Clinical Implications of Molecular Imaging Research

Radionuclide Imaging of Myocardial Metabolism

Linda R. Peterson, MD; Robert J. Gropler, MD

Cardiac health is dependent on the heart’s ability to utilize different substrates to support overall oxidative metabolism to generate ATP. Indeed, a loss in plasticity in substrate preference is characteristic of a variety cardiac diseases such as diabetic heart disease, in which fatty acid metabolism predominates, and dilated cardiomyopathy, in which glucose metabolism predominates. Because of the pleiotropic actions of myocardial substrate metabolism, a loss in plasticity in substrate preference can have detrimental effects well beyond impairment of energy production, including perturbations in various cell signaling pathways, alterations in cell growth, and decreased cell survival.

Despite the rapid growth in our understanding of the relationship between altered myocardial metabolism and cardiac disease, many important questions remain. For example, what are the key determinants of changes in myocardial substrate use? When these changes do occur, to what extent are they adaptive or have the propensity to become maladaptive? And are these metabolic patterns of prognostic significance? Although transgenic models targeting vital aspects of myocardial substrate use are providing mechanistic insights into myocardial metabolic-functional relationships in various cardiac diseases, the relevance of the observed phenotypes to the corresponding human condition is frequently unclear. Likewise, applied genomics have identified numerous gene variants intimately involved in the regulation of myocardial substrates use, yet identifying all clinically relevant genetic variants remains elusive. As a consequence, there is an ever-growing demand for accurate noninvasive imaging approaches of myocardial substrate metabolism that provide links between the bench and the bedside. In this regard, radionuclide approaches have led the way. The most notable links between the bench and the bedside. In this regard, radionuclide approaches have led the way.

Methods to Image Myocardial Metabolism

Radionuclide approaches for imaging of myocardial metabolism are single-photon emission computed tomography (SPECT) and PET. A summary of each technique is listed below.

Single-Photon Emission Computed Tomography

The advantages to SPECT for cardiac metabolic imaging include the inherent high sensitivity of the radionuclide method to measure metabolic processes, wide availability of the technology, the ability to measure myocardial function simultaneously, and the long physical half-life of SPECT radiotracers. The half-life is an important attribute because it allows delivery of radiotracer from a central radiopharmacy to multiple geographical locations. The major disadvantage of SPECT is the inability to quantify cellular metabolic processes primarily because of the technical limitations of SPECT (relatively poor temporal and spatial resolution and inaccurate correction for photon attenuation) and the complexity of the metabolism of the radiotracers used in SPECT imaging relative to the metabolic process of interest.

Metabolic processes that can be measured by SPECT include glucose metabolism and fatty acid metabolism (Table 1).

Glucose Metabolism

No SPECT-specific radiotracers are currently available to measure myocardial glucose metabolism, and SPECT is not typically used for its assessment. However, when combined with the appropriate detection scheme or collimator design, myocardial glucose metabolism can be assessed with SPECT and FDG.1

Fatty Acid Metabolism

One of the earliest and most promising SPECT radiotracers of fatty acid metabolism was 15-(p-iodophenyl)-pentadecanoic acid (IPPA). This radiotracer demonstrated rapid accumulation in the heart and exhibited clearance kinetics that followed a biexponential function characteristic for 11C-palmitate. Moreover, the clearance rates correlated directly with β-oxidation. However, the poor temporal resolution of SPECT systems could not take advantage of the rapid turnover of IPPA. As a consequence, quantification of myocardial fatty acid metabolism was not possible and image quality was poor. This led to the development of branched-chain analogs of IPPA, such as 123I-β-methyl-P-iodophenylpentadecanoic acid (BMIPP) (Table 1). Alkyl branching inhibits β-oxidation shunting radiolabel to the...
Myocardial Oxygen Consumption

15O-oxygen is readily applicable in studies requiring repetitive assessments, such as those with an acute pharmacological intervention. Its major disadvantages are the need for a multiple-tracer study (to account for myocardial blood flow and blood volume) and fairly complex compartmental modeling to obtain the measurements.5,6

11C-Acetate

Acetate is a 2-carbon fatty acid whose primary metabolic fate is rapid conversion to acetyl-CoA and metabolism through the tricarboxylic acid cycle. Because of the close coupling between the tricarboxylic acid cycle and oxidative phosphorylation, myocardial turnover of 11C-acetate reflects overall oxidative metabolism or MVO2. Either exponential curve fitting or compartmental modeling is used to calculate MVO2. Modeling is typically preferable when cardiac output is low because marked dispersion of the input function and spillover of activity from the lungs to the myocardium decrease the accuracy of the curve-fitting method.7–10 However, modeling is more complex than exponential curve-fitting and requires correction of blood radioactivity for 11CO2.

