

5. Since the improvement in viability occurred in 13 of the 73 segments (20%), is this significant from a decision-analysis standpoint?

Incidentally, in close to 20%–30% of fixed  $^{201}\text{Tl}$  defects, in the absence of Q-waves there is likely viable myocardium by  $^{201}\text{Tl}$  reinjection.

I am sure that Dr. Abraham will agree that methodologic limitations should be addressed and that new data are needed to confirm these preliminary PET data.

One of the most pressing problems with a PET study of the heart is that we do not know what the FDG molecule really traces in the heart (9). Thus, there is no certainty at all that the ATP-producing oxidative metabolism of glucose can be evaluated by FDG. A  $^{99\text{m}}\text{Tc}$ -glucose tracer would indeed be a better radionuclide for glucose metabolism.

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**REPLY:** We appreciate the thoughtful comments as well as the time and effort expended by Dr. Bianco in response to our CPC.

We would, however, take issue with the statement that “. . .no investigation has shown that an area of myocardium can be akinetic, hypoperfused, and metabolically active.” As noted, Tillisch et al. (1) compared regional PET perfusion and metabolism patterns (utilizing  $^{13}\text{N}$ -ammonia and  $^{18}\text{FDG}$ , re-

spectively) with preoperative wall motion (WM). They were able to predict the functional response of the myocardium to revascularization with a high degree of accuracy. Among the total of 73 myocardial segments analyzed was a subset (albeit small) of 14 segments noted to be akinetic preoperatively. Six of 14 (43%) of these were noted to improve at least one full grade following revascularization. Although neither the preoperative  $^{13}\text{N}$ -ammonia nor  $^{18}\text{FDG}$  uptake in these particular segments was described, it seems reasonable to assume that they were hypoperfused, yet metabolically active preoperatively by PET criteria, both intuitively, and on the basis of other data.

Several years ago, Brunken et al. (2) examined regional perfusion (with  $^{13}\text{N}$ -ammonia), glucose metabolism (with  $^{18}\text{FDG}$ ), and regional WM in patients with chronic Q-wave myocardial infarction by ECG. These investigators found that neither WM analysis (including akinetic segments) nor analysis of ST-segment and T-wave changes on resting ECG allowed differentiation between regions of ischemia and infarction as identified by PET criteria. A substantial proportion (54%) of Q-wave regions exhibited evidence of residual tissue metabolism as assessed by  $^{18}\text{FDG}$  uptake. Routinely used clinical tests did not reliably differentiate hypoperfused but viable regions from regions of completed transmural infarction. More recent work by Fudo et al. (3) has confirmed these findings. These investigators used PET to evaluate 22 patients who had sustained previous anterior wall myocardial infarction. Myocardial perfusion was assessed at rest and during exercise stress with  $^{13}\text{N}$ -ammonia, and this was compared to resting  $^{18}\text{FDG}$  uptake in the fasting state. A diffuse mismatch between perfusion and metabolism was found in 3/7 akinetic segments, and in 3/8 dyskinetic segments.

Finally, Brunken et al. (4) have demonstrated residual metabolic activity with  $^{18}\text{FDG}$  in 58% of fixed defects on thallium scintigraphy at 4 hr. However, this study did not include an analysis of regional wall motion. In a conceptually similar report, Tamaki et al. (5) performed PET imaging (with  $^{13}\text{N}$ -ammonia and  $^{18}\text{FDG}$ ) and SPECT-thallium perfusion studies in 28 patients with healed myocardial infarction. The scintigraphic data were correlated with regional wall motion. Among a total of 39 myocardial segments demonstrating fixed thallium defects at 3 hr, 15 (38%) showed an increase in  $^{18}\text{FDG}$  uptake. Of these 15 segments, 5 (33%) were either akinetic or dyskinetic. Additionally two of these five segments (40%) with fixed thallium defects and grossly abnormal wall motion, yet increased  $^{18}\text{FDG}$  uptake, had severely decreased perfusion to the same regions as measured by  $^{13}\text{N}$ -ammonia.

