EDITORIAL

Euglycemic Hyperinsulinemic Clamp and Oral Glucose Load in Stimulating Myocardial Glucose Utilization During Positron Emission Tomography

The editors of the *Journal* invited an "opposing view." Implicit in the invitation is the bias to present reasons as to why the assessment of myocardial viability should be better or more accurate under conditions of preferred or augmented glucose rather than of free-fatty acid utilization by normal myocardium. The invitation entails a second issue, an examination of the merits of the hyperinsulinemic euglycemic clamp vis-a-vis the more traditional oral glucose loading for shifting the myocardium's substrate selection to glucose. Central to both issues is the noninvasive identification of viable myocardium or, more correctly, of myocardium with an impairment of contractile function which improves or recovers if blood flow is restored. Such reversible impairment of contractile function has been ascribed to pathophysiologic conditions ranging from acute ischemia to stunning and hibernation (*1,2*). The mechanisms mediating such reversible impairment of contractile function remain understood poorly. Yet, animal experimental and clinical investigations have pointed out the association of such reversibility with a segmental augmentation of exogenous glucose utilization as demonstrated on positron emission tomography (PET) with ^{18}F-deoxyglucose (*3–9*).

The reasons for the selective increase in exogenous glucose utilization await clarification. Alterations in the regulatory mechanisms that govern substrate selection and account for the selectively enhanced glucose utilization may reside at the cell membrane or at the transmembranous substrate transport systems, at the level of transport of acyl-CoA units to the inner mitochondrial membrane or beta-oxidation. More generally, there may be an impairment in overall mitochondrial function. Observations of enhanced anaerobic glycolysis in postischemic myocardium may support the latter possibility (*10*). Replenish-

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EDITORIAL

Myocardial FDG PET Studies with the Fasting, Oral Glucose-Loading or Insulin Clamp Methods

Metabolic characterization of various cardiac disorders should be important in the study of the myocardium. In addition to the regional assessment of perfusion by SPECT and PET, assessment of cardiac energy metabolism by PET permits characterization of the metabolic consequence of cardiac disorders. The major energy production in the myocardium is oxidative phosphorylation and synthesis of high-energy phosphates. In contrast to brain, the heart uses multiple energy substrates for its energy metabolism, such as free-fatty acids, glucose, lactate, pyruvate, ketone bodies and amino acids (*1,2*). In the normal well-oxygenated heart under fasting condition, free-fatty acid is the predominant source of energy production. After a carbohydrate meal, on the other hand, plasma-glucose and insulin levels increase, plasma fatty acid levels decrease, and consequently, the heart primarily uses glucose as an energy source. In the ischemic myocardium, oxidative fatty acid metabolism is decreased as a result of the decrease in oxygen delivery, and exogenous glucose uptake and glycolytic flux are increased. In the nonreversible, infarcted myocardium, energy metabolism no longer persists. Based on these experimental data, maintained FDG uptake in a segment with hypoperfusion has been proposed as a marker of ischemic but compromised myocardium, while a concordant decrease of perfusion and FDG uptake has been considered a marker of irreversible myocardium. Thus, PET with ^{13}N-ammonia and FDG as tracers for myocardial perfusion and exogenous glucose utilization has been used to assess tissue viability (*3,4*). Clinical studies showed that hypoperfused areas with impaired function but maintained FDG uptake exhibiting a mismatch of perfusion and metabolism are likely to improve regional function after restoration of blood flow (*5,6*).

Because the myocardial uptake of

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ment of regionally depleted glycogen stores is another possibility (*7,10*).

Regardless of the underlying mechanism and its location within the biochemical machinery, these alterations prevent reversibly dysfunctional myocardium from fully participating in changes in myocardial substrate selection in response to changes in circulating plasma substrate and hormone levels. For example, in instances of adequate glucose and high insulin concentrations in plasma, normal myocardium utilizes more glucose and thus accumulates ^{18}F-deoxyglucose. The corresponding pattern of the blood flow metabolism mismatch entails a segmental reduction in blood flow, while ^{18}F-deoxyglucose uptake is normal or may be decreased but is less than blood flow. Conversely, when plasma free-fatty acid levels are high and glucose and insulin concentrations are low, as for example under conditions of fasting, myocardium preferentially utilizes free-fatty acid and thus retains little if any ^{18}F-deoxyglucose. Tracer uptake is then selectively increased in reversibly dysfunctional myocardium, resulting in a blood flow metabolism mismatch pattern in which myocardial ^{18}F-deoxyglucose uptake is confined to regions with reduced myocardial blood flow. The strikingly different presentations of the blood flow metabolism mismatch patterns in studies performed after glucose administration, as compared to studies performed under fasting conditions, suggest that glucose utilization in "viable myocardium" cannot be suppressed to the same extent as in normal myocardium (*4,6, 11*). Studies in the same patients under both conditions lend direct support to this notion. A preliminary report in ten patients with prior myocardial infarction (*12*) describes an 83% decline in glucose utilization rates in normal myocardium from the glucose-loaded to the fasted state (0.59 ± 0.12 to 0.10 ± 0.07 μmol/min/g). While glucose utilization rates also decreased in the mismatched peri-infarction zone, the decline averaged only 69%. Moreover, while glucose utilization rates in viable myocardium were similar to those in normal myocardium in the glucose-loaded state, they were nearly two times higher relative to normal myocardium in the fasted state (0.18 ± 0.06 versus 0.10 ± 0.7 μmol/min/g). The fact that glucose utilization declined in "viable myocardium" may be attributable to some albeit limited participation of ischemically injured myocardium or to an admixture of normal myocytes. Similar observations were noted in an animal model of myocardial stunning with attenuated changes in glucose utilization rates in postischemic myocardium in response to marked changes in plasma-substrate and insulin levels (*13*).

