Insights Into Coronary Artery Disease Gained From Metabolic Imaging

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Positron emission tomography offers the possibility of evaluating and quantifying regional myocardial blood flow and metabolism. Used in patients with coronary artery disease, positron emission tomography has demonstrated sustained metabolic activity in regions with reduced blood flow and impaired contractile function, and it thereby enables differentiation between viable myocardium and myocardium that has succumbed to necrosis and scar formation. Viable myocardial regions identified by metabolic rather than functional or blood-flow criteria are frequently observed in patients after an acute coronary event and in patients with stable coronary artery disease. Positron emission tomography reflects either acute myocardial ischemia, "hibernation," as well as "myocardial stunning." Findings from metabolic imaging have proved useful in characterizing more accurately coronary artery disease and its functional consequences. These findings have been found equally useful for clinical management. (Circulation 1988;78:496–505)

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pplication of positron emission tomography (PET) to the heart has given considerable impetus to the study of regional myocardial metabolism in human myocardium. Regional myocardial blood flow, glucose utilization, fatty acid metabolism, and, more recently, oxygen consumption can now be evaluated noninvasively and can be quantified.1,2 These accomplishments have generated considerable interest in applying this new technology to the study of human cardiac disease. It is therefore important to ask whether insights into coronary artery disease can be gained from metabolic imaging. Such insights relate to both the pathophysiology of human coronary artery disease and its metabolic expression as well as to clinical and therapeutic consequences. This review will attempt to answer these questions and focus on metabolic findings in patients with stable coronary artery disease. It will further examine the significance of these findings within the context of observations on metabolism in acutely ischemic and posts ischemic myocardium in humans and relate these findings to biochemical knowledge derived from animal experiments and in vitro experimental systems. Finally, how these insights may relate to the clinical characterization and treatment of coronary artery disease and its functional consequences will be discussed.

Tools for Metabolic Imaging

The tools for probing regional myocardial metabolism in humans are unique to PET. They include a quantitative imaging capability and, therefore, the possibility of using tracer kinetic principles in human subjects so that blood flow and substrate fluxes can be quantified noninvasively. Another important feature of PET is the large number of available positron emitting tracers for probing in various aspects of tissue function. Clinical investigations thus far have used only a few tracers. They include 15O-labeled water, 18F, and 11N-labeled ammonia as tracers of blood flow and 18F-2-deoxyglucose (FDG), 11C-labeled palmitate, and 11C-labeled acetate as tracers of exogenous glucose utilization, myocardial fatty acid metabolism, and myocardial oxygen consumption, respectively.1,2

Although 15O-labeled water and 18F are equally useful as tracers of blood flow, most of our clinical investigations have used 11N-labeled ammonia.3–5 The tracer rapidly exchanges through diffusion from blood into myocardium where it is retained in proportion to blood flow. The initial capillary transit extraction fraction averages about 80% at baseline

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flows. The $^{13}$N label is trapped metabolically in myocardium mostly through the glutamate-glutamine reaction. The trapping mechanism appears to be relatively insensitive to acute alterations in myocardial metabolism and to acute ischemia. The regional concentrations of $^{13}$N activity, therefore, reflect myocardial blood flow. The possibility of quantifying noninvasively regional myocardial blood flow with this tracer and an appropriate tracer kinetic model has recently been established.\textsuperscript{6,7}

$^{13}$C-Labeled palmitate has been found useful for the evaluation of regional myocardial fatty acid metabolism. The tracer accumulates initially in myocardium in proportion to blood flow. Animal experiments and clinical studies have demonstrated a biexponential clearance of $^{13}$C activity from myocardium and have defined its relation to myocardial fatty acid metabolism.\textsuperscript{1,2} The two clearance curve components reflect the metabolic fate of fatty acid between immediate oxidation and intermediate storage in the endogenous lipid pool. Relative size and slope of each curve component change in response to altered substrate selection and oxygen consumption and correctly indicate changes in oxidation and storage of fatty acid. Consistent with an impairment in fatty acid oxidation, the relative size and slope of the early clearance curve component are decreased in ischemia. Substantial back-diffusion of nonmetabolized tracer from myocardium into blood during ischemia limits the value of the externally recorded tissue $^{13}$C clearance rate as an indicator of the rate of fatty acid oxidation.\textsuperscript{2} The evaluation of myocardial fatty acid metabolism with $^{13}$C-labeled palmitate has remained, therefore, largely qualitative.