Carbohydrate Metabolism

18F-Fluorodeoxyglucose

This radiotracer competes with glucose first for facilitated transport into the sarcolemma then for hexokinase-mediated phosphorylation. In general, FDG-6-phosphate is trapped in the cytosol and the myocardial uptake of FDG is thought to reflect overall anaerobic and aerobic myocardial glycolytic flux.11,12 Myocardial glucose uptake can be assessed in either relative or in absolute terms (ie, in nmol L−1·min−1). To calculate the rates of glucose uptake, a mathematical correction—called the “lumped constant”—must be used. The lumped constant was originally derived to account for the difference in the kinetics of FDG from that of glucose for glucose transport and hexokinase-mediated phosphorylation.13 This value may vary, depending on the prevailing plasma substrate and hormonal conditions, which may decrease the accuracy of the measurement of myocardial glucose uptake.14,15 The limited metabolic fate of FDG in tissue precludes determination of the intracellular metabolism of glucose (ie, glycogen formation versus glycolysis).

Carbon-11 Glucose

Quantification of myocardial glucose metabolism has been performed with PET using glucose radiolabeled in the 1-carbon position with 11C (11C-glucose). An advantage of this approach is the elimination of a lumped constant correction because 11C-glucose is chemically identical to unlabeled glucose and thus has the same metabolic fate as glucose. Other advantages include more accurate measurements of myocardial glucose uptake compared with FDG and the ability to estimate the metabolic fate of extracted glucose (Figures 1 and 2).16–18 Disadvantages of this method include a fairly complex synthesis of the tracer, the short physical half-life of 11C, which requires an on-site cyclotron, compartmental modeling that is more demanding with 11C-glucose than it is with FDG, and the need to correct the arterial input function for the production of 11CO2 and 11C-lactate.

Table 1. Currently Used Radiotracers of Metabolism

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-Life</th>
<th>Compound</th>
<th>Present Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td></td>
<td></td>
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<tr>
<td>123I</td>
<td>13.3 h</td>
<td>IPPA</td>
<td>Fatty acid uptake, oxidation, and storage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMIPP</td>
<td>Fatty acid storage</td>
</tr>
<tr>
<td>PET</td>
<td></td>
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<tr>
<td>15O</td>
<td>2.04 min</td>
<td>15O2</td>
<td>Oxygen consumption</td>
</tr>
<tr>
<td>11C</td>
<td>20.4 min</td>
<td>Acetate*</td>
<td>Oxygen consumption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palmitate</td>
<td>Fatty acid uptake, oxidation, and storage</td>
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<td></td>
<td></td>
<td>Glucose</td>
<td>Glucose uptake, glycolysis, oxidation, and glycogen turnover</td>
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<td></td>
<td></td>
<td>Lactate</td>
<td>Lactate uptake and oxidation</td>
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<tr>
<td>18F</td>
<td>110 min</td>
<td>Deoxyglucose</td>
<td>Glucose uptake</td>
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<td></td>
<td></td>
<td>FTP</td>
<td>Fatty acid uptake and oxidation</td>
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<td></td>
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<tr>
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<td></td>
<td>FCPHA</td>
<td>Fatty acid uptake and oxidation</td>
</tr>
</tbody>
</table>

See text for names of compounds.

11C-acetate measures the oxidative metabolism of the tricarboxylic acid cycle and is an indirect index for total MVO2.
Lactate metabolism in the heart is a key source of energy production, particularly during periods of increased cardiac work. To date, however, the ability to measure myocardial lactate has been limited by the lack of availability of an appropriate radiotracer and analysis scheme. Recently, a multicompartmental model was developed for the assessment of myocardial lactate metabolism using PET and L-3-11C-lactate. PET-derived extraction of lactate correlated well with lactate oxidation measured by arterial and coronary sinus sampling over a wide range of conditions (Figure 3).

Fatty Acid Metabolism

11C-Palmitate

Currently, mathematical modeling techniques are applied to myocardial kinetics to measure various aspects of myocardial fatty acid metabolism uptake, such as uptake, oxidation, and storage. Recently, 11C-palmitate in conjunction with 3D PET has also been used to measure myocardial triglyceride degradation and oxidation in a canine model. In this study, the myocardial triglyceride pool was prelabeled with 11C-palmitate 45 minutes before 3D PET data acquisition. The major advantage of 11C-palmitate is that its myocardial kinetics are identical to unlabeled palmitate. The use of 11C-palmitate does have several disadvantages, including reduced image quality and specificity, a more complex

\[ y = 0.71x + 0.01; \quad R = 0.98, P < 0.0001, n = 22 \]

Fractional glucose oxidation (ART/CS)

\[ y = 0.97x + 0.01; \quad R = 0.97, P < 0.0001, n = 22 \]