The observations suggest that if study conditions could be developed that consistently and reproducibly suppress ^{18}F-deoxyglucose uptake in normal myocardium, then any regionally enhanced (or nonsuppressible) tracer uptake represents "viable" myocardium. In fact, early studies in our laboratory employed an overnight fast but several limitations soon became apparent. First, fasting either overnight or for only 5 or 6 hr resulted in metabolic images of poor diagnostic quality for the majority of patients. Myocardium was either not visualized at all, or possible regional increases in ^{18}F-deoxyglucose uptake could not be separated with certainty from image artifacts, or intense blood-pool activity obscured myocardial activity. Other laboratories experienced similar problems. Berry et al. (*14*), for example, noted that only 56% of studies in patients and 41% of studies in normal volunteers had clinically interpretable images. More recent studies at our laboratory revealed a similar trend. In a series of 18 normal volunteers studied under fasting conditions, the ^{18}F-deoxyglucose images were of sub-optimal or nondiagnostic quality in 7 (39%) (*15*). More importantly, fasting did not consistently suppress glucose utilization in normal myocardium. Glucose utilization rates as determined by PATLAK graphical analysis ranged from 0.02 to 0.60 μmol/min/g (*15*).

Even if diagnostically adequate images could be obtained, limitations would remain. Because the abnormal increase in ^{18}F-deoxyglucose uptake cannot be compared to that in normal myocardium, the true magnitude of preserved metabolic activity as an index of reversible dysfunction remains uncertain. For example, even a highly intense ^{18}F-deoxyglucose signal relative to low or absent uptake in normal myocardium may reflect only a small amount of viable myocardium of little, if any, consequence for an improvement in segmental function. This might explain, at least in part, the generally lower predictive accuracies for the postrevascularization outcome in segmental contractile function in the study by Tamaki et al. (*16*) as compared to that by Tillisch et al. (*5*) with the glucose-load approach. A possible solution might be the quantification of regional rates of glucose utilization in such dysfunctional segments. Such measurements would be predicated on the assumption that the magnitude of metabolic rates does in fact correlate with the amount of viable myocardium and, in turn, the degree of an improvement in contractile function that can be achieved after conventional revascularization. The validity of this assumption however, awaits verification.

The apparent limitations of the fasting approach prompted the development of a study protocol that employs oral glucose loading (*4*). The approach offers several advantages:

1. It yields diagnostically adequate images in the majority of patients.
2. It minimizes the apparent heterogeneity in myocardial ^{18}F-deoxyglucose uptake as recently described (*17*) and thus alleviates related interpretative difficulties. For example, the posterolateral wall may exhibit markedly increased tracer up-

take in normal subjects when evaluated under fasting conditions which becomes less apparent after glucose loading.

3. Lastly, it permits the use of circumferential activity profile techniques to both the blood flow and the ^{18}F-deoxyglucose images (*4,5*).

This approach therefore attempts to relate qualitative values of regional glucose utilization rates in viable myocardium to those in normal myocardium and to obtain semiquantitative estimates of the disparity between glucose utilization and blood flow in dysfunctional regions. Although this approach is likely to miss small regions or islands of viable myocardium and thus may be less sensitive, it appears to be more specific in identifying regions of myocardial viability that are sufficiently large to cause an improvement in segmental function if revascularized adequately. Overall, this approach has proved to be rather satisfactory, especially in the assessment of myocardial viability in the clinical setting. As pointed out by Berry and co-workers (*14*), oral glucose loading produced ^{18}F-deoxyglucose uptake images of adequate or even excellent diagnostic quality in more than 85% of all patients and normal subjects. Other investigators reported optimal image quality in more than 90% of nondiabetic patients with glucose loading (*18*).

In spite of this success, the oral glucose loading approach is not without limitations. First, if oral administration of 50 or 100 g of dextrose were to produce inconsistent or variable rates of glucose utilization in normal myocardium, it then could limit the value of ^{18}F-deoxyglucose uptake in normal myocardium as a reference for tracer uptake in viable myocardium. Second, quantification of regional glucose utilization rates through tracer kinetic models requires steady-state conditions that may not be present after oral glucose loading. In order to minimize the latter limitations, the intravenous administration of ^{18}F-deoxyglucose is delayed for 60 min after oral glucose loading when glucose and insulin have reached relatively stable concentrations in plasma. Third, the question of how to best identify myocardial viability in patients with diabetes mellitus remains unresolved. Given their high prevalence of coronary artery disease, these patients represent a substantial fraction of all patients in whom the identification of viable myocardium is clinically important. Although segmental increases in ^{18}F-deoxyglucose uptake can frequently be identified in dysfunctional myocardium, adequate interpretation of such images is frequently hampered by the high blood-pool activity.