FDG traces the initial metabolic step of exogenous glucose. The compound is transported from blood into myocardium in proportion to glucose and then competes with glucose for hexokinase. The phosphorylated tracer, FDG-6-phosphate, becomes virtually trapped in myocardium because 1) it is, unlike glucose-6-phosphate, a poor substrate for glycogen synthesis, glycolysis, and the pentose phosphate shunt, 2) dephosphorylation is slow, and 3) the cell membrane is relatively impermeable to it. Because of practically unidirectional transport and trapping of FDG in myocardium, $^{18}$F tissue concentrations at 40–60 minutes after intravenous administration represent qualitatively regional rates of glucose utilization. With a tracer kinetic model, adopted from that used and validated in the brain, regional rates of glucose utilization can be obtained noninvasively in myocardium.\textsuperscript{8–10} It is important to emphasize that FDG traces only the initial metabolic steps of exogenous glucose utilization, but it precludes direct measurements of metabolic events beyond the branching point of glycolysis and glycogen synthesis. Thus, the fraction of exogenous glucose entering glycolysis or the contribution of glucose derived from glycogen to total glycolytic flux cannot be measured directly. A substantial fraction of exogenous glucose, possibly as high as 60–70%, is initially synthesized to glycogen.\textsuperscript{11} Homeostasis, however, requires that the rate of glycogen formation is equal to the rate of glycogen breakdown. The FDG method should, therefore, indirectly yield rates of glucose flux through glycolysis. This obviously does not apply to non–steady-state conditions when glycogen stores are either depleted or replenished, as, for example, during reperfusion after an ischemic episode.

**Regional Myocardial Metabolic Abnormalities in Patients With Coronary Artery Disease at Rest**

Several clinical investigations have described a distinct segmental metabolic abnormality in patients with stable coronary artery disease when studied at rest.\textsuperscript{5,12–14} With $^{13}$N-labeled ammonia and FDG, these studies reported regions with decreased blood flow but with increased FDG uptake (Figures 1–4), which

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Positron emission tomograms of myocardial blood flow (MBF) and glucose utilization in a normal volunteer. Six contiguous cross-sectional images were acquired from the base of the left ventricle (Plane 1) to the inferior wall (Plane 6) after intravenous administration of $^{13}$N-labeled ammonia ($^{13}$NH$_3$) and intravenous injection of $^{18}$F-labeled 2-deoxyglucose ($^{18}$FDG). Heart viewed from the subject’s feet. Note the homogeneous distribution of both tracers throughout the left ventricular myocardium indicating homogeneous distribution of blood flow and glucose metabolism.
is a pattern defined as “blood flow–metabolism mismatch.” A second pattern has been observed in which the segmental reduction in blood flow is paralleled by a proportionate decrease in FDG uptake. This second pattern is subsequently referred to as “blood flow–metabolism match.”

Because the blood flow–metabolism mismatch was initially observed in patients with episodes of angina during the PET study, it was ascribed to acute myocardial ischemia. This explanation was based on earlier animal findings in which a similar pattern had been demonstrated during acute, pacing-induced myocardial ischemia. However, subsequent studies rendered such explanations less likely, for the majority of patients were asymptomatic and without electrocardiographic evidence of acute myocardial ischemia at the time of the PET study. Furthermore, neither pattern was found to be strongly related to antecedent myocardial infarction as evidenced by a characteristic history of chest pain and electrocardiographic or enzyme changes, or both, or by pathological Q waves. In fact, either pattern could occur in myocardial regions with chronically pathological Q waves.

