest that metabolic imaging using PET may have a role in the assessment of patients soon after MI. First, patency of the infarct-related vessel following thrombolysis is generally less than 85% (*60–62*). Second, a significant number of patients have a significant residual stenosis in the infarct-related artery despite successful reperfusion (*62*). Third, the success of reperfusion in preserving myocardium may be difficult to assess since myocardial contractile function may be reversibly depressed by myocardial stunning (*63,64*). The extent of myocardial salvage and the amount of residual jeopardized myocardium are therefore important clinical questions that must be addressed early following such intervention. Metabolic imaging may be helpful in the identification of viable myocardium at risk. Specifically, it may help to identify myocardium that may benefit from further aggressive therapeutic interventions, such as angioplasty and coronary artery by-pass surgery (*65,66*).

The initial PET studies in patients with acute MI were performed in the pre-thrombolytic era. These studies showed that regional impairment of ^{11}C-palmitate and FDG uptake correlated closely with the electrocardiographic site of infarction or with regional wall motion abnormalities (*19,67*). FDG studies performed in patients within 72 hr of acute MI showed varying patterns of metabolic activity in the infarct territory (*68*). Decreased metabolic activity in the infarct territory was highly predictive for no subsequent change in function. On the other hand, maintained FDG uptake was associated with a variable functional outcome. Failure of myocardium to recover despite evidence of metabolic activity was attributed to the lack of interventional therapy. Comparison of the metabolic findings with coronary angiography revealed that FDG uptake was significantly higher in patients with residual antegrade flow in the infarct artery than in patients with an occluded artery, confirming the beneficial effect of residual blood flow in the infarct territory (*64*). A recent study comparing FDG uptake and dobutamine echocardiography in 17 patients treated with thrombolytic therapy soon after acute MI also suggested variable functional outcome in segments with maintained metabolic activity, whereas absence of metabolic activity was associated with no further change in regional function (*69*). These results were similar to those seen in patients before the introduction of thrombolytic therapy and may reflect the spatial heterogeneity of ischemic injury, which cannot be fully resolved by current imaging technology.

Metabolic imaging with ^{11}C-palmitate has been used to demonstrate improved metabolic activity in reperfused myocardium following successful coronary thrombolysis (*70*). In patients studied with ^{11}C-acetate and PET in the acute stage of Q-wave infarction, impairment of oxidative metabolism ranged from marked depression of ^{11}C-acetate clearance rates at the center of the infarct to a mild decrease in hypoperfused peri-infarction zones that were delineated by blood flow imaging (*71*). Longitudinal studies with ^{11}C-acetate indicate that regional oxygen consumption may be an independent marker of residual tissue viability, which can be used for further stratification of therapeutic interventions (*72*). Thus, both FDG and ^{11}C-acetate appear to be promising tracers for the definition of tissue viability in the subacute phase of MI.

Despite the promise of metabolic imaging by PET with FDG in subacute MI, potential difficulties have become apparent. Most of the patients currently treated with thrombolytic therapy receive heparin infusion for a prolonged time period. Heparin infusion leads to elevation of plasma free-fatty acid levels (*73*), which may suppress FDG uptake by the myocardium (*54,55*). High circulating catecholamine levels may also suppress myocardial glucose utilization by virtue of their anti-insulin effects (*74*). These factors may limit the evaluation of regional tissue viability using PET with FDG in the early postinfarction period. In addition, delayed FDG uptake following reperfusion has been observed in the animal model (*75*) and may further complicate the metabolic evaluation of patients soon after acute MI.

Based on the limited clinical experience with metabolic imaging in patients with acute MI, cautious interpretation of PET studies in this patient population is required. Clearly, further studies are required to define the prognostic value of metabolic imaging with ^{11}C-acetate or FDG before PET can be routinely applied for therapeutic stratification of these patients.

Assessment of Myocardial Viability in Stable Coronary Artery Disease Using FDG. Regional and global assessment of function, perfusion, and coronary anatomy in patients with proven coronary artery disease have been shown to provide important diagnostic and prognostic information. However, definition of tissue viability in patients with a history of previous myocardial infarction remains an important diagnostic problem. Since large clinical studies have shown that patients with impaired left ventricular function benefit most from revascularization (*76,77*), the differentiation between infarcted and ischemically-compromised but viable myocardium has become of major clinical importance.