Fractional glycolysis (ART/CS)

Figure 1. Correlation in dog hearts between Fick-derived (x-axis) measurements of the rate of myocardial glucose utilization (rMGU) and PET-derived (y-axis) rMGU using 1-11C-glucose (A), FDG before correcting PET values for the lumped constant (LC) (B), FDG after correcting PET values by the LC (C), and FDG after correcting PET values by a variable LC (LCv) (D) that accounts for varying substrate, hormonal, and work environments. Correlation with Fick-derived values was significantly close when 1-11C-glucose (A) as opposed to 18F-FDG was used, regardless of whether an LC was used or the type of LC used (B through D). Reproduced with permission from Springer Science & Business Media, © 2002, Herrero et al.16

Figure 2. Correlation between PET and arterial and coronary sinus (ART/CS) measurement of fractional glycolysis (A) and glucose oxidation (B). Reproduced with permission from Springer Science & Business Media, © 2007, Herrero et al.18

11C-Lactate

Lactate metabolism in the heart is a key source of energy production, particularly during periods of increased cardiac work. To date, however, the ability to measure myocardial lactate has been limited by the lack of availability of an appropriate radiotracer and analysis scheme. Recently, a multicompartmental model was developed for the assessment of myocardial lactate metabolism using PET and L-3-11C-lactate. PET-derived extraction of lactate correlated well with lactate oxidation measured by arterial and coronary sinus sampling over a wide range of conditions (Figure 3).19
analysis, and the need for an on-site cyclotron and radiopharmaceutical production capability.

**Fatty Acid Analogues**

Most of the PET tracers in this category have been designed to reflect myocardial \(\beta\)-oxidation. 14-(R,S)-\(^{18}\)F-fluoro-6-thiaheptadecanoic acid (FTHA) was one of the first radiotracers developed using this approach. Myocardial uptake and retention tracked accordingly with changes in substrate delivery, blood flow, and work load in animal models.\(^{22,23}\) The effects of various diseases such as coronary artery disease and dilated cardiomyopathy on myocardial fatty acid metabolism have been evaluated with PET using this radiotracer.\(^{24,25}\) However, uptake and retention of FTHA has proven insensitive to the inhibition of \(\beta\)-oxidation by hypoxia, reducing enthusiasm for this radiotracer to measure myocardial fatty acid metabolism. To circumvent this problem, 16-\(^{18}\)F-fluoro-4-thia-palmitate (FTP) has been developed. This radiotracer retains the metabolic trapping function that is proportional to fatty acid oxidation under normal oxygenation and hypoxic conditions.\(^{26}\) Similar to FDG, quantification of myocardial fatty acid metabolism with FTP requires the use of a lumped constant to correct for kinetic differences between the radiotracer and unlabeled palmitate. To circumvent this problem, 16-\(^{18}\)F-fluoro-4-thia-palmitate (FTP) has been developed. This radiotracer retains the metabolic trapping function that is proportional to fatty acid oxidation under normal oxygenation and hypoxic conditions.\(^{26}\) Similar to FDG, quantification of myocardial fatty acid metabolism with FTP requires the use of a lumped constant to correct for kinetic differences between the radiotracer and unlabeled palmitate. Furthermore, the extent to which myocardial fatty acid uptake can be separated from oxidation based on the myocardial kinetics of FTP is unknown. Recently, a new F-18–labeled fatty acid radiotracer, trans-9(RS)-\(^{18}\)F-fluoro-3,4(RS,RS) methyleneheptadecanoic acid (FCPHA), was developed.\(^{27}\) This radiotracer is also trapped after undergoing several steps of \(\beta\)-oxidation, with uptake in the rat heart approaching 1.5% injected dose per gram of tissue at 5 minutes. However, the impact of alterations in plasma substrates, work load, and blood flow on myocardial kinetics is unknown.

**Overview of Myocardial Metabolism: Plasticity in Substrate Use**

The heart is an omnivore capable of switching between one substrate to another for energy production. Substrate switching depends on numerous factors such as the plasma substrate environment, neurohumoral milieu, and level of cardiac work (Figure 4).\(^{28}\) Alterations in substrate switching can either represent an acute or chronic adaptation in response to either short or prolonged alterations in the physiological environment. The inter-regulation of short-term modulation is based on an effective interplay between various substrates, with the metabolism of one substrate automatically inhibiting the pathway of another substrate via rapid enzymatic changes.