The blood flow–metabolism mismatch was associated with several other abnormalities. Wall motion is invariably abnormal. However, wall motion is equally impaired in segments with blood flow–metabolism matches. Second, segmental blood flow is always reduced. Measurements of relative reductions in blood flow suggested, however, that the blood flow–metabolism mismatch pattern depended upon some residual blood flow. The pattern was not observed in regions in which flow was reduced to less than 20% of that in control myocardium. Conversely, it was invariably present in regions in which flow was reduced but still greater than 40% of that in normal myocardium. Third, FDG uptake in segments with blood flow–metabolism mismatches is fixed, failing to change in response to alterations in substrate availability and shifts in substrate selection by normal myocardium (Figures 3 and 4). Such changes can be induced by oral or intravenous administration of glucose in fasted humans or in animals and can be
weeks after coronary artery bypass grafting. Conversely, no improvement was observed in 92% of regions with a blood flow–metabolism match.

In summary, the absolute or relative increase in FDG uptake in segments with reduced blood flow and impaired contractile function appears to identify viable myocardium in which function improves when blood flow is restored. The pattern appears to be consistent with the notion of "hibernating myocardium" and possibly represents its metabolic counterpart.

Hibernating Myocardium and Metabolic Imaging

Striking improvements in left ventricular ejection fraction and regional wall motion after coronary revascularization have been reported. Such improvements imply the existence of a long-term loss or impairment of contractile function that was reversed by restoring blood flow. Rahimtoola referred to such myocardial segments as "hibernating." This concept, reemphasized recently by Braunwald and Rutherford, maintains that 1) chronically reduced blood flow results in impairment or loss of contractile function that is permanent unless 2) it is reversed by restoration of blood flow, 3) impairment of contractile function may exert a protective effect by minimizing energy requirements and preventing or delaying necrosis and fibrosis, and 4) some residual blood flow is required for removal of inhibitory metabolites and for preservation of tissue viability. These criteria closely match those of blood flow–metabolism mismatch and suggest that augmented FDG uptake in hypoperfused and dysfunctional segments represents the metabolic counterpart of hibernating myocardium.

Although clinically useful, the term "hibernation" implies achievement of a new steady state or balance between decreased supply and decreased demand. This is especially important if hibernation or viability is to be maintained indefinitely and progression to necrosis and fibrosis be avoided. It also implies the existence of "chronic myocardial ischemia," which has remained controversial and which raises several questions. For example, is there evidence that supports the existence of chronic myocardial ischemia? Second, can a severely limited supply meet a demand that is low because of impaired contractile function but still be adequate to maintain viable tissue? Thus, can a precarious and probably unstable balance between demand and supply be maintained indefinitely? Third, is there evidence that exogenous glucose utilization serves as a primary substrate for ischemic myocardium? If so, does FDG correctly trace exogenous glucose utilization in myocardial ischemia? Fourth, is it possible that the observed metabolic pattern is the result of repeated episodes of acute ischemia and of stunning? With metabolic imaging, segmental increases in FDG uptake are common to acute myocardial ischemia as well as myocardial stunning.
Chronic Myocardial Ischemia or Repeated Episodes of Acute Ischemia?

There is some experimental evidence that ischemia can be maintained for some time without resulting in significant amounts of tissue necrosis. For example, by partially occluding the circumflex coronary artery for 5 hours in conscious dogs, Matsuzaki et al.\(^20\) were able to achieve a sustained 38% reduction in systolic wall thickening associated with a 66% reduction in blood flow to the subendocardium. After gradual restoration of blood flow during a 20-minute period, segmental function recovered fully within 1 week without significant necrosis and postmortem histology. Furthermore, Opie et al.\(^21\) demonstrated that altered substrate metabolism could be maintained relatively constant for periods of up to 2 hours in small myocardial regions of ischemia. Coronary occlusion was followed by an initial decline in tissue glycogen stores to 50% of control. Thereafter, glycogen stores remained constant. Fatty acid oxidation declined and was associated with greater utilization of glucose that was metabolized to lactate and CO\(_2\). The altered substrate utilization remained relatively constant during the 2-hour study period. Both studies suggest the possibility of maintaining a precarious balance between demand and supply for some time and avoidance of significant necrosis.