The "sine qua non" of tissue viability is the presence of residual metabolic activity sufficient to support the integrity of cell membranes. Consequently, the use of radiopharmaceuticals that trace cardiac metabolism has been proposed for the definition of tissue viability. In early studies, ^{11}C-palmitate was used to delineate the extent of infarcted tissue in patients with previous myocardial infarction (*19,67*). Carbon-11-palmitate uptake defects were larger and more pronounced in patients with Q-wave infarction compared with defects observed in patients with non-Q-wave infarction. These observations were based on the uptake of ^{11}C-palmitate, which predominantly reflects perfusion rather than the activity of fatty acid metabolic pathways. No data validating ^{11}C-palmitate kinetics as a marker of tissue viability are currently available.

The major impetus to the use of PET for the assessment of myocardial viability came from a study by Marshall et al. (*56*). This study was the first to apply FDG to the evaluation of patients with prior myocardial infarction and found a high incidence of FDG uptake in segments with reduced flow. Residual FDG uptake correlated with the presence of postinfarction angina, the site of ischemic electrocardiographic changes during ischemia, and the presence of severe coronary artery disease. Intuitively, these data were highly suggestive of the presence of residual metabolic activity in segments of presumed prior myocardial infarction. These exciting findings spawned a number of subsequent studies in which FDG uptake was correlated with other markers of tissue viability (*78–82*). Brunken et al. compared the results of metabolic PET imaging with electrocardiographic criteria of infarct extent and regional wall motion in 16 patients with Q-wave infarction (*78*). Approximately 60% of left ventricular segments with electrocardiographic or wall motion abnormality criteria of infarction had preserved FDG uptake. Regional wall motion scores were similar in segments with and without FDG uptake demonstrating the unique information provided by PET.

Having demonstrated that FDG uptake was preserved in segments that would have been classified as representing MI by previously used criteria of viability, subsequent studies addressed the predictive value of FDG uptake for tissue recovery following surgical revascularization. Tillisch et al. compared preoperative PET findings in hypokinetic left ventricular segments with the degree of functional recovery in these segments 6 wk after revascularization (*65*). FDG uptake in the presence of reduced flow was 85% predictive for recovery, while the absence of metabolic activity in segments with flow defects was associated with lack of recovery in contractile function (Table 1). These findings were subsequently supported by data from Tamaki et al. who showed that 78% of segments with preserved FDG uptake had improvement in contractile function following surgical revascularization, compared with recovery in only 22% of segments without FDG uptake (*66*). These two studies differed in the metabolic standardization used before FDG imaging. Tillisch et al. used oral glucose loading before administration of FDG, whereas Tamaki et al. studied their patients under fasting conditions. These methodologic differences may explain the slightly varying results.

We have performed similar analysis of 29 patients who had coronary revascularization following clinical FDG studies in our laboratory (*83*). Although these data are preliminary, we found that the predictive value of preserved or relatively increased FDG uptake in areas of reduced perfusion for recovery of contractile function following revascularization was dependent on the degree of preoperative wall motion abnormality. In our study, the positive and negative predictive value of FDG uptake patterns were highest in segments with severe regional asynergy. Improvement in regional wall motion occurred

TABLE 1
Percentage of Fixed ^{201}Tl Defects at 4 Hours that Demonstrate "Viability" by Other Techniques

Author	N	Fixed defect	"Viable"	Percent	Technique
Brunken (*79*)	12	36	21	58	^{201}Tl planar/PET with FDG
Tamaki (*80*)	28	39	15	38	^{201}Tl SPECT/PET with FDG
Brunken (*82*)	26	101	47	47	^{201}Tl SPECT/PET with FDG
Gibson (*97*)	43	42	19	45	^{201}Tl planar/^{201}Tl post-op
	52	16	12	75	^{201}Tl planar/^{201}Tl post-op
Kiat (*99*)	21	122	74	61	^{201}Tl SPECT/24-hr redistribution
Dilsizian (*100*)	100	85	42	49	^{201}Tl SPECT/Reinjection ^{201}Tl
Ohtani (*101*)	24	32	15	47	^{201}Tl SPECT/Reinjection ^{201}Tl
Total	306	473	245	52	