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**Figure 3.** Representative PET time-activity curves of L-3-\(^{11}\)C-lactate obtained from intralipid (IL), insulin clamp (CLAMP), lactate infusion (LACTATE), or lactate and phenylephrine (LAC/PHEN) studies and corresponding myocardial images obtained 5 to 10 minutes after tracer injection and depicting primarily early tracer uptake. Images are displayed on horizontal long axis. Blood \(^{11}\)C indicates \(^{11}\)C time-activity curves obtained from region of interest placed on left atrium; blood \(^{11}\)C-lactate, blood \(^{11}\)C time-activity curves after removing \(^{11}\)CO\(_2\), \(^{11}\)C-neutral, and \(^{11}\)C-basic metabolites; myocardial \(^{11}\)C, \(^{11}\)C time-activity curves obtained from region of interest placed on lateral wall. A indicates apical wall; S, septal wall; L, lateral wall; LV, left ventricle. Reproduced with permission from Springer Science & Business Media, © 2007, Herrero et al.\(^{19}\)

**Figure 4.** Summary of myocardial substrate metabolism demonstrating the need for flexibility in myocardial substrate use to maintain myocardial health. DCM indicates dilated cardiomyopathy; IR, insulin resistance; DM, diabetes mellitus. Reproduced with permission from Springer Science & Business Media, © 2008, Herrero et al.\(^{100}\)
In contrast, chronic metabolic adaptations reflect alterations in gene expression regulating various metabolic pathways. These gene expression changes can occur at the transcriptional and/or post-translational level through the coordinated upregulation of enzymes and proteins in key metabolic pathways. For example, in diabetes mellitus, the nuclear receptor peroxisome proliferator-activated receptor-α (PPARα, a key regulator of fatty acid metabolism) mRNA is increased, and there is a concomitant upregulation in genes controlling fatty acid oxidation (Table 2). In contrast, pressure-overload hypertrophy PPARα activity is reduced, leading to a downregulation of genes controlling fat metabolism and in turn leading to an upregulation of glucose use (Table 2). Discussed in the sections that follow is how metabolic imaging has helped characterize these changes in myocardial substrate preference due to these chronic adaptations in various disease processes.

**Aging and Sex**

Marked changes in myocardial substrate metabolism occur with age (Table 2). The fetal heart is typified by a preference for glucose primarily because of the relative hypoxia that occurs in utero. Immediately after birth, fatty acids become the preferred energy source. In experimental models of aging, the contribution of fatty acid oxidation to overall myocardial substrate metabolism declines with advancing age. It appears that the cause for the decrease in fatty acid oxidation is multifactorial, ranging from changes in mitochondrial lipid content, oxygen free radical injury, key enzyme systems, and an age-related decline in myocardial PPARα activity. Healthy older humans demonstrate a similar metabolic shift. However, despite the preference for glucose use in the resting state, older individuals demonstrated a blunted increase in glucose utilization in response to dobutamine when compared with younger individuals. Fortunately, these age-related changes in substrate metabolism are not irreversible, as the impairment in metabolic reserve can be ameliorated by endurance exercise training.

Sex is also a determinant of the pattern in the myocardial substrate metabolism (Table 2). For example, in female rats, myocardial glucose metabolism was lower and fatty acid metabolism was higher compared with male rats. These observations were confirmed in young healthy volunteers using PET with 11C-glucose and 11C-palmitate. Women exhibited lower levels of glucose metabolism compared with men. Although no differences in myocardial fatty acid metabolism were noted, women also exhibited higher MVO₂ compared with men as measured by PET with 11C-acetate. It appears that these sex differences in substrate metabolism become more pronounced as one transitions to more pathological conditions, such as obesity. In addition to the changes in glucose metabolism and MVO₂, obese women exhibited higher fatty acid uptake and oxidation compared with obese men. The differences in myocardial metabolism could not be explained by differences in myocardial blood flow, insulin sensitivity, or hemodynamics. However, it should be noted that fatty acid release into the plasma is higher in women compared with men primarily due to a percent higher fat mass. Thus, differences in myocardial fatty acid delivery may be contributing to these metabolic differences. Sex hormone stimulation may also play a role because results of animal studies have shown that estrogen decreases glucose oxidation, gluconeogenesis, and glycogenolysis and increases fatty acid oxidation in liver and skeletal muscle. Indeed, in a small retrospective study, PET-derived measurements of myocardial fatty acid metabolism in postmenopausal women were higher compared with postmenopausal women not receiving hormonal replacement therapy or age-matched men. Although requiring further study, these sex and age differences in metabolism may provide a partial explanation for the age- and sex-related outcome differences for various cardiovascular diseases in which altered myocardial metabolism plays a role. Moreover, these observations highlight the need to account for age and sex differences when performing measurements of myocardial substrate metabolism.

