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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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

by accentuating the differences between ischemic tissue with increased uptake of FDG and normal tissue with less uptake (*7–9*). Conversely, in the glucose-loaded study, both normal and ischemic myocardium may show an increase in glucose utilization, while the infarcted myocardium may be shown as an area of decreased glucose utilization. Thus, the glucose-loaded study would seem preferable for identifying viable myocardium (*3–5,10*). Investigators have attempted to standardize the metabolic environment by performing PET studies either in the fasting state or following glucose loading, depending on the metabolic questions being addressed.

Unfortunately the quality of myocardial FDG images may be poor in the fasting condition, due to reduced myocardial FDG uptake and slower clearance of FDG from the blood, as compared to the glucose-loaded condition (*10*). In addition, a recent report suggested heterogeneity of FDG uptake in normal myocardium, particularly in the fasting condition, reducing the specificity of the procedure (*11*). This heterogeneity is reduced, but it does exist in the glucose-loaded condition as well (*12*). Based on these results, one should interpret FDG images in a quantitative manner by comparing the patient's FDG distribution with that of the normal values, rather than by looking at the relative distribution of FDG and perfusion in the myocardium (*13*).

In a glucose-loaded FDG study, on the other hand, FDG distribution in the myocardium is usually similar to myocardial perfusion due to an increase in FDG uptake in normal myocardium. In the fed state, a subtle difference between FDG distribution and perfusion in ischemic myocardium may not be recognized. FDG distribution in the fasting state, on the other hand, provides independent metabolic information that is strikingly different from myocardial perfusion. In a recent study of children with Kawasaki disease, wall motion abnormality was often observed in the segments showing normal perfusion with an increase in FDG uptake in the fasting state (*9*). Similar findings were also observed in the revascularized myocardium (*6,14*). Such metabolic abnormalities may be seen only in the fasting state, but not in glucose-loaded state. In this respect, the FDG study under fasting seems to be sensitive for detecting metabolically abnormal segments, independent from myocardial perfusion. To enhance the specificity of the findings, FDG distribution should be displayed in a certain quantitative manner rather than as relative FDG uptake within the left ventricular myocardium (*13*).

In patients with diabetes mellitus, who have a high prevalence of coronary artery disease, a FDG PET study may have limited value because of relatively poor image quality due to decreased uptake of FDG in the myocardium. In these patients, myocardial FDG uptake can be normalized by pretreatment with intravenous insulin (*15*). Administration of insulin to these patients may enhance image quality through direct augmentation of glucose metabolism by decreasing free-fatty acid and glucose levels and by enhancing FDG clearance activity from the blood (*15*). The euglycemic hyperinsulinemic clamp technique has been used for obtaining postabsorptive steady-state (*16*), which seems to be valuable for quantitative measurement of regional glucose utilization on PET study.

The article by Knuuti et al. (*17*) in this issue of the *Journal* nicely demonstrated the superior quality of FDG images with both higher myocardial uptake and lower plasma activity with the insulin clamp technique. A higher mean fractional utilization (K_i) of FDG was also observed on Patlak graphic analysis with this method than the routinely used oral glucose-loaded technique. More importantly, the Patlak approach requires a steady-state condition for quantitative analysis of regional metabolic rate of glucose (*18*). In this respect, either the euglycemic hyperinsulinemic clamp or fasting technique seems to be suitable for maintaining a metabolic steady-state during the PET study (*13*), and thus a quantitative measurement of regional glucose utilization may be more accurately performed. Conversely, the oral glucose-loaded state showed a gradual change in plasma-glucose and insulin levels, which should alter the metabolic rate of glucose in the myocardium during PET acquisition. In addition, plasma-glucose and insulin levels may be different among subjects studied when FDG was administered 60 min after oral glucose loading.

However, the euglycemic hyperinsulinemic clamp technique is a rather cumbersome procedure, requiring frequent measurement of plasma-glucose and insulin levels to maintain steady-state, as compared to the simple oral glucose or fasting FDG studies. To keep glucose metabolism in a stable condition, the fasting state seems to be the most simple and reliable choice when plasma-glucose and insulin levels do not change during the study.

In patients with diabetes or those showing abnormal glucose tolerance, uninterpretable images may be observed with lower myocardial FDG uptake and higher plasma concentration in the glucose-loaded state (*12*). Therefore, the insulin clamp technique seems to be necessary for obtaining high quality FDG images with reliable measurements of regional glucose metabolic rate. On the other hand, in patients with normal glucose tolerance, both the insulin clamp and oral glucose-loading techniques may possibly show similar results. It would be interesting to know how often differences occur and how striking are these differences in FDG uptake between the two studies. Whether an FDG PET study should be performed with this rather cumbersome but elegant technique in all subjects or only in selected patients with abnormal glucose tolerance remains to be determined.

Since a variety of FDG PET studies have been introduced, a standardization of the FDG PET study is required. One should know the physio-

logic differences of glucose metabolism under fasting, oral glucose-loading and insulin clamp conditions. In this sense, plasma-glucose and glucose and insulin levels should be checked before FDG is administered to understand energy substrate conditions in each subject. Since abnormal glucose tolerance may often be seen in patients with coronary artery disease, the euglycemic hyperinsulinemic clamp technique reported by Knuuti et al. seems to be attractive and possibly more reliable. However, if FDG PET will play a major clinical role in assessing tissue viability and selecting patients for revascularization in the near future, a simple and reliable technique for performing the test should be designed.

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