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# LETTERS TO THE EDITOR

## F-18 Fluorodeoxyglucose and Cardiac Metabolism

The study of Hicks et al. (1) comparing regional myocardial fluorodeoxyglucose and C-11 acetate data in male volunteers who received hyperinsulinemic-euglycemic clamping with and without lipid emulsion infusion is elegant, well conceived and well executed; the results are presented in a straightforward manner. In this letter, I make some statements and also ask the authors to consider and discuss some hypotheses and facts in relation to cardiac studies with F-18 fluorodeoxyglucose and positron emission tomography.

They report "significant regional variation in glucose metabolism" and lower glucose utilization, particularly in the septum compared with other walls. This finding could not be related to myocardial oxidative metabolism as independently measured with C-11 acetate and was probably independent of regional perfusion. They state that F-18 fluorodeoxyglucose "may not perfectly trace glucose metabolism." *Comment:* The term "perfectly" appears ambiguous. In their study glucose metabolic rates were assessed with F-18 fluorodeoxyglucose and positron emission tomography and were expressed as μmol/g per min. Thus, the accuracy of such metabolic rates as related to oxidative metabolism remains indeterminate.

They further state that the absolute values of glucose utilization derived from Patlak analysis may not be identical with true exogenous glucose utilization. *Question:* How close are they?

They suggest that standardization of the metabolic conditions by the use of glucose and insulin infusion in individuals undergoing positron emission tomography studies with F-18 fluorodeoxyglucose will minimize regional inhomogeneity in F-18 fluorodeoxyglucose uptake. *Comment:* F-18 fluorodeoxyglucose and positron emission tomography have been recommended for clinical differentiation of myocardial viability from scarring on the basis of a study by Tillisch et al. (2). That research used a scanner with low spatial resolution and without the addition of the glucose-insulin infusion. In retrospect, what was the accuracy of that study for the claims reported?

The authors state: "Without direct estimation of glucose oxidation rates. . . ." *Comment:* The authors are correct in wondering about glucose oxidation rates. New users of positron emission tomography currently are told that they should give the patient glucola and assume that this induces the heart to consume glucose preferentially. However, Wisneski et al. (3) showed that despite a significant amount of exogenous glucose administered (with a concomitant insulin increase) glucose oxidation accounted for only 32% of total glucose extracted; >50% of the extracted glucose was probably initially synthesized as glycogen. These findings were recently confirmed and extended by Saddik and Lopaschuk (4). They showed that in rat hearts perfused with 11 m*M* (2-H-3/U-C-14) glucose and low fat perfusate, 14% of the extracted glucose is oxidized while 86% of extracted glucose undergoes glycolysis. Thus, it appears reasonable to conclude that >60% of myocardial oxidation under these conditions was derived from exogenous and endogenous palmitate metabolism. The authors also demonstrated that insulin did not modify exogenous fatty acid metabolism. Therefore, under most physiologic conditions except from increased work (Camici et al. [5]), glucose (in the presence or absence of insulin) is not the primary source for myocardial oxidative metabolism.

Even if F-18 fluorodeoxyglucose measured glucose oxidative metabolism, which it does not, substrate selection by the heart under almost all circumstances is from exogenous fatty acids and from endogenous triglycerides, as well as lactate. Positron emission tomography F-18 fluorodeoxyglucose measures only glucose uptake and it is inaccurate to use F-18 fluorodeoxyglucose to measure glucose metabolic rates (6).

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### References

1. Hicks RJ, Herman WH, Kalff V, et al. Quantitative evaluation of regional substrate metabolism in the human heart by positron emission tomography. J Am Coll Cardiol 1991;18:101–11.
2. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med 1986;314:884–8.
3. Wisneski JA, Stanley WC, Neese RA, Gertz EW. Effects of acute hyperglycemia on myocardial glycolytic activity in humans. J Clin Invest 1990;85:1648–56.
4. Saddik M, Lopaschuk GD. Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts. J Biol Chem 1991;266:8162–70.
5. Camici P, Marraccini P, Lorenzoni R, et al. Metabolic markers of stress-induced myocardial ischemia. Circulation 1991;83(suppl III):III-8–13.
6. Bianco JA, Wilson M. Should F-18 deoxyglucose scans be indicated for care of patients with coronary artery disease? Cardiology 1991;79:219–26.