**Diabetes Mellitus**

Cardiovascular disease is the leading cause of death in patients with type 1 and type 2 diabetes mellitus, with atherosclerosis accounting for approximately 80% of the cases. However, even in the absence of concomitant coronary artery disease, left ventricular hypertrophy with systolic and diastolic dysfunction can occur—the so-called diabetic cardiomyopathy. There is extensive evidence to suggest that abnormalities in myocardial substrate metabolism also contribute to this cardiomyopathic process. As mentioned previously, the overdependence on fatty acid metabolism and a decrease in glucose use typifies the metabolic phenotype in diabetes (Table 2). Particularly in type 2 diabetes mellitus, the elevation in fatty acid metabolism reflects the effects of peripheral insulin resistance that increase plasma fatty acid levels, resulting in higher fatty acid delivery to the myocardium. This results in higher myocardial fatty acid uptake, which activates key transcriptional pathways such as the PPARα/PGC-1 signaling network, resulting in further myocardial fatty acid uptake and oxidation. Both insulin-mediated glucose transport and glucose transporter expression decline in diabetes mellitus. However, rates of myocardial glucose uptake are frequently normal as the result of hyperglycemia. The increase in myocardial fatty acid metabolism results in higher citrate levels, which inhibit phosphofructokinase. Glucose oxidation is inhibited at the level of pyruvate dehydrogenase complex. Consequently, the maintenance of myocardial glucose uptake but a decrease in
its downstream metabolism results in an accumulation of glucose metabolites. Potential detrimental effects associated with this shift in metabolism include impaired mechanical function in response to increased myocardial work, depletion of tricarboxylic acid cycle intermediates needed for anaplerosis, electric instability, a greater sensitivity to myocardial ischemia, and myocardial lipid and glucose metabolite accumulation leading to increased oxidative stress and apoptosis.47–49

Small-animal radionuclide imaging has helped clarify the mechanisms responsible for the metabolic alterations that occur in diabetes mellitus. For example, mice with cardiac-restricted overexpression of PPARα (a metabolic phenotype similar to diabetic hearts) demonstrate an increase in fatty acid uptake and an abnormal suppression of glucose uptake using small-animal PET with 11C-palmitate and FDG. 50 However, the small size of the mouse heart permits only semiquantitative measurements of tracer uptake, highlighting the imaging challenges that still must be overcome before quantification of metabolic processes are possible in this species. In contrast, quantitative measures of myocardial substrate metabolism are now possible with small-animal PET in rat heart. Rates of myocardial glucose uptake correlate directly and closely and GLUT 4 gene expression in the Zucker-Diabetic-Fat (ZDF) rat, a model of type 2 diabetes mellitus (Figure 5).51 Moreover, rates of myocardial glucose uptake and fatty acid uptake and oxidation measured with PET in the same disease model demonstrated the importance of increased fatty acid delivery to defining the metabolic phenotype in diabetes.52

Numerous studies have used PET with FDG to characterize myocardial glucose metabolism in patients with diabetes mellitus.53–55 In general, rates myocardial glucose uptake are reduced in patients with either type 1 or type 2 diabetes mellitus compared with nondiabetics, except under conditions of marked hyperglycemia or supraphysiological levels in plasma insulin (such as occurs with a hyperinsulinemic-euglycemic clamp (Table 2). A recent study using PET and 11C-glucose and 11C-palmitate in patients with type 1 diabetes mellitus demonstrated that the decline in myocardial glucose uptake is paralleled by an increase in fatty acid uptake and oxidation compared with nondiabetics. The decline in glucose uptake was primarily due to decreased glucose transport mechanisms, whereas the increase in myocardial fatty acid metabolism was due to increased plasma fatty acid levels.56 Consistent with what has been observed in experimental models of diabetes mellitus, there are reduced rates of glycolysis and glucose oxidation. This reduction becomes more pronounced with increases in cardiac work induced by dobutamine (Figure 6).57 However, despite the overdependence on fatty acid metabolism, the diabetic heart still is responsive to changes in plasma insulin and fatty acid levels, but at a cost. Higher insulin levels are needed to achieve the same level of glucose uptake and glucose oxidation compared with nondiabetics, which suggests myocardial insulin resistance. In response to higher plasma fatty acid levels, myocardial fatty acid uptake is increased. However, limitations on the downstream fatty acid oxidation rate results in a greater esterification rate.57,58

![Figure 5](http://circimaging.ahajournals.org/) Regression model M3 was used to characterize dependence of fractional myocardial glucose uptake (MGUp) on gene expression of GLUT-4 with \( R^2 = 0.81 \), which is significant at \( P = 0.0003 \). Reproduced with permission from Springer Science & Business Media, © 2008, Shoghi et al.51