Although commonly considered as an imbalance of supply and demand, Poole-Wilson\(^22\) defines ischemia as an "imbalance between consumption of ATP and blood flow." This definition addresses more specifically factors that appear critical in human coronary artery disease. Obviously, there must be a minimum consumption of adenosine 5'-triphosphate (ATP) that is critical for cell survival. This value may approach the estimate of 10% of all energy that is generated and dispensed for various functions in the normal beating heart and serves to "keep the cell alive in the absence of any electrical and mechanical activity."\(^23\) Newsholme and Leech\(^24\) suggested that if oxygen is absent, production of ATP in amounts adequate for survival could be generated through anaerobic glycolysis. This, however, assumes sufficient supply of exogenous glucose and removal of metabolites that inhibit glycolysis. This then assigns a critical role to blood flow for cell survival. Thus, further reductions of already limited blood flow can result in higher lactate and proton concentrations in the cytosol, which then would further impinge upon the already limited production of ATP.

Although such a balance between consumption of ATP and blood flow can be maintained for some time under experimental conditions, increased vaso-reactivity and intermittent deposition of platelets in coronary artery disease are likely to cause periodic reductions of an already critically impaired blood flow. There is evidence for repeated additional reductions in blood flow in patients with coronary artery disease. They can be caused by routine daily activities, mental stress, and cigarette smoking.\(^25\) Such variations in flow may result in slow progression of ischemia to necrosis and fibrosis, which argues against the possibility that viability can be sustained indefinitely. Episodes of acute ischemia are followed by stunning or recovery, which remains incomplete because of renewed ischemic insults.\(^26\) As demonstrated in animal experiments, such alternation between ischemia and repertusion is likely to account for the permanent impairment of contractile function in hibernating myocardium.\(^27\) Thus, rather than reflecting a state of chronic ischemia, hibernating myocardium may reflect a state of alternating episodes of ischemia and recovery. This would imply that tissue viability cannot be maintained indefinitely. Restoration of blood flow would then be critical to reverse the progression of ischemia to necrosis. Findings in metabolic imaging would also be consistent with intermittent episodes of ischemia and stunning in hibernating myocardium. Both conditions, acute ischemia and post-ischemia or stunning, are associated with relative increases in FDG uptake in segments with either normal or reduced blood flow.

Biochemical Basis of Ischemia

A brief review of metabolic changes in acute myocardial ischemia will set the stage for examining findings on metabolic imaging in acutely ischemic myocardium. Numerous investigations have probed the metabolic changes occurring in acutely ischemic myocardium.\(^28,29\) Although in aerobic myocardium, fatty acid is the predominant fuel source; in ischemic myocardium, glucose becomes the most important substrate. This switchover is due to a number of alterations at key regulatory steps. The supply of glucose is increased in ischemia both by increased breakdown of tissue glycogen as a result of activation of glycogen phosphorylase and by increased transport of exogenous glucose. However, glycogen stores are limited and are exhausted within minutes in total ischemia. Phosphorylation of glucose by hexokinase and of fructose-6-phosphate by phosphofructokinase are increased by relief of product inhibition and allosteric activation, respectively. Control of the rate of glycolysis now shifts to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which is inhibited by lactate and decreased intracellular pH. GAPDH also requires oxidized nicotinamide adenine dinucleotide (NAD\(^+\)) and is inhibited by reduced nicotinamide adenine dinucleotide (NADH). Oxidative disposition of pyruvate by pyruvate dehydrogenase–mediated acetyl coenzyme A production is also limited by accumulation of NADH and acetyl coenzyme A, which inhibit pyruvate dehydrogenase allosterically and also stimulate covalent inactivation of pyruvate dehydrogenase by pyruvate dehydrogenase kinase. Conversion of pyruvate to lactate by the equilibrium enzyme lactate dehydrogenase allows regeneration of cytosolic NAD\(^+\) from NADH, thus allowing the GAPDH reaction to continue. Thus,
removal of lactate by residual flow is of overwhelming importance because accumulation of lactate will prevent further regeneration of NAD$^+$ from NADH by lactate dehydrogenase by shifting the equilibrium toward pyruvate and will also inhibit GAPDH directly.