Various standardization schemes have been devised for these patients. Obviously, the normal diabetic regimen should be maintained and glucose should not be administered. Despite this, a recent survey of 48 diabetic patients indicated a complete failure rate of 10% for ^{18}F-deoxyglucose imaging (*18*). Another study reported a 28% incidence of uninterpretable ^{18}F-deoxyglucose studies in 36 diabetic patients (19). Intravenous administration of supplemental regular insulin doses raised the success rate to 88% (as compared to only 58% without insulin), which approached that reported for nondiabetic patients (*19*). Administration of adequate amounts of insulin appeared to be critical.

The potential shortcomings of the oral glucose-load approach together with the limitations in diabetic patients prompted the introduction of the hyperinsulinemic euglycemic technique (*20*). In a study of nine normal subjects, the hyperinsulinemic-euglycemic clamp resulted in an average myocardial glucose utilization rate of 0.35 μmol/min/g. The reported standard deviation of 0.12 μmol/min/g implied a relatively low intersubject variability and thus the achievement of comparable levels of glucose utilization rates. Preliminary studies supported the utility of this approach in patients with diabetes mellitus. Plasma-glucose levels, glucose utilization rates and myocardium-to-blood-pool ^{18}F activity ratios with this new method were similar in normal subjects and in insulin-dependent diabetic patients (*21*).

Despite these apparent advantages, the hyperinsulinemic-euglycemic approach prompted new questions. For example, did it selectively affect the magnitude of blood flow metabolism mismatches or, more specifically, rates of glucose utilization in reversibly dysfunctional myocardium? Did the improvement in image quality justify the use of the labor-intensive clamp approach with repeated monitoring of plasma-glucose levels in the clinical setting, as compared to the more simple oral glucose loading? To what extent did the clamp approach result in more consistent rates of glucose utilization in normal myocardium, and did it, in fact, render the logistically easier oral glucose administration obsolete?

The study by Knuuti et al. (*22*) in this issue of the *Journal* provides answers to several of these clinically and investigationally relevant questions. Both approaches, the technically demanding hyperinsulinemic-euglycemic clamp and the easy glucose-loading, produce comparable levels of glucose utilization in normal myocardium. Both result in similar interindividual variations in glucose utilization rates. They average 26.3% after glucose loading and 22.5% with the clamp and are thus relatively small. Accordingly, both methods achieve comparable and reproducible levels of glucose utilization rates. Remarkably, the enhanced tracer clearance from blood, for example, as indicated by the higher fractional phosphorylation rates or by K for ^{18}F-deoxyglucose in myocardium during the hyperinsulinemic-euglycemic clamp, improves the myocardium-to-blood-pool activity ratio by a factor of three and results in images of high diagnostic quality. As the study demonstrates further, the relative distribution of tracer uptake and of glucose utilization rates between normal and ischemically compromised myocar-

dium is virtually identical for both approaches. This observation argues against a selective or differential effect of the clamp approach on reversibly dysfunctional myocardium. Lastly, the study convincingly demonstrates that the clamp produces stable insulin and glucose concentrations in plasma as a prerequisite for quantifying rates of glucose utilization with the ^{18}F-deoxyglucose tracer kinetic model.

The authors correctly conclude that the clamp approach will be especially useful if rates of regional glucose utilization are to be quantified. Furthermore, given the complexities of the euglycemic-hyperinsulinemic approach, the authors' contention of the adequacy of the glucose-loading approach for more qualitative studies in the clinical setting appears to be reasonable and justified. While the observations further support the utility of the clamp approach in diabetic patients, the need for it in the clinical setting is not necessarily compelling. While neither negating the importance nor the appropriateness of the authors' recommendations, experience in our laboratory has demonstrated that diagnostically adequate images can in fact be obtained in diabetic patients without the clamp approach. What is critical in these patients is the maintenance of the regular diabetic regimen, the careful pretest screening of plasma-glucose levels, and, if necessary, administration of supplemental doses of regular insulin. As several studies report, the image quality appears to be inversely related to plasma-glucose concentrations (*18,19*). Thus, insulin doses need to be adequate to suppress plasma-glucose levels. If performed appropriately, the approach has, in our experience, rendered similarly clinically useful and interpretable studies of myocardial viability in diabetic patients.

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FDG depends on plasma substrate levels, careful attention should be paid to the nutritional status of the patient when interpreting FDG images. In the fasting condition, only ischemic myocardium shows an increase in glucose utilization, whereas its utilization may be suppressed both in the normal and infarcted myocardium. Thus, fasting patients prior to an FDG scan should make this technique quite sensitive for identifying the ischemic myocardium