TABLE 1
Effect of Choice of Acid on Extraction of d,1- and meso-^{99m}Tc-HM-PAO into Aqueous Solutions

Aqueous phase	pH	% Extracted into aqueous solution*	
		d,1	meso
Water	6.4	14.0 ± 1.2	10.6 ± 0.8
HCl	3.0	37.0 ± 2.9	25.2 ± 1.2
Acetic acid	3.0	28.7 ± 3.0	20.1 ± 1.5

* Mean ± s.d. for 4 determinations.

did contribute to the effects observed, although this contribution is relatively small, as he demonstrated (*2*). However, in his experiments pH was adjusted with HCl and there may be an effect of chloride ion concentration as well as hydrogen ion concentration. The results in Table 1 show that when acetic acid rather than HCl was used to adjust the pH to 3, there was less transformation of either isomer of ^{99m}Tc-HM-PAO into hydrophilic species.

The observation that there was no interaction with GSH in neutral or mildly basic medium is puzzling. In attempting to reproduce these results, we found that interaction was slower, but not stopped. Furthermore, the experiments in which Neirinckx et al. determined interaction rates of d,1- and meso-^{99m}Tc-HM-PAO with GSH were carried out at pH 7.4 (*3*).

We, too, have noted that ^{99m}Tc-HM-PAO interacts with L-cysteine (Cys), and also with ascorbic acid, both of which we were evaluating as potential antioxidant stabilizers. The interaction with Cys should not be surprising, since Cys is a component of GSH (Glu-Cys-Gly). We have now repeated the concentration-effect and reaction-rate experiments reported previously (*1*) with Cys in place of GSH. The results can be summarized as follows:

1. The interaction of ^{99m}Tc-HM-PAO with Cys shows a sigmoidal relationship similar to that with GSH (see Fig. 1 in ref. *1*).
2. The disappearance rates for the isomers of ^{99m}Tc-HM-PAO in the presence of 0.05 mg/ml Cys HCl (approximately equimolar to 0.1 mg/ml GSH) were: d,1 0.052 min^{-1}; meso 0.017 min^{-1}. These values for interaction with Cys differ by a factor of 3 between the isomers, compared to 7-8 with GSH (*1*).

Thus, ^{99m}Tc-HM-PAO interacts with Cys but this interaction appears to be less stereoselective than that with GSH and may not be sufficient to explain the differential retention of the isomers in the brain. Furthermore, as discussed by Neirinckx et al. (*3*), GSH constitutes the bulk of all free thiols in mammalian tissue and is present in millimolar concentrations similar to those used in the in vitro experiments. We feel that the evidence still supports GSH as the main but not the only biologic target of ^{99m}Tc-HM-PAO.

REFERENCES

1. Ballinger JR, Reid RH, Gulenchyn KY. Technetium-99m HM-PAO stereoisomers: differences in interaction with glutathione. *J Nucl Med* 1988; 29:1998–2000.
2. Lang JJ. Interaction of ^{99m}Tc-HM-PAO with glutathione [Letter]. *J Nucl Med* 1990; 31:1115.
3. Neirinckx RD, Burke JF, Harrison RC, Forster AM, Andersen AR, Lassen NA. The retention mechanism of technetium-99m-HM-PAO: intracellular reaction with glutathione. *J Cereb Blood Flow Metab* 1988; 8:S4–S12.

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PET Cardiac Viability

TO THE EDITOR: The clinical pathologic conference (CPC) discussed by Abraham (*1*) is timely, important, and elegant. Owing to my own particular research with this subject (*2–4*), I have reviewed clinical PET data on cardiac viability.

In the established evolution of acute infarction, recently reviewed (*5*) acute infarction without reperfusion has no viability. Reperfused myocardium may evolve into subendocardial, midmyocardial, and transmural necrosis, or fractions thereof. Salvaged myocardium is viable.

Hibernation is an attractive clinical state without sound experimental proof. Specifically, a recent conference on viability so concluded (*6*), since no investigation has shown that an area of myocardium can be akinetic, hypoperfused, and metabolically active. The clinical measurement of regional blood flow has only been reported by one group (*7*) and the data is preliminary.