FDG = Fluorine-18-fluorodeoxyglucose.
^{201}Tl planar = Planar ^{201}Tl redistribution imaging at 3–4 hr after stress.
^{201}Tl SPECT = Single-photon emission computed tomographic ^{201}Tl redistribution imaging 3–4 hr after stress.
Reinjection ^{201}Tl = thallium imaging following reinjection of approximately 1 mCi of ^{201}Tl 3–4 hr after stress.
24-hr redistribution = thallium redistribution imaging approximately 24 hr after stress imaging.

in 75% of segments with akinesis or dyskinesis and relatively increased FDG uptake preoperatively. The absence of FDG uptake in regions of severe regional wall motion abnormality had a 90% predictive accuracy for lack of recovery in contractile function following revascularization. This study differed significantly in design from the preceding studies by Tillisch and Tamaki in that PET results were made available to referring clinicians. These results may have helped to guide clinical management, including the decision to perform revascularization. Importantly, global left ventricular ejection fraction improved significantly in patients within our study population who had severely impaired left ventricular function and were selected for revascularization based on PET results. These segmental and global functional data support the contention that metabolic imaging may be most useful in patients with severely impaired regional and global function.

Figure 7 shows a PET study obtained in a patient with ischemic cardiomyopathy and left ventricular ejection fraction of 11% considered for cardiac transplantation. Following the PET study, which showed considerable amount of viable tissue, surgical revascularization was recommended. This procedure led to a marked subsequent improvement in symptoms and an increase in resting ejection fraction to 24%.

Clearly, these anecdotal and experimental data support the utility of metabolic imaging with PET and FDG for the detection of ischemically-compromised but viable myocardium. However, PET is currently an expensive modality and has limited clinical availability. The wider use of PET viability studies may depend on whether this approach provides incremental diagnostic information compared with less expensive and more routinely available techniques. More importantly, comparison with results obtained using ^{201}Tl myocardial imaging is required. The presence of redistribution of stress-induced ^{201}Tl defects is widely accepted as a marker of tissue viability, and patients with these findings are not usually referred for assessment of myocardial viability by PET. The clinical dilemma arises when persistent ^{201}Tl defects are present 3–4 hr after stress, since recent reports indicate that the standard technique of stress-redistribution ^{201}Tl imaging overestimates the extent of nonviable myocardium. Based on PET, ^{201}Tl redistribution imaging at 24 hr after stress, and ^{201}Tl findings following revascularization, a considerable number of segments with fixed defects on ^{201}Tl images after 4 hr of redistribution did have evidence of viability. The results of these studies are summarized in Table 1.

Most recently, ^{201}Tl reinjection has been proposed as a technique that provides improved detection of viable myocardium compared with 4-hr redistribution images and is more practical than 24-hr delayed ^{201}Tl imaging. Table 2 compares the results of ^{201}Tl imaging using standard 4-hr redistribution imaging with the reinjection technique for the identification of viable tissue. Current research focuses on the direct comparison of ^{201}Tl reinjection and PET

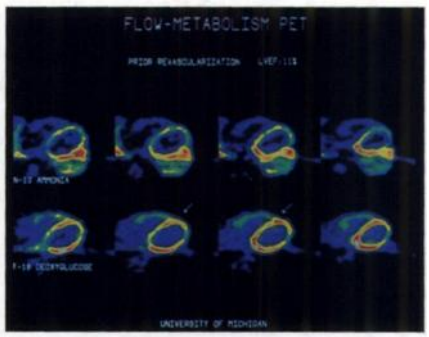

FIGURE 7. Selected transaxial images of ^{13}N-ammonia (above) and FDG (below) obtained in a patient being considered for cardiac transplantation. The images are displayed from the mid-ventricular level on the left towards the diaphragmatic surface on the right. The heart is significantly dilated. Resting perfusion was inhomogeneous and particularly reduced in the septum. FDG retention in the heart was, in comparison, relatively well preserved, especially in the septum (arrow) indicating viable, but compromised myocardium. The patient underwent surgical revascularization with improvement of global left ventricular function and marked improvement of symptoms.