There is no energy-yielding nonoxidative alternative pathway to β-oxidation of fatty acids, which is in contrast to the production of lactate from glucose. Limitation of oxygen supply, and resultant slowing of the electron transport chain, leads to a rapid increase in the mitochondrial NADH:NAD$^+$ ratio and to inhibition of NAD$^+$-dependent β-oxidation. As a consequence of inhibition of β-oxidation, long-chain acyl-coenzyme A and acyl-carnitine intermembranes accumulate intracellularly, accompanied by decreases in fatty acid uptake, activation, and transport of fatty acyl-coenzyme A into the mitochondria. Fatty acid esterification is also increased because of elevated levels of α-glycerol phosphate as a result of constraint of glycolysis at GAPDH.

The role of contained anaerobic glycolysis in maintenance of cellular viability in ischemia may be particularly crucial in view of the proposed functional compartmentation of energy derived from glycolysis and oxidative metabolism. Experimental evidence obtained with specific inhibitors suggests that ATP produced by glycolysis is used preferentially for membrane function, whereas ATP derived from oxidative metabolism is used preferentially for contractile function.

Metabolic Imaging in Acute Myocardial Ischemia

The feasibility of demonstrating noninvasively metabolic consequences of acute myocardial ischemia was first examined in dog experiments. These studies revealed markedly increased FDG uptake as well as regional changes in 11C-labeled palmitate clearance kinetics in myocardial segments with attenuated increases in blood flow during atrial pacing. These changes were consistent with an impairment in fatty acid oxidation and a disproportionately greater deposition of fatty acid in the endogenous lipid pool as well as with an increase in glycolytic flux. Metabolic imaging in patients with coronary artery disease during and immediately after exercise-induced angina revealed a similar pattern. Segments with relative decreases in blood flow during exercise revealed normal or increased FDG uptake after examined at peak exercise or 20 minutes later when relative flow deficits had resolved. Other studies in patients with coronary artery disease reveal an attenuated response in 11C-labeled palmitate tissue kinetics to increases in heart rate. The tissue kinetics of 11C-labeled palmitate suggest that fatty acid oxidation is increased in response to higher workloads, yet the increase remains attenuated in segments subtended by stenosed coronary arteries relative to segments supplied by normal coronary arteries. These findings indicate an inadequate increase in fatty acid oxidation and further suggest the possibility of a compensatory metabolic mechanism. Pacing at subanginal levels induced new wall motion abnormalities in only five of 10 patients despite an attenuated response of the 11C-labeled palmitate kinetics in all 10 patients. Although it is possible that two-dimensional echocardiography failed to detect subtle pacing-induced dysfunction, it is also possible that the impaired response in fatty acid oxidation was compensated for by enhanced oxidation of glucose that was responsible for maintaining segmental function normal. For the same amount of oxygen, more ATP can be generated by oxidizing glucose instead of fatty acid. If the existence of such a compensatory mechanism can be established, it would indicate, first, that mild states of hypoxia can be compensated for by shifting from fatty acid to glucose oxidation and, second, that such mild states of ischemia can be demonstrated noninvasively by means of metabolic imaging.

