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Nonuniformity in Myocardial Accumulation of Fluorine-18-Fluorodeoxyglucose in Normal Fasted Humans

TO THE EDITOR: A recent paper by Gropler et al. (*1*), reporting the heterogeneity of fluorodeoxyglucose (FDG) myocardial uptake in fasted humans, raises a number of issues concerning the physiologic pattern of regional glucose myocardial consumption and the methodology for evaluation of this variable by use of FDG and PET. The study of Dr. Gropler also prompted an editorial by Schwaiger and Hicks (*2*), who pointed out the need to perform FDG studies of myocardial metabolism under strictly defined and monitored conditions and suggested that more work is needed in this area before drawing conclusions.

We want to comment on the clinical implications of the heterogeneity of FDG uptake under "fasting" conditions and on Dr. Gropler's statement "It therefore appears essential to recognize that results of PET cardiac studies with FDG are likely to be definitive under those conditions in which the metabolic question of interest can be optimally answered with the patient studied in the postprandial state."

It seems to us that issues related to myocardial metabolism and their implications in the evaluation of this function with imaging techniques cannot be addressed unless the following requirements are met:

1. A definition of fasting or fed state based upon biochemical criteria (plasma concentration of glucose, free-fatty acid (FFA) and insulin) rather than on chronologic criteria (hours of fasting), unless chronologic criteria ensure that the subject is either in the fed state, i.e., following glucose load, or postabsorptive state, i.e., overnight fasting. Indeed the measurement of some plasma variables does not ensure that the tissue examined is in a steady-state. It has been shown that the relative proportion of oxygen uptake for carbohydrate oxydation versus FFA oxydation in the human heart decreases quite slowly from the postprandial to the fasting state, and that glucose oxidation in the heart is still high after fasting only few hours, i.e., an intermediate condition between the postprandial one and the overnight fasting (*3*). In addition, it has been shown that the insulin level appears to be a more important predictor of glucose metabolism than FFA in the glucose-loaded state (*4*) and that insulin action persists, beyond the disappearance of insulin from the plasma, in various organs (*5*) and in cultured cells (*6*), possibly due to intracellular multiphasic feed-back control mechanisms of enzymatic activities (*7*, *8*).
   In Dr. Gropler's study, all subjects were fasted for 5–8 hr only and insulin levels were not measured. Thus, the study was carried out under conditions that might not be representative of a fasting state, since the patient's status was not documented by biochemical records other than glucose and FFA-plasma concentrations. It seems unlikely that from these data conclusions can be drawn about the assessment of myocardial metabolism with FDG after overnight fasting.
   We have examined the uptake of FDG in four normal subjects twice within 24 hr, by administering FDG after 5 hr and after 16 hr of overnight fasting, respectively. Although no FDG uptake was observed after overnight fasting in any of the four subjects, a diffuse FDG uptake was observed in two subjects when the heart scan was performed 5 hr after the administration of FDG (unpublished data).
2. A complete cardiologic evaluation of the subject under examination, in order to rule out any possible heterogeneity in the FDG uptake due to previously undetected myocardial disease. It is known that in skeletal muscle oxygen consumption and heat production are directly related to the duration and degree of muscle tension (*9*); the free wall of the left ventricle has the greatest radius of curvature and, accordingly, the highest calculated wall tension. Any condition apt to cause an increase in the tension of the inferoposterior wall, such as mitral valve prolapse and intense physical training, could well determine the observed avidity of FDG after 5–8 hr fasting.
   In their paper, Gropler et al. do not state which procedure was followed to rule out the presence of myocardial diseases in his subjects, although he provides the clinical criteria on which the diagnosis of normality was based. Under these circumstances, the FDG uptake has been uniquely considered as an indication of a physiologic heterogeneity in glucose metabolic rate. Although this explanation is certainly plausible, other causes such as the presence of minimal myocardial pathology cannot be excluded.
   We have used PET and FDG to study 11 subjects without record of cardiovascular disease after overnight fasting for at least 16 hr before FDG administration, and found FDG uptake localized to the free wall in three subjects (unpublished data). A complete Doppler-echocardiographic study was performed and a mild mitral regurgitation with slight prolapse of the posterior leaflet was observed in the subjects with FDG uptake in the free wall.
3. Maintainance of rest conditions during the study in order to avoid artifacts due to changes in the workload. Dr. Gropler states that four of the subjects examined were removed from the scanner after the injection of the tracer. Since the heart responds quickly to a higher workload by incrementing glucose use, there is the possibility that, at least in these four subjects, an increase in cardiac work induced by physical activity during the 30 min off the tomograph induced some myocardial uptake of FDG. It appears from Table 3 of Dr. Gropler's paper that the rate pressure product was consistently higher following the glucose load study; however, Table 2 shows an important reduction in the measured myocardial blood flow following glucose loading, without concurrent changes in acetate kinetics. Could this be due to a lack of a steady-state during the studies?

