Acute Myocardial Ischemia

Opie and Camici discuss the research of Kalff et al. (*6*), in which FDG uptake during acute myocardial ischemia without reperfusion was higher than myocardial blood flow until regional cardiac blood flows were less than 20% of normal. However, Opie and Camici say that Kalff et al. did not measure glycolytic flux or cell necrosis. Thus, the issue of myocardial cell protection cannot be proven.

In our studies (*7*) of myocardial ischemia with reperfusion using high-resolution cardiac autoradiography and quantitative histology (not referenced in the editorial), FDG uptake occurred in some areas that showed acute myocardial infarction. We have postulated that under these conditions, FDG uptake may be occurring in inflammatory cells such as macrophages (*8*). There are data that indicate that FDG and PET are less reliable as a metabolic descriptor in patients with recent myocardial infarction (*9,10*). According to Opie (*11*), PET imaging may not completely resolve cell admixture (viable versus nonviable cells during ischemia). After all, border zones in the ischemic myocardium are less than 1 mm in width. Thus the role of FDG in the evaluation of acute myocardial infarction is unclear.

Conclusion

FDG and PET may have major limitations in assessing the hypothesis that glucose metabolism and glycolysis may sustain myocardial viability in myocardial ischemia. Certainly, ^{11}C-glucose, ^{15}O-water, or ^{11}C-acetate or NMR spectroscopy (e.g., ^{13}C turnover studies of the Krebs cycle) may provide the means to test the hypothesis that glycolysis delays or prevents ischemic cell death.

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REPLY: Dr. Bianco refers to the question of myocardial ischemia followed by reperfusion, a subject we had not emphasized in our editorial (thus explaining why his recent article (*1*) had not been referenced). In his article, it is evident that the longer the duration of ischemia in his rabbit heart model, the less uptake of deoxyglucose administered during the reperfusion period. As stressed by Dr. Bianco in his letter, the measurement of the uptake of tissue deoxyglucose does not allow the computation of glucose oxidation nor of glycogen synthesis. However, the uptake of deoxyglucose reflects the utilization of exogenous glucose since both share the same transmembrane transporter, although with different affinities, and are good substrates for hexokinase. If the value of the lumped constant (a factor which corrects for the differences in affinity between glucose and deoxyglucose is known, then exogenous glucose utilization (μmol/min·g) can be computed with deoxyglucose. Certain suggestions can be made in relation to the data in the article by Sebre et al. (*1*), bearing in mind the above observations. The severity and consequences of acute myocardial ischemia are dictated by a number of factors, including the degree of coronary blood flow reduction and its duration, which in addition seems to be a species-specific phenomenon. However, it is reasonable to assume that ischemia times of up to 15–20 min should not induce significant tissue necrosis. Under these circumstances, myocardial glycogen breakdown is invariably activated while the uptake of exogenous glucose is dependent on residual flow. This explains why increased postischemic deoxyglucose uptake, which probably reflects tissue glycogen repletion, can be easily detected following an episode of transient ischemia. By contrast, deoxyglucose uptake during transient ischemic episodes may be variable (*2*). The shorter the duration of ischemia, the more likely the myocardium will be viable, which would explain the greater relative uptake of deoxyglucose after 15 min of ischemia compared with 30 min in the paper by Sebre (*1*). This is not given by the ^{201}Tl data in their Table 2.

In postischemic, but predominantly nonviable myocardium, there is a mixture of dead and viable cells, so that deoxyglucose data would reflect low overall rates of uptake although a high rate may be present in viable postischemic cells. This may explain the apparently poor performance of deoxyglucose as a marker of necrosis, as shown in Sebre et al.'s Fig. 1.

In clinical studies, however, the myocardial signal derived from deoxyglucose would be compared with that derived from $^{13}NH_3$ or another flow marker. The concept would be that a reduction of deoxyglucose uptake may occur both in viable and nonviable myocardium. Only in viable myocardium is the reduction of deoxyglucose less relative to that of the degree of reduction of flow in that segment. As far as we can see, this concept is not negated by the data of Sebre et al., in which coronary flow was apparently not measured. Our editorial did not touch on the subject of hibernation, however, this subject is covered in a recent review by one of us (Uren and Camici, *Cardiovasc Drugs and Therap*, 1992;6:273–279). That article emphasizes that the mismatch of blood flow to metabolism has a high predictive accuracy for the recovery of contractile function after revascularization.

We agree with Bianco that factors governing the uptake of deoxyglucose are complex and cannot be simplified. As we stated in our editorial: "crucial data must still be collected" to show a relationship between decreased glycolytic flux and cell necrosis. We agree that multiple approaches, experimental and

clinical, using a variety of tracers according to the exact scientific problem posed, are likely to be fruitful.

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Detection of Cardiovascular Infections with Radiolabeled Leukocytes

TO THE EDITOR: Dr. Cerqueira's editorial in the August 1992 issue of the *Journal* comments on the expanding role of nuclear imaging in the diagnosis of cardiovascular infection utilizing radiolabeled leukocytes. The editorial describes radiolabeled red blood cell (RBC) and platelet contamination of leukocyte preparations as a major complication in the identification of cardiovascular infections. The presence of radiolabeled contaminants is alleged to cause enhanced uptake in areas of hemorrhage and thrombosis, resulting in false-positive scan results.

Dr. Cerqueira discusses limitations of granulocyte isolation and purification techniques commonly utilized in leukocyte labeling procedures, which result in products with nonspecific cell isolation or involve time and equipment requirements which limit their use in most clinical settings. I would like to make Dr. Cerqueira and the editors aware of an improved sedimentation method (*1*), which significantly reduces RBC contamination of leukocyte preparations prior to radiolabeling. This process produces a final product with remarkable reduction in RBC contamination and maintains leukocyte viability with minimal cell manipulation (*2*).

The improved sedimentation method of labeled leukocyte preparation purification was introduced to nuclear pharmacists at the 1990 American Pharmaceutical Association National Meeting (*2*) and at the 1991 American Pharmaceutical Association, Nuclear Pharmacy Division Session entitled, "Novel Approaches to Infectious Disease Imaging" (*3*). Quantitative analysis of sedimentation method results were presented at the 1992 Society of Nuclear Medicine Meeting (*4*). The authors demonstrated improved WBC-to-RBC ratios and improved liver-to-spleen ratios with ^{111}In-labeled leukocyte preparations when the improved sedimentation method of cell separation was incorporated into the cell labeling procedure. These researchers confirmed previous findings (*2,3*), concluding that the improved sedimentation method produced a better pharmaceutical preparation with potentially better clinical images (*4*).

A complete discussion of RBC contamination removal should also include a review of cell lysis, a process of residual erythrocyte removal by exposure to hypotonic saline. The use of cell lysis in leukocyte preparations may be categorized among purification procedures having limited clinical utility. Granulocytes are known to tolerate a narrow range of osmolalities (*5*). It is also likely that granulocytes in WBC suspensions are especially sensitive to lysis (*6*). It should therefore be considered that cell lysis introduces risk to leukocyte viability, thus increasing the potential for producing variable results.

Radiolabeled leukocytes dispensed to clinicians in nuclear medicine departments should currently provide pharmaceutical preparations of viable radiolabeled leukocyte preparations, free from significant RBC contamination. Nuclear pharmacists continue to direct research in the area of enhanced labeling techniques, and in this manner, work toward the common goal of expanding diagnostic capabilities of radiolabeled leukocyte preparations.

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