Metabolic Imaging in Stunned Myocardium

Studies with 82Rb and FDG in patients with coronary artery disease provide evidence for persistence of blood flow and metabolic abnormalities for some time after an acute ischemic episode. Earlier studies have suggested that exercise-induced blood-flow defects persisted longer than angina and electrocardiographic changes. Although Selwyn et al have attributed the delayed resolution of a defect on serial 82Rb images to a transient abnormality in cation exchange, sustained segmental dysfunction for some time after exercise could have equally accounted for such defects because impaired wall motion artifically decreases observed tracer tissue concentrations. Studies with FDG further indicate that after exercise-induced ischemia and even after segmental blood-flow defects have resolved, FDG uptake remained augmented. Camici et al ascribe this observation to replenishment of glycogen stores. Evidence coming from animal experiments was consistent with the clinical findings. Reperfusion after experimental coronary artery occlusions of 30–180 minutes duration resulted in markedly enhanced segmental FDG uptake. Different from the patient studies, however, was that FDG uptake remained depressed early after reperfusion but was markedly elevated at 24 hours of reperfusion. Differences in severity and duration of ischemia probably explain the temporal differences in segmental FDG uptake between animal and patient studies. Other studies demonstrate prolonged abnormalities of fatty acid metabolism in postischemic or stunned myocardium as demonstrated by segmentally abnormal clearance kinetics of 11C-labeled palmitate, which slowly returned to normal. However, even after only 15-minutes of coronary occlusion, 11C-labeled palmitate clearance remained abnormal for as long as 4–5 hours. The abnormal clearance kinetics of 11C palmitate indicated impaired fatty acid oxidation. It is uncertain whether the impairment is at the level of transfer of acyl-
coenzyme A units from cytosol into mitochondria or is caused by an injury to mitochondria. Although more recent studies with $^{13}$C-labeled glucose and $^{13}$C-labeled lactate indicate that anaerobic glycolysis remained elevated even at 24 hours of reperfusion, which suggests mitochondrial injury, a large fraction of glucose was also oxidized, which indicates that mitochondrial function is maintained to some extent. More recent studies with $^{13}$C-labeled acetate examined tricarboxylic acid cycle flux directly. These studies observed an initial, though only mild (30%), impairment of tricarboxylic acid cycle flux after a short coronary occlusion of 20 minutes, which, however, had largely resolved at 24 hours.

The now well-established spatial and temporal heterogeneity of ischemic injury and its recovery from it complicates the interpretation of metabolic findings. Nevertheless, observations obtained by metabolic imaging indicate that a transient ischemic injury is followed by a prolonged disturbance of substrate metabolism. It includes increased glucose utilization and impaired fatty acid oxidation and oxidative metabolism. These metabolic abnormalities recover only slowly, and after an extensive ischemic insult, they may persist for as long as a week. Finally, these studies have also demonstrated that almost invariably recovery of metabolism, largely reflected by a surge in glycolytic flux, precedes recovery or restoration of contractile function.

**Acute Myocardial Infarction: Between Ischemia, Necrosis, and Stunning**

When examined within 3 days of onset of acute symptoms, metabolic imaging in patients with acute myocardial infarction revealed both blood flow--metabolism mismatches and matches. In 13 consecutive patients with anterior infarctions and 32 segments with decreased blood flow, 16 segments revealed increased and 16 segments revealed decreased FDG uptake. Thus, viability was maintained in half of the acutely infarcted segments. The subsequent functional outcome in these regions was of even greater interest. When reevaluated with two-dimensional echocardiography several weeks later, function was found to be unchanged or even had deteriorated further in all segments with a metabolic match during the early postinfarction period. By contrast, function had spontaneously improved in half of the segments with an early postinfarction mismatch. This suggested that a blood flow--metabolism match during the early postinfarction period indicates necrosis. Less certain is the significance of the blood flow--metabolism mismatch. Although blood flow was reduced equally in both types of segments, spontaneous reperfusion may have accounted for the subsequent improvement in contractile function. Consistent with such possibility are arteriographic findings at an average of 4.4 days after infarction.

Although not strictly comparable to the conditions at the time of the metabolic study, the arteriographic findings suggest a dependency of persistent metabolic activity on residual blood flow. Thus, some blood flow appears to be essential for surviving the initial ischemic episode, and the metabolic pattern may, therefore, have represented stunned myocardium. This would entail subsequent restoration of blood flow and metabolism. Marshall et al. presented preliminary evidence for such a possibility, which, however, awaits confirmation by more systematic studies. Progression of ischemia to necrosis and fibrosis may account for the lack of functional recovery. Preliminary evidence for such a possibility has been provided by Schwaiger et al. in a patient in whom repeat metabolic imaging revealed that the "mismatch" had converted to a "match." As a third possibility, residual metabolic activity and, thus, viability may be maintained for some time after an acute myocardial infarction. The prevalence of the mismatch pattern in patients several weeks after infarction as demonstrated by Marshall et al. is in support of this third possibility. In summary, blood flow--metabolism matches during the early postinfarction period appear to represent necrosis. Conversely, blood flow--metabolism mismatches appear to identify myocardium that is 1) stunned and in which contractile function subsequently improves spontaneously, 2) myocardium that has survived the initial ischemic insult but subsequently succumbs to necrosis and is replaced by scar tissue, and 3) myocardium that enters a state of hibernation.