![Figure 6](http://circimaging.ahajournals.org/) Measurements of overall myocardial glucose uptake (MGU), glycolysis, glucose oxidation, and glycogen synthesis for normal volunteers (NV), type 1 diabetic patients studied under baseline metabolic conditions (DM1), and diabetic patients studied during hyperinsulinemic-euglycemic clamp (DM1-C) both at rest (open bars) and during dobutamine (closed bars). Reproduced with permission from Herrero et al.57
Therapeutic strategies are being designed to decrease fatty acid delivery to the myocardium in an attempt to reduce its overdependence on fatty acid metabolism and improve its energetic profile and function. The use of the insulin-sensitizing agent troglitazone in ZDF rats reduces plasma fatty acid levels, myocardial lipid accumulation, and apoptosis and improves left ventricular function. In PET with FDG studies, patients with type 2 diabetes mellitus demonstrated a nearly 40% increase in insulin-stimulated myocardial glucose uptake 26 weeks after treatment with rosiglitazone. This implies reduced fatty acid uptake, which was attributed in large part to suppression in plasma fatty acid levels. Similar metabolic changes were not seen with the biguanide metformin, whose mechanism of action is designed to reduce hepatic glucose production. Of note, the improvement in insulin-stimulated glucose metabolism could not be predicted by changes in the plasma glucose or HbA1c levels. These data suggest that metabolic imaging may provide unique insights into therapeutic myocardial metabolic modulation not attainable with more readily available peripheral blood measures.

Obesity and Insulin Resistance
Given that obesity is associated with increased fat mass and plasma lipid levels, it is not surprising that obesity induces a marked increase in myocardial fatty acid metabolism (Table 2). In both dietary-induced and transgenic models of obesity, myocardial fatty acid uptake and oxidation are significantly increased. Using PET and 13C-acetate and 13C-palmitate, it is now apparent that similar abnormalities in myocardial fatty acid metabolism occur in humans with obesity. For example, in otherwise healthy young obese women, myocardial fatty acid metabolism increases with an increase in body mass index, with the overdependence in fatty acid metabolism becoming more pronounced with worsening insulin resistance. There is little change in myocardial glucose metabolism. The increase in myocardial fatty acid use is paralleled by an increase in MVo2 and a decrease in energy transduction. These findings suggest that metabolic changes in obesity may play a role in the pathogenesis of cardiac dysfunction, which is more pronounced in obese women.

Of note, it appears that the myocardial metabolic response to obesity differs between women and men. In contrast to obese women, obese men exhibit a greater impairment in myocardial glucose metabolism per level plasma insulin, suggesting greater myocardial insulin resistance. In addition, obesity had less effect on myocardial fatty acid metabolism in men. In contrast, MVo2 is higher in the obese women compared with obese men. Thus it appears there appears to be a complex interplay between sex and obesity in influencing myocardial substrate metabolism.

Ischemia
With the induction of myocardial ischemia, fatty acid oxidation ceases and glucose becomes the primary substrate for both increased anaerobic glycolysis and for continued albeit diminished oxidative metabolism (Table 2). This metabolic switch is a prerequisite for continued energy production and cell survival. When the ischemic insult is reversed, oxygen availability increases and oxidative metabolism resumes. It appears that these abnormalities in myocardial substrate metabolism may persist well after the resolution of ischemia—so-called “ischemic memory.” Demonstration of either accelerated myocardial glucose metabolism or reduced fatty acid metabolism using FDG and BMIPP, respectively, has been used to document this phenomena. For example, increased myocardial FDG uptake has been shown in patients with unstable angina during pain-free episodes. Similar observations have been made with SPECT using BMIPP. It is apparent that in patients with acute chest pain that abnormalities in myocardial BMIPP uptake may persist 24 to 36 hours after the resolution of symptoms. Moreover, one study suggests that this “metabolic fingerprint” appears superior to perfusion imaging for identifying coronary artery disease as the cause of the chest pain and for assigning a prognosis. The persistence in the metabolic defect increases the flexibility of radiotracer administration for it allows for delivery of a unit dose after the patient has already been evaluated. This is in contrast to the use of perfusion radiotracers, which frequently must be available on-site because of the narrow time window from the resolution of symptoms and normalization of the flow deficit. Recent studies also suggest that patterns of reduced fatty acid metabolism may be a marker of cardiac risk in certain high-risk patient populations. For example, in patients with end-stage renal disease, cardiac death was significantly associated with highly abnormal BMIPP uptake. Metabolic imaging with either FDG or BMIPP has also been used for direct ischemia detection during stress testing. In this circumstance, the thought process is that abnormalities in vasodilator reserve delineated with perfusion tracers will underestimate ischemia if oxygen demand and supply remain balanced. Results of initial studies in which FDG was injected during exercise appear to support this contention, with a greater detection rate for moderate to severe coronary artery stenoses compared with perfusion imaging. Moreover, it appears that defects in either glucose or fatty acid metabolism with exercise will persist for 24 hours (Figure 7). However, despite these promising results, numerous questions still remain as to the optimal imaging protocols, the impact of alterations in the plasma substrate environment on diagnostic accuracy, the usefulness of metabolic imaging in diabetic patients, whether the information obtained from metabolic imaging adds a significant amount of diagnostic and prognostic information to that provided by perfusion imaging, and whether the metabolic imaging information alters clinical management.