These data are consistent with studies demonstrating thallium uptake by reinjection (6) or 24-hr delayed thallium imaging (7) in 20%–30% of segments with defects thought to be fixed at 4 hr. Also, histologic studies have shown that about one-fifth of akinetic or dyskinetic anterior wall abnormalities, with Q-waves, will exhibit only mild or moderate fibrosis on endomyocardial biopsy. (8) In addition, Flameng et al. (9) have found that biopsies of akinetic anterior left ventricular walls revealed a high proportion of cells with histologic degeneration without frank necrosis. These changes consisted of myofibrillar lysis, clumping of cytoskeletal filaments and mitochondria, swelling of nuclei, and ultrastructural changes in mitochondria. Segments with this “cellular degeneration” on biopsy exhibited delayed functional improvement after revas-

cularization. This suggests that the degenerating cells were viable and capable of repair once perfusion was restored. Preoperative compromise of regional ventricular function was dependent upon both the extent of fibrosis and the number of "degenerating cells." However, the degree of post-revascularization functional improvement was limited only by the amount of (irreversible) fibrosis, and not the number of functionally impaired but viable cells.

In aggregate, these and other histologic, metabolic, and functional data, coupled with scintigraphic evaluation of perfusion, provide a sound theoretical construct for the clinically recognized phenomenon of myocardial hibernation. We do, however, agree with the assertions of Dr. Bianco, which were echoed in a recent editorial on this subject (10) that stated that our knowledge of the processes involved in myocardial hibernation is still in an embryonic stage.

We also concur with Dr. Bianco's assessment of the limitations of the Tilisch paper. Our discussion was meant to focus mainly on the detection of viable myocardium via techniques employing single-photon agents. The PET data were not presented to either imply methodologic infallibility of this particular study, or of positron emission tomography in general. We wished only to provide correlative information derived from a very different imaging modality. Also, this report is notable in that it represents one of only a paucity of studies investigating the actual mechanical response of the myocardium to revascularization, rather than merely demonstrating improved perfusion. We would, however, caution against equating lack of improvement in the septal region with lack of benefit from revascularization, since there is known to be a high incidence of septal motion abnormalities following cardiopulmonary bypass in patients with normal septal motion preoperatively (11-15). This finding has been ascribed to translational motion of the heart anteriorly in the thorax, due to sternal-cardiac adhesions (12) or pericardial disruption (13). Abnormal septal contractility has also been described (14,15) and is not felt to be ischemically mediated (15). Most, but not all of these abnormalities have been shown to decrease or resolve on late (12-16-mo) follow-up studies (12,14).

We share Dr. Bianco's reluctance to embrace PET assessment of  $^{18}\text{F}$ FDG uptake as the gold standard for determination of myocardial viability. Tamaki (16) has recently shown a sensitivity and specificity of 78% for the prediction of postrevascularization functional improvement, utilizing PET assessment of  $^{13}\text{N}$ -ammonia and  $^{18}\text{F}$ FDG following CABG, seemingly confirming Tilisch's earlier results (1). However, both studies examined relatively small numbers of patients. The Tilisch report included 17 patients (73 myocardial segments analyzed) and Tamaki reported on 22 patients (51 myocardial segments analyzed). Clearly, larger-scale, more definitive clinical trials are necessary.

Other positron-emitting tracers may also have utility for viability assessment. A recent study (17) compared prevascularization assessment of myocardial viability with  $^{18}\text{F}$ FDG and  $^{11}\text{C}$ -acetate. Initial oxidative metabolism ( $^{11}\text{C}$ -acetate clearance) was 28% greater in regions destined to improve following PTCA or CABG, compared to those without improvement ( $p > 0.05$ ). Relative FDG uptake tended to be greater in such regions as well ( $p = \text{NS}$ ), but did not correlate with  $^{11}\text{C}$ -acetate in all cases. Myocardial blood flow, assessed with  $^{15}\text{O}$ -water was not significantly different among patients

with and without postrevascularization improvement. Thus, persistence of oxidative metabolism may be required for functional improvement after revascularization, and its demonstration with  $^{11}\text{C}$ -acetate is another potential marker of viability.

Additional techniques using single-photon agents to detect viable myocardium are also being developed. These include  $^{123}\text{I}$ -labeled fatty acid uptake (18) and comparison of myocardial uptake of  $^{201}\text{Tl}$  and  $^{111}\text{In}$ -labeled antimyosin antibody (19).

The most accurate and practical single-photon technique to assess myocardial viability remains to be determined. Carefully designed comparison studies will be needed to assess the incremental value and cost-effectiveness of clinical cardiac PET in comparison to these and other competing modalities.

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