**Insights of Clinical Relevance**

Among the many observations on metabolic imaging in coronary artery disease, the pattern of a blood flow--metabolism mismatch in patients with stable coronary artery disease appears to be of greatest clinical significance. It signifies the presence of myocardium that is hibernating but is likely to resume contractile function if blood flow is restored. Several clinical investigations indicate its prevalence in patients with chronic coronary artery disease with or without antecedent myocardial infarction. For example, in three subsequent clinical studies that included a total of 50 patients, examination by PET revealed 199 myocardial regions with decreased blood flow (flow was examined in seven regions in each patient). Loss of contractile function was attributed to hibernation in 42% of segments as evidenced by a blood flow--metabolism mismatch. Injury in the remaining 58% of segments was irreversible as demonstrated by a match between blood flow and metabolism.

Because impairment of contractile function and reduced blood flow are clinical presentations common to both types of tissue injury, the task is then to distinguish between these two presentations. Neither the degree of wall motion impairment, abnormalities on electrocardiography, nor reductions in resting blood flow adequately differentiate between necrosis or scar formation and hibernating myocardium. $^{201}$TI redistribution scintigraphy has been advocated as the most
accurate means. Although complete and partial resolu-
tion of immediate poststress or postinjection defects
are reasonably accurate indicators of viable myocar-
dium, persistent 201Tl defects overestimate the inci-
dence of scar tissue. Judging from postinterventional
201Tl studies, viable and recoverable myocardium still
exist in 50–75% of fixed defects. A similar incidence of
viable myocardium in fixed defects on planar or
single-photon emission computed tomography 201Tl
scintigraphy has been demonstrated by metabolic
imaging with FDG and blood flow and PET.14,41 Thus,
residual metabolic activity as the hallmark of viability
may best identify hibernating myocardium. Because
increased uptake as the marker of tissue viability
yields a positive signal, it is more easily detected by
imaging than by “negative” signal or a defect. It
should be emphasized that the prevalence of the
mismatch pattern in our studies may have been related
to patient selection. Although these patients were
consecutive, they were selected for presence of seg-
mental wall motion abnormalities. This may also
account for the low left ventricular ejection fractions
in our patients, which averaged 31%.14,41

From these findings, several clinical conditions
emerge that may significantly benefit from metabolic
imaging. These include 1) severe left ventricular
dysfunction in coronary artery disease, 2) differenti-
ation between idiopathic and ischemic dilated cardio-
myopathy, 3) viability after acute myocardial infar-
cation, and 4) early assessment of responses to therapy.

Severe Left Ventricular Dysfunction

Patients with severe left ventricular dysfunction
represent a group in whom surgical revascularization
could especially improve left ventricular ejection
fraction, functional state, and long-term survival but
who face a higher surgical risk. Long-term survival
on medical therapy is relatively poor. Data from the
Coronary Artery Surgery Study (CASS) indicate a
7-year survival rate of only 34% in patients with a left
ventricular ejection fraction of less than 35%.42 The
same study suggests an improvement of the 7-year
survival rate to 63% after surgical revascularization.

Long-term survival is especially low for patients with
a left ventricular ejection fraction of less than 25%
and extensive wall motion abnormalities. Seven-year
survival rates in these patients were only 15% on
medical therapy but significantly higher after surgical
revascularization (68%, p<0.002). Surgical revascu-
larization may also improve left ventricular function.