Hypertension/Left Ventricular Hypertrophy
There are numerous lines of evidence to support the notion of a relationship between abnormalities in myocardial substrate metabolism and left ventricular hypertrophy. In experimental models of pressure-overload left ventricular hypertrophy, myocardial fatty acid oxidation is decreased and there is an increase in glucose use. Moreover, interventions that inhibit mitochondrial fatty acid oxidation result in cardiac hypertrophy. In humans, variants in genes regulating key aspects of myocardial fatty acid metabolism ranging from PPARα to various key β-oxidative enzymes are associated with left ventricular hypertrophy.
In a rat model of hypertrophy, PET with FDG demonstrated that myocardial glucose uptake tracked directly with increasing hypertrophy confirming this shift in substrate preference in vivo (Table 2). Similar results have been found in humans. PET with 11C-palmitate in humans has shown the reduction in myocardial fatty acid oxidation is an independent predictor of left ventricular mass in hypertension. Combining measurements of left ventricular myocardial external work (either by echocardiography or MRI) with measurements of MVO₂ performed by PET with 11C-acetate or 15O-oxygen, it is possible to estimate cardiac efficiency. Using this approach in patients with hypertension-induced left ventricular hypertrophy has shown that the decline in myocardial fatty acid metabolism is associated with a decline in efficiency, a condition that may increase the potential for the development of heart failure. Another potential application of PET is the phenotyping of patients with genetic variants related to myocyte growth. For example, patients with mild hypertrophic cardiomyopathy (attributable to a known specific variant in the α-tropomyosin gene), it was observed that there was increased myocardial perfusion, fatty acid metabolism, and efficiency, but, in patients with advanced hypertrophy, these metabolic alterations decreased. Although requiring further study in larger patient populations, this study suggests that metabolic imaging may identify relevant gene variants without waiting for more end-stage manifestations such as left ventricular remodeling and dysfunction to occur.

Nonischemic Dilated Cardiomyopathy
In experimental models of heart failure, the progression from cardiac hypertrophy to ventricular dysfunction is paralleled by a decrease in the expression of genes encoding for enzymes regulating β-oxidation. This causes a shift in myocardial substrate metabolism to primarily glucose use similar to that seen in the fetal heart (Table 2). Paralleling these metabolic changes is the reexpression of fetal isoforms of a variety of contractile and calcium regulatory proteins. The reactivation of the metabolic fetal gene program may have numerous detrimental consequences on myocardial contractile function ranging from energy deprivation to the inability to process fatty acids, which in turn leads to accumulation of nonoxidized toxic fatty acid derivatives and lipotoxicity. Underscoring the importance of this metabolic shift in the pathogenesis of heart failure is the robust discovery and development of novel therapeutics that target specific aspects of cellular metabolism such as the partial fatty acid oxidation of myocardial glucose uptake tracked directly with increasing hypertrophy confirming this shift in substrate preference in vivo (Table 2).
oxidation antagonists and the insulin sensitizer glucagon-like peptide-1.81

Both SPECT and PET techniques have documented in humans the metabolic shift associated with cardiomyopathy. For example, SPECT with BMIPP demonstrated reduced myocardial uptake and increased clearance of radiotracer in patients with dilated cardiomyopathy compared with control subjects.82 Moreover, the magnitude of these metabolic abnormalities correlated with other measurements of heart failure severity such as left ventricular size and plasma b-natriuretic peptide levels. It appears that these abnormalities in BMIPP kinetics reflect the combined effects of reduced fatty acid uptake and oxidation, as evidenced by PET with $^{11}$C-palmitate studies in similar patients. In this same $^{11}$C-palmitate study, myocardial glucose metabolism was higher in the cardiomyopathic patients compared with control subjects, confirming the metabolic shift.83 Similarly, PET has also been used provide mechanistic insights into the myocardial metabolic abnormalities associated with heart failure. Rapid, marked lowering of fatty acid delivery with acipimox results in reduced fatty acid uptake, $\text{MVO}_2$, and cardiac work and no change in cardiac efficiency in normal volunteers. However, in patients with nonischemic dilated cardiomyopathy treated with acipimox, there is a decrease in myocardial fatty acid uptake and cardiac work, no change in $\text{MVO}_2$, and a decline in efficiency.84 Although limited by a small sample size, these results appear to reinforce the central role of a loss in flexibility in myocardial substrate metabolism in the pathogenesis of heart failure, with even minor changes in substrate delivery having detrimental consequences on cardiac energy transduction.