metabolic imaging. Preliminary results of Tamaki demonstrated a 22% incidence of FDG uptake in segments with persistent defects following ^{201}Tl reinjection (*84*). Bonow et al. studied 16 patients with PET and ^{201}Tl SPECT including reinjection (*85*). These patients were characterized by chronic coronary artery disease and severely impaired left ventricular function (LVEF 27% ± 9%). In the absence of metabolic activity, there was close agreement between PET and ^{201}Tl results. Only 11% of left ventricular segments with reduced FDG uptake demonstrated increased ^{201}Tl uptake following reinjection. However, 59% of persistent ^{201}Tl defects with PET evidence of viability did not demonstrate improved ^{201}Tl uptake following reinjection. The discrepancy between FDG and ^{201}Tl results was greatest in segments with <50% reduction of regional ^{201}Tl activity. Segments with severe "irreversible" ^{201}Tl defects (>50% ^{201}Tl-reduction) exhibited decreased FDG uptake in 88% of the cases indicating agreement of both techniques. Thus, the diagnostic gain provided by PET imaging appears to be related to the degree of regional ^{201}Tl reduction with greater likelihood of tissue viability in segments with mild to moderate "irreversible" defects following ^{201}Tl reinjection.

Myocardium with normal resting myocardial perfusion is likely to be viable. In keeping with this contention, there is increasing evidence that resting blood flow determination either by separate tracer injection (^{82}Rb, ^{13}N-ammonia, ^{99m}Tc-isonitriles) or ^{201}Tl reinjection provides improved detection of viable tissue. The incremental diagnostic and prognostic information provided by metabolic imaging with FDG beyond that obtained by truly resting perfusion has to be further defined (*80,85*). The theoretical advantage of FDG over imaging of resting myocardial perfusion is in the detection of viable myocardium in areas

TABLE 2
Imaging Diagnosis Predictive Values for Recovery or Lack of Recovery in Contractile Function Following Revascularization

Author	Technique	N	"Viable"* with recovery	"Scar"† with no recovery
Tillisch (*65*)	PET with FDG/NH_3	17	35/41 (85%)	24/26 (92%)
Tamaki (*66*)	PET with FDG/NH_3	22	18/23 (75%)	18/23 (78%)
Ohtani (*101*)	Redistribution ^{201}Tl	24	23/31 (74%)	16/30 (53%)
	Reinjection ^{201}Tl	24	10/14 (71%)	22/26 (85%)
Dilsizian (*100*)	Reinjection ^{201}Tl	20	13/13 (100%)	8/8 (100%)
Kiat (*99*)	Redistribution ^{201}Tl	21	67/73 (85%)	34/122 (28%)
	24-hr redistribution	21	70/74 (95%)	30/48 (63%)

* "Viable" = fulfilling imaging criteria for viability.
† "Scar" = not fulfilling imaging criteria for viability.
FDG/NH3 = fluorine-18-fluorodeoxyglucose and ^{13}N-ammonia.
Redistribution ^{201}Tl = thallium redistribution imaging at 3–4 hr after stress.
Reinjection ^{201}Tl = thallium imaging following reinjection of approximately 1 mCi of ^{201}Tl 3–4 hr after stress.
24-hr redistribution = thallium redistribution imaging approximately 24 hr after stress imaging.

with reduced perfusion under resting conditions. Since glucose utilization may be enhanced in ischemically-compromised myocardium, FDG uptake may serve as a "hot spot marker" of jeopardized tissue and be especially useful in patients with severely reduced perfusion to multiple segments (Fig. 7).

Based on our experience, we recommend PET viability studies in patients with severely impaired regional or global function, coronary anatomy suitable for revascularization regions of wall motion abnormality, and the absence of reversible perfusion abnormalities on ^{201}Tl imaging following reinjection. Furthermore, we recommend standardization of metabolic conditions by use of oral glucose loading or, in the case of patients with diabetes mellitus, glucose infusion supplemented by insulin infusion.

Evaluation of Cardiomyopathy

Our understanding of the pathophysiology of dilated cardiomyopathy is limited. Thus, in contrast to ischemic heart disease, we cannot rely on experimental data to guide metabolic imaging approaches using tracer techniques for the diagnosis and staging of the disease process. With few exceptions, such as carnitine deficiency (*86*), there is little evidence that myocardial substrate metabolism is directly associated with the disease process. Therefore, metabolic imaging may only indirectly reflect the deterioration of overall left ventricular performance, which may be used for the assessment of therapy.