For example, Rankin et al43 reported an improve-
ment of segmental wall motion associated with
improved left ventricular ejection fraction in 37% of
patients. On the other hand, Alderman et al44 have
reported no such significant improvement in left
ventricular function in patients with ejection frac-
tions of less than 34%. These authors suggested
further that the surgical benefits were most apparent
in patients with ejection fractions of less than 26%.
Such benefits may initially be offset by a relatively
high operative and perioperative mortality.45 This
may be as high as 7% and thus 3–4 times greater than
in patients with normal left ventricular function.

The task, therefore, is to identify those patients
who are most likely to benefit from bypass graft
surgery as compared with those who would not.
This entails identification of viability in segments
with impaired contractile function as well as the
extent of viable myocardium because the latter may
determine the magnitude of postsurgical improve-
ment of left ventricular function.14 Metabolic imag-
ing appears superior to most other diagnostic tools
for identification of viable myocardium. It also
provides estimates of the extent of viable myocardium
in relation to the extent of scar tissue and of
normal myocardium and thus may prove useful in
predicting the degree of postsurgical improvement
in left ventricular function.

Dilated Cardiomyopathy

The pathogenesis of dilated cardiomyopathies
often remains unknown, yet its determination may
have therapeutic consequences. If it results, for
example, from extensive coronary artery disease
and if large segments of viable myocardium are
present, surgical intervention may be warranted.
Comparing patients with idiopathic cardiomyopa-
thy to patients with ischemic dilated cardiomy-
opathy, Mody and colleagues46 have demonstrated
relatively homogeneous blood flow and glucose
utilization in idiopathic cardiomyopathy. In con-
trast, ischemic cardiomyopathy revealed large dis-
crete regions of reduced blood flow corresponding
to vascular territories. About 50% of such regions
were fibrotic by metabolic criteria, whereas glucose
metabolism was preserved in the remaining 50%.

Metabolic imaging therefore distinguished better
between idiopathic and ischemic cardiomyopathy
than did electrocardiogram and functional criteria.

PET, therefore, aids in elucidating the patho-
genesis of dilated cardiomyopathy and may prove
useful when it cannot be adequately defined by history
and electrocardiographic or functional criteria.

Acute Myocardial Infarction

Metabolic imaging at 24–72 hours after onset of
acute symptoms identifies necrosis or fibrosis, as
well as viability, in regions with impaired contrac-
tile function and decreased blood flow. In addition
to being more suitable for determining the size of an
infarct, PET also provides estimates of the extent of
functionally impaired but viable, irreversibly injured,
and normal myocardium and their fractional distri-
bution in a given left ventricle. Interrogation of left
ventricular myocardium along these lines may ulti-
ately prove useful for guiding therapy in patients
early after an acute myocardial infarction. In view
of the previously noted differences in functional
outcome that range from spontaneous recovery of
contractile function to hibernation to progression of
ischemia to necrosis and fibrosis, the task will be to
establish criteria that differentiate between these
states and to predict more precisely specific functional outcomes.

On the other hand, one can readily envision several useful applications for metabolic imaging, especially in instances of thrombolysis where absence or presence of metabolic activity will identify viable myocardium and where, based on arteriographic criteria, the need for further restoration of blood flow by angioplasty or bypass graft surgery could be established. Of course, further investigations are needed to more clearly define and document this specific clinical application.

Future Development and Possibilities

True volume images are now becoming possible with newer, state-of-the-art PET scanners. This is likely to result in more accurate estimates of the extent of normal, reversible, and irreversibly injured myocardium and, therefore, in better characterization of extent and consequences of coronary artery disease. Techniques for noninvasive quantification of blood flow and glucose utilization, only recently developed and validated, should further contribute to better characterization of the severity of an ischemic insult in a given myocardial segment and for stratification of patients for medical and interventional treatment. Finally, the emergence of new tracer approaches, as for example radiolabeled monoclonal antibodies to myosin, and 11C-labeled acetate, are likely to provide new insights into the dynamic nature and temporal and spatial heterogeneity of the functional and metabolic consequences of coronary artery disease.

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