Metabolic imaging can also been used to study the effects of various treatments for cardiomyopathy. For example, treatment with the selective $\beta$-blocker metoprolol results in a reduction in oxidative metabolism and an improvement in cardiac efficiency as measured by PET in patients with heart failure.85 Cardiac efficiency has been shown to improve after either exercise training or cardiac resynchronization therapy, implicating improved myocardial energy transduction as a potential mechanism.86,87 Partial fatty acid oxidation inhibitors have been proposed for the treatment of heart failure, based on the theory that decreasing myocardial fatty acid oxidation should increase the oxidation of glucose, leading to a more favorable energetic state and improved left ventricular function. In support of this hypothesis is the finding that the administration of trimetazidine to patients with dilated cardiomyopathy results in a significant improvement in left ventricular ejection fraction.88 However, the therapy resulted in only a mild decrease in myocardial fatty acid oxidation. Thus, it appears that the improvement in left ventricular function reflects more than a shift in metabolism and probably is influenced by other factors such as improved whole-body insulin resistance and synergistic effects with $\beta$-blockade. In patients with dilated cardiomyopathy, it appears that the fraction of myocardial glucose uptake, as measured by PET with FDG, predicts the effectiveness of $\beta$-blocker therapy.89 Moreover, in patients with ischemic cardiomyopathy, the extent of viable myocardium as measured with PET and FDG correlated with the hemodynamic response after cardiac resynchronization therapy, suggesting a role for PET in discriminating responders from nonresponders to this therapy.90 Thus, metabolic imaging can also be used to predict the response to specific therapies in patients with heart failure.

Right Ventricular Imaging

In contradistinction to the left ventricle, there are relatively few imaging studies of the myocardial metabolism of the right ventricle. In pulmonary hypertension, glucose uptake, as measured by PET with FDG, appears to be increased in the right ventricular free wall.91 The degree of glucose uptake correlates with the mean pulmonary artery pressure. Moreover, the amount of glucose uptake decreases after successful treatment of pulmonary hypertension with epoprostenol.91 Other studies using either PET or SPECT have shown that increased pulmonary artery pressures are also related to increased overall oxidative metabolism and impaired fatty acid metabolism.92,93 In heart failure, right ventricular oxidative metabolism decreases after exercise training.86

Beyond the Myocardium: Vascular Imaging

Based on the premise that glucose metabolism is increased in activated macrophages that are a key component of athero-
sclerotic plaque, FDG is being evaluated for the detection of “biologically active” atherosclerosis. Several groups have established that inflamed arterial vessels have increased uptake of FDG as measured by PET. The increased uptake has been noted in animal models of atherosclerosis and verified in humans with atherosclerosis of the carotid artery and aorta. Moreover, a significant correlation between FDG uptake and CD68 cell staining has recently been established. It appears that vascular FDG imaging is fairly reproducible, suggesting a role for monitoring of therapy. Indeed, a decrease in carotid artery FDG uptake is correlative with an increase in plasma high-density lipoprotein levels after statin therapy or lifestyle modifications (Figure 8).

However, many questions remain about this technique such as the site of localization of radiotracer (eg, plaque or smooth muscle), the suitability of the method for evaluating the coronary arteries, and whether the information provides more refined risk stratification compared with other more widely applicable methods or if it alters therapy.

**Future Directions**

Despite the success of metabolic imaging in furthering our understanding of disease mechanism and in identifying and evaluating potential novel therapeutics for various forms of cardiovascular disease, advances are needed in several areas. There must be continued improvement in instrumentation design for imaging of humans and small animals. For example, advances in PET detector design and postdetector electronics will further increase counting statistics, which would improve the ability to perform more complex compartmental modeling permitting more complete characterization of the metabolism of a given substrate. New designs in SPECT technology may also allow for dynamic data acquisitions permitting quantitative or semiquantitative measurements of substrate metabolism. There is also a fundamental need for the development of new radiotracers that help further characterize key metabolic pathways involved in substrate uptake, storage, or oxidation that are linked to disease manifestations. Moreover, new radiotracers are needed to provide insights into the links between substrate metabolism and cell growth, cell survival, and energy transduction. To facilitate their widespread usage, these radiotracers should be radiolabeled with F-18, I-123, or Tc-99m and exhibit kinetics that can be assessed with readily exportable image analysis schemes. These advancements will facilitate appropriately powered clinical trials designed to answer key questions about the utility of metabolic imaging for diagnosis, risk stratification, and monitoring of therapy in specific patient populations. This knowledge should lead to the expansion of the clinical utility of metabolic imaging.

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None.

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Peterson and Gropler Myocardial Metabolic Imaging 221


Radionuclide Imaging of Myocardial Metabolism
Linda R. Peterson and Robert J. Gropler

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