### *Reply*

**F-18 fluorodeoxyglucose tissue retention and myocardial glucose utilization.** We recognize, and acknowledged in the Discussion section of our article, the assumptions and potential inaccuracies inherent in the use of the fluorine-18 (F-18) fluorodeoxyglucose tracer kinetic model for estimating myocardial glucose utilization. As Bianco correctly asserts, the retention of F-18 fluorodeoxyglucose within the heart reflects not only the oxidative metabolism of glucose but also its incorporation into glycogen and metabolism through anaerobic glycolysis. Increased F-18 fluorodeoxyglucose uptake by the heart may not necessarily correlate with increased or preferential oxidative metabolism of glucose. However, under steady state conditions, myocardial F-18 fluorodeoxyglucose retention is expected to reflect glycolytic flux, and several animal studies under such conditions have documented a close agreement of F-18 fluorodeoxyglucose-estimated and directly measured glucose utilization (1,2). We believe that the euglycemic-hyperinsulinemic clamping as used in our study produces a stable metabolic environment in which F-18 fluorodeoxyglucose tissue retention correlates with exogenous myocardial glucose utilization.

The importance of our findings, however, was not in the quantitative evaluation of myocardial glucose utilization as such, but in the confirmation of regional variations in F-18 fluorodeoxyglucose retention (which had previously been observed in qualitative semiquantitative studies (3–5) using quantitative methodology. A knowledge of this variation and that it can be minimized by strict metabolic control has significant implications for the use of F-18 fluorodeoxyglucose with positron emission tomography to assess cardiac disease, as outlined in the study.



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**F-18 fluorodeoxyglucose retention in the septum.** Bianco also addresses the relevance of our findings to the previous study by Tillisch et al. (his Ref 2). Specifically, he appears to be questioning the accuracy of the metabolic characterization of myocardial viability used in that study, which has subsequently served as a basis for supporting the use of positron emission tomography with F-18 fluorodeoxyglucose for the selection of patients who may benefit from revascularization. Our study clearly addresses a different issue and, thus, does not provide data validating F-18 fluorodeoxyglucose as marker for tissue viability. However, our findings do not lessen the importance of this previous investigation, especially given that other groups have also demonstrated the positive predictive value of qualitative positron emission tomographic criteria of viability for recovery after revascularization and, perhaps more important, the negative predictive power of the absence of such criteria for lack of recovery (6,7). However, Bianco's question is pertinent to the evaluation of viability in the interventricular septum. Because of the difficulties associated with assessing postoperative wall motion in the septum after coronary artery bypass surgery as a result of the frequent development of paradoxic septal motion, the septum was excluded from analysis in the study by Tillisch et al. Therefore, the potential problems associated with assessing the significance of altered F-18 fluorodeoxyglucose retention in this region may not have been recognized. We have discussed the problems with evaluation of F-18 fluorodeoxyglucose retention in the septum at greater length elsewhere (8).

**Use of oral glucose loading with positron emission tomography.** Finally, we agree that the use of oral glucose loading in patients undergoing positron emission tomography with F-18 fluorodeoxyglucose may not induce the heart to use glucose preferentially. The likely mechanism of enhanced F-18 fluorodeoxyglucose image quality after glucose administration is enhanced tissue uptake and blood clearance of glucose and F-18 fluorodeoxyglucose due to concomitant insulin response. Although insulin is not required for myocardial glucose uptake, its presence does stimulate glucose uptake, apparently by increasing transmembrane transport (9). Although the use of oral glucose loading to enhance F-18 fluorodeoxyglucose image quality is largely empiric, it provided the first and important recognition of the importance of metabolic milieu on F-18 fluorodeoxyglucose image quality and offers a reasonably powerful means of standardizing metabolic conditions in most patients. We have extended the approach to metabolic standardization with more sophisticated control of metabolic state in the experimental setting (8) and more recently in clinical studies (9) by use of glucose infusion (10,11) combined with insulin supplementation. This approach has allowed study of diabetic patients, who form an important group of patients with coronary artery disease and in whom positron emission tomography with F-18 fluorodeoxyglucose has either been precluded or is often of suboptimal quality.