Since the clinical differentiation between dilated and ischemic cardiomyopathy is difficult in patients without prior history of MI, Mody-Vaghaiwalla et al. defined the diagnostic value of PET in combination with ^{13}N-ammonia and FDG for the differentiation of ischemic heart disease and primary cardiomyopathy (*87*). Patients with cardiomyopathy were characterized by more homogeneous blood flow and metabolic patterns than patients with ischemic heart disease. Similar findings were reported by Geltman et al. using ^{11}C-palmitate, who reported more pronounced defects of ^{11}C-palmitate uptake in patients with coronary artery disease (*88*). However, this group of investigators observed heterogeneity of regional ^{11}C-palmitate uptake in patients with idiopathic dilated cardiomyopathy, which was unrelated to ^{201}Tl perfusion defects or wall motion abnormalities. The authors hypothesized that the heterogeneity in regional substrate metabolism observed in nonischemic cardiomyopathy may reflect the disparate nature of the destructive myocardial process.

Evaluation by Schelbert et al. of fatty acid metabolism under fasting conditions and following oral glucose load indicated that patients with severely impaired left ventricular function can demonstrate a paradoxical response of ^{11}C-palmitate kinetics to glucose loading (*46*). In the normal heart, glucose loading led to delayed ^{11}C tissue clearance compared with fasting values, whereas ^{11}C-palmitate clearance was more rapid in some patients with severe left ventricular impairment. The biochemical mechanism and significance of this observation are not clear. Further studies are required to assess this phenomenon.

More recently, ^{11}C-acetate has been employed to characterize oxidative metabolism in patients with dilated cardiomyopathy (*89*). Myocardial oxygen consumption, as reflected by ^{11}C-acetate clearance rate constants, was found to be higher in this patient population than in normals. However, ^{11}C clearance rate constants corrected for left ventricular loading conditions were lower in patients with cardiomyopathy than in the normal heart. Since myocardial oxygen consumption is dependent on the contractile state of the left ventricle, decreased oxidative metabolism relative to loading conditions may reflect the impaired contractile state of the diseased heart. Recent experimental data by Wolpers et al. indicate that ^{11}C-acetate kinetics in combination with echocardiographic parameters of mechanical work may be used to noninvasively define cardiac efficiency, which reflects overall left ventricular perform-

ance (*90*). Such measurements are expected to be useful in the serial evaluation of therapeutic efficacy in patients with cardiomyopathy. Sophisticated evaluation of myocardial energetics may serve as objective end points of such therapy and may be useful in research as well as clinical assessment of the disease process.

Other Cardiomyopathies

Grover-McKay et al. have compared regional glucose and fatty acid metabolism in patients with hypertrophic cardiomyopathy (*91*). Due to the hypertrophy of the interventricular septum, regional determination of tracer concentration may be affected by partial volume effect. However, following correction for the difference in regional wall thickness, significantly decreased FDG uptake was observed in the septum compared with the lateral wall. Such differences were not matched by concordant changes in ^{11}C-palmitate kinetics. A similar metabolic pattern has also been described in the normal heart (*48*). Consequently, the regional variation in glucose metabolism in the hypertrophic heart is of unclear pathophysiologic significance. The etiology of this apparent heterogeneity in glucose metabolism requires further evaluation in both the diseased and normal heart.

Duchenne's muscular dystrophy has been shown to selectively involve the posterolateral wall of the left ventricle as the initial and primary site of myocardial dystrophy (*92*). Electrocardiographic changes in this patient population suggest myocardial damage in corresponding ventricular segments. Perloff et al. investigated 15 patients with Duchenne's muscular dystrophy and reported regional decreased ^{13}N-ammonia uptake but maintained or increased FDG uptake in the posterolateral wall (*93*). This finding occurred in about 90% of patients with electrocardiographic evidence of left ventricular involvement. Again, the pathophysiologic, diagnostic, and prognostic implications of such observations need to be defined further.