As the comment in the CPC states, a paper by Tillisch et al. (*8*) indicated that the detection of myocardial viability by PET would have predictive value before revascularization. I must say that I was less convinced by the data. Seventeen consecutive patients with coronary disease and resting wall motion (WM) abnormalities had: a PET study (nitrogen-13-ammonia and fluorodeoxyglucose (FDG), a WM study before surgery, and a WM study after surgery. Of the 17 patients, 15 had prior infraction and EKG Q-waves. Patients had two- or three-vessel disease and a preoperative ejection fraction of 32% ± 14%. Before operation, 73 segments had abnormal WM. Postoperatively, WM improved in 37 (51%) of the segments. Most of the septal (77%) abnormalities did not improve. The inferior wall of the heart could not have been assessed since only axial PET slices were obtained. Of 16 revascularized areas that had preoperative PET viability (higher FDG uptake than ^{13}N-ammonia hypoperfusion), 13 had improved WM after operation. There was no correlation between preoperative WM and degree of postoperative improvement of WM, or lack thereof.

The following questions need answering:

1. The PET device used had a resolution of 1.8 cm or greater. Was this a factor in results?
2. The evaluation of WM was nonquantitative. Did this bias the comparison?
3. The PET planes and the WM planes could not have been accurately matched. Was this important?
4. If the septal regions with abnormalities did not improve and since the inferior wall was not evaluated (there were no short-axis or long-axis images used), what exactly did the data reflect?

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}Tl defects, in the absence of Q-waves there is likely viable myocardium by ^{201}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 ^{99m}Tc-glucose tracer would indeed be a better radionuclide for glucose metabolism.

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REFERENCES

1. Abraham SA. Evaluation of residual myocardial viability in a patient with acute myocardial infarction. *J Nucl Med* 1990; 31:225–230.
2. Bianco JA, Bakanauskas J, Carlson M, et al. Augmented uptake of 2-C-14-D-deoxyglucose in reversibly-injured myocardium. *Eur J Nucl Med* 1988; 13:557–562.
3. Bianco JA, Subramanian R, Holden J, et al. C-14 deoxyglucose (C-14 DG) deposition in ischemia and reperfusion [Abstract] *J Nucl Med* 1989; 30:797.
4. Subramanian R, Sebree L, Holden J, et al. Tl-201 and C-14 deoxyglucose uptake in rabbit heart in acute ischemia and necrosis [Abstract]. *J Mol Cell Cardiol* 1989; 21(suppl II): S.6.
5. Reimer KA, Murry CE, Richard VJ. The role of neutrophils and free radicals in the ischemic-reperfused heart: why the confusion and controversy? *J Mol Cell Cardiol* 1989; 21:1225–1239.
6. Councils of Clinical Cardiology and Basic Science, American Heart Association. Scientific Conference on Myocardial cell viability. July 10–12, 1989, Santa Fe, New Mexico.
7. Walsh MN, Geltman EM, Steele RL. et al. Augmented myocardial perfusion reserve after coronary angioplasty quantified by positron emission tomography with O-15-water. *J Am Coll Cardiol* 1990; 15:119–127.
8. Tillisch J, Brunken R, Marshall RC, et al. Reversibility of cardiac wall motion abnormalities predicted by positron tomography. *N Engl J Med* 1986; 314:884–888.
9. Camici P, Ferrannini E, Opie LH. Myocardial metabolism in ischemic heart disease: basic principles and application to imaging by positron emission tomography. *Prog Cardiovasc Dis* 1989; 32:217–238.

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}N-ammonia and ^{18}FDG, respectively) 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}N-ammonia nor ^{18}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}N-ammonia), glucose metabolism (with ^{18}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}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}N-ammonia, and this was compared to resting ^{18}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}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}N-ammonia and ^{18}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}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}FDG uptake, had severely decreased perfusion to the same regions as measured by ^{13}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-