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### References

1. Krivokapich J, Huang S-C, Phelps ME, et al. Estimation of rabbit myocardial metabolic rate for glucose using fluorodeoxyglucose. American Physiological Society 1982.
2. Ratib O, Phelps ME, Huang SC, Henze E, et al. Positron tomography with deoxyglucose for estimating local myocardial glucose metabolism. J Nucl Med 1982;23:577–86.
3. Camici P, Araujo L, Spinks T, Lammertsma AA, Jones T, Maseri A. Myocardial glucose utilization in ischaemic heart disease: preliminary results with F18-fluorodeoxyglucose and positron emission tomography. Eur Heart J 1986;7:19–23.
4. Marshall RC, Tillisch JH, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia in man with positron computed tomography, 18F-labeled fluorodeoxyglucose and N-13 ammonia. Circulation 1983;67:766–78.
5. Gropler RJ, Siegal BA, Lee KJ, et al. Nonuniformity in myocardial accumulation of F-18 fluorodeoxyglucose in normal fasted humans. J Nucl Med (in press).
6. Tamaki N, Yonekura Y, Yamashita K, et al. Positron emission tomography using fluorine-18 deoxyglucose in evaluation of coronary artery bypass grafting. Am J Cardiol 1989;64:860–5.
7. Al-Aouar ZR, Eitzman D, Hepner A, et al. PET assessment of myocardial tissue viability: University of Michigan experience (abstr). J Nucl Med 1990;31:801.
8. Schwaiger M, Hicks R. The clinical role of metabolic imaging of the heart by positron emission tomography. J Nucl Med 1991;32:565–78.
9. Young LH, Seres JA, Lasala JM. Insulin stimulates heart glucose uptake in vivo by increasing the sarcolemma glucose transport VMax (abstr). J Am Coll Cardiol 1991;17:369A.
10. Hicks RJ, vom Dahl J, Lee KS, Herman WH, Kalff V, Schwaiger M. Insulin-glucose clamp for standardization of metabolic conditions during F-18 fluoro-deoxyglucose PET imaging (abstr). J Am Coll Cardiol 1991;17:381A.
11. vom Dahl J, Hicks RJ, Lee KS, Eitzman D, Al-Aouar Z, Schwaiger M. Positron emission tomography myocardial viability studies in patients with diabetes mellitus (abstr). J Am Coll Cardiol 1991;17:121A.

## Ventricular Hypertrophy, Diuretic Drugs and Arrhythmias

In the study by Szlachcic et al. (1) on the role of ischemia and left ventricular hypertrophy in the genesis of ventricular arrhythmias, we are puzzled by the greater prevalence of ventricular arrhythmias in patients previously treated with diuretic drugs. We wonder whether the influence of diuretic drugs could be explained by a greater left ventricular mass. It is not clear from the Methods section whether adjustment was made for the degree of left ventricular hypertrophy quantitatively. We have previously shown (2) that there is a graded and continuous relation between the extent of left ventricular hypertrophy and the frequency and complexity of ventricular arrhythmias. Therefore, performing such an analysis may help to explain the apparent influence of diuretic drugs.

We note that the authors stated that no previous studies had systematically or prospectively attempted to exclude patients with underlying ischemic heart disease. In fact, in our study (2), patients with coronary artery disease as defined by the presence of ≥25% reduction in lumen diameter by coronary arteriogram were systematically and prospectively excluded.

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### References

1. Szlachcic J, Tubau JF, O'Kelly B, Ammon S, Daiss K, Massie BM. What is the role of silent coronary artery disease and left ventricular hypertrophy in the genesis of