Evaluation of Valvular Heart Disease

Echocardiography in combination with Doppler measurements allows accurate noninvasive diagnosis and staging of valvular heart disease. However, in patients with proven aortic or mitral regurgitation, optimal timing of valve replacement remains a therapeutic challenge to the cardiologist. Assessment of left ventricular contractile performance by conventional techniques is of limited value due to the abnormal loading conditions of the left ventricle. Preliminary studies employing ^{11}C-acetate in this patient population indicate that myocardial oxygen consumption, as assessed by ^{11}C-acetate, in combination with measures of left ventricular stress and work may provide sensitive characterization of the energetics of left ventricular performance in this patient population (*94*). As observed in patients with cardiomyopathy, myocardial oxygen consumption appears to be disproportionately decreased with respect to loading conditions in patients with aortic valve disease and impaired left ventricular contractile function. These preliminary data are promising, but require further clinical validation before ^{11}C-acetate can be used as a marker for left ventricular performance in patients with valvular heart disease. At the present time, no clearly defined approach is available to support clinical staging of the severity of valvular heart disease using PET.

Future Perspectives

Most clinical studies employ qualitative interpretation of PET images. Recent advances of PET instrumentation providing higher spatial and temporal resolution have markedly improved the regional assessment of tracer tissue concentration (*95,96*). The development and validation of tracer kinetic models will enable more accurate measurements of substrate utilization rates. Future research must focus on the definition of quantitative threshold values of metabolic parameters that more specifically characterize the severity of metabolic change in the human heart. The wider application of PET as both a clinical imaging modality and a sophisticated research tool depends on the development and validation of new radiopharmaceuticals. Besides new metabolic tracers, the use of radiolabeled cardiovascular drugs may permit the in vivo definition of pharmacokinetics. The use of radiopharmaceuticals such as ^{18}F-misonidazole, which are retained in hypoxic tissue, may allow the specific delineation of ischemic myocardium.

We are confident that future development of PET metabolic imaging methodology and its wider application due to the increasing number of clinical PET facilities will remedy the current paucity of information relating to the diagnostic and prognostic value of this technique in a variety of cardiac diseases. More importantly, cost-benefit comparisons between PET and conventional imaging approaches will define the rational use of this more expensive technology to provide improved treatment of patients with ischemic heart diseases.

CONCLUSION

In combination with flow and metabolic tracers, PET provides accurate detection of significant coronary artery disease and has been shown to identify viable but compromised myocardium in patients with advanced ischemic heart disease. Metabolic definition of tissue viability has proven clinically useful for the selection of patients considered for revascularization. Application of PET in nonischemic heart disease requires further clinical validation and must be considered experimental at this time. Further developments of instrumentation, analysis software, and radiopharmaceuticals will make PET an important clinical and research tool in the noninvasive characterization of cardiac diseases.

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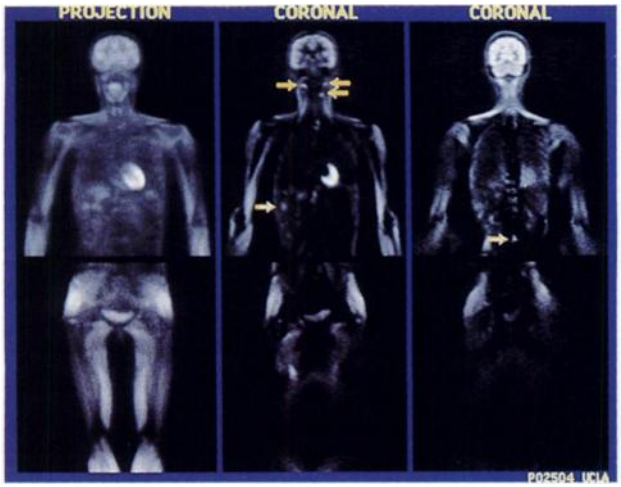
(continued from page 5A)

FIRST IMPRESSIONS



SUBJECT:
A 42-yr-old woman diagnosed with breast carcinoma with a high tissue amplification of the HER-2/neu oncogene, which has been shown to be associated with poor prognosis.

PURPOSE:
The patient was studied to investigate the sensitivity of the FDG total-body technique in detecting metastatic lesions. At the time of the FDG study, there was no biochemical evidence nor clinical suspicion of liver metastases.

TRACER:
10 mCi FDG

ROUTE OF ADMINISTRATION:
Intravenous

TIME AFTER INJECTION:
40 min

INSTRUMENTATION:
Siemens ECAT Scanner

CONTRIBUTORS:
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