Our results, obtained after 5 hr of fasting, are in keeping with the findings of inconsistent myocardial FDG uptake after 5–8 hr

of fasting reported by Dr. Gropler. However, evidence of heterogeneity in normal subjects following longer, yet still physiologic, fasting periods is still lacking. Thus, at the present time there is no evidence for rejecting the use of protocols based upon overnight fasting when metabolic conditions appear to be more stable.

Finally, based upon the above considerations and the results of Dr. Gropler's studies, it is evident that at the present status of knowledge the FDG method can be properly used only in subjects with normal carbohydrate metabolism.

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REPLY: We appreciate the thoughtful comments of Dr. Fragasso and his colleagues with regard to our study recently published in the *Journal* (*1*). We concur with many of the points made by the authors. However, certain comments are in order.

1. We agree that various levels of fasting (with subsequent changes in the pattern of myocardial substrate utilization) can occur and can influence the myocardial uptake of ^{18}F-fluorodeoxyglucose (FDG). The aim of our study was to demonstrate that regional myocardial FDG accumulation differed in the fasted and fed state, but we obviously could not study all possible levels of substrate availability. Our observations have recently been corroborated by others, where similar patterns of heterogenous myocardial accumulation of FDG were observed in normal humans subjected to a more prolonged fast (i.e., >12 hr) (*2*).
2. Occult myocardial disease or regional differences in myocardial contractility certainly would be potentially confounding variables. However, as outlined in our paper, we felt these were unlikely explanations for the differences we observed in regional FDG accumulation. All the subjects studied were under 30 yr of age and healthy, and thus, had a very low likelihood of having occult myocardial disease. Because the regional differences in myocardial accumulation of FDG were sensitive to the pattern of substrates presented to the heart, it would have to be postulated that regional contractile performance is sensitive to levels of serum substrates as well. There is no evidence in the literature to support this hypothesis. Finally, our observations that myocardial oxidative metabolism (based on the measurement of ^{11}C-acetate tissue kinetics) was regionally homogeneous speak against the presence of regional differences in myocardial contractile performance. Although, Fragasso and colleague's observation of mild mitral regurgitation with slight prolapse of the posterior leaflet in three of their subjects demonstrating relatively increased myocardial uptake of FDG localized to the free wall is interesting, without the echocardiographic evaluation of all of their subjects (those with and without localized myocardial accumulation of FDG), the significance of these findings cannot be ascertained.

Finally, as our understanding of myocardial carbohydrate metabolism, under both normal and pathologic conditions, continues to evolve, so will our understanding of myocardial FDG kinetics. We share the concern expressed by Fragasso et al. regarding the accurate interpretation of patterns of myocardial accumulation of FDG in relation to cardiac pathophysiology. However, we believe unique insights into myocardial metabolism can be obtained with this tracer, provided that the relationship of myocardial uptake of FDG to substrate availability is appreciated and that such studies are performed under conditions where the substrate environment is controlled.

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ART: Ambiguous Radioimaging Terminology

TO THE EDITOR: I am awed by your vanity in proposing a new acronym for the already historic term PET, which was coined by a prominent PET pioneer many years ago. I also disagree that the term PET is any more misleading than the term you suggest—ART (*1*). It is true that positrons are not imaged during PET. However your substitution of annihilation radiation is ill conceived because of its ambiguity. You see there are many types of