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Editorial Comment

The Ins and Outs of Thallium Kinetics*

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Diagnosis of coronary artery disease by thallium perfusion imaging is based on relative differences in the uptake and washout of activity in normal and ischemic myocardium. Although the term "kinetics" implies a highly technical, complicated process, it is actually fairly simple. Understanding of thallium kinetics requires knowing what affects thallium transport into and out of the myocardium. Thallium is taken up by the myocardium in proportion to flow and then passively exits. At any given time after administration of tracer, regional activity represents the difference between continued myocardial extraction and clearance of thallium.

Thallium uptake: the ins. Several investigators have tested the effects of various interventions on thallium uptake by the cell. The contribution of active transport by way of the sodium-potassium adenosine triphosphatase (ATPase) pump has probably been overemphasized as a determinant of thallium uptake. Early work with myocardial cell culture preparations (1), in which flow was not a factor, suggested that addition of digitalis glycosides to the culture medium inhibited thallium accumulation. However, subsequent whole animal studies (2–4) demonstrated that the majority of uptake was passive and flow dependent. Interventions such as alkalosis, administration of insulin or beta-adrenergic blocking agents, hypoxemia, ischemia and infarction, have not been shown to alter thallium uptake except by changing flow (2–6).

Thallium clearance: the outs. Egress of thallium from the myocardium also seems to be largely a passive process depending on simple diffusion and membrane permeability. Although clinical experience suggests that flow is a significant determinant of clearance, experimental studies have produced mixed results in confirming these observations (7–10). Washout of thallium increases after irreversible ischemic damage presumably because of leakage of tracer through the cell membrane (11–13).

Redistribution. Thallium defects on initial stress studies are due to ischemia, scar or attenuation artifacts. To differentiate viable, ischemic tissue from myocardial scar, delayed (that is, "redistribution") images are acquired 4 to 24 h after the initial studies. Ischemic areas appear to "fill in," whereas infarcts remain "fixed." Interpretation of these changes in appearance is where most of the confusion in thallium kinetics occurs. The defect appears to improve at the time of late imaging primarily because the rate of washout is faster for normal tissue than for ischemic segments. Activity may appear to be more homogeneous and the defect is said to be reversible. This appearance of improvement is also assisted by the normal rest level of flow distal to a <90% diameter stenosis in contrast to the typical low rest flow of an infarcted segment. Thus, the percent difference between normal and ischemic viable regions decreases with time whereas an infarcted segment has minimal additional thallium uptake and appears unchanged.

Thallium images are almost universally presented by using a gray or color scale in which the area with the greatest activity is at the top and everything else is scaled accordingly. By the time that redistribution images are acquired, true activity has decreased in the normal, ischemic and infarcted areas of the heart. When the images are displayed, activity is again shown on a scale that presents the highest activity at the top and the studies are said to be "normalized to peak counts." Thus, even though there may have been a 30% to 60% decrease in true counts in the normal region, the region appears just as bright as it did during the stress study. The ischemic area also loses counts but at a slower rate of clearance so that the image now appears to show improvement. An infarct has a much lower initial uptake at stress and even with a very slow washout still has far fewer counts than does normal tissue.

The present study. To illustrate these principles, let us examine the kinetics in the control group in the study by Hegewald et al. (14) in the current issue of the Journal (their Fig. 7 and Table 4). Mean activity (expressed as percent peak stress counts) is 100 in the normal region and 62 in the ischemic region. On the late images, activity in the normal region falls to 47 but is normalized to 100 and counts in the defect fall to 35 but are normalized to 74 (that is, $35 \times 100/47$). The defect appears to show partial improvement and suggests the presence of some viable myocardium.

Because the image interpretation is dependent on differences in washout rate between normal and abnormal regions, filling in of a defect could be due to either a slow washout of the ischemic region or a rapid washout of the normal region, or both, independent of changes in the ischemic tissue.

Effect of ribose. In their study, Hegewald et al. (14) present evidence that infusion of ribose increases the number of reversible defects. This increase seems to be due to both an increased clearance from the normal region and a decreased clearance from the defect. Why would ribose have a diametrically opposite effect on kinetics in normal and ischemic tissue? Given that prolonged hypoxia does not

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appear to alter washout rates, it is difficult to ascribe these changes to a direct metabolic effect. Another limitation to the study is that regional wall motion was either normal or hypokinetic in the majority of segments showing reversibility with ribose. The challenge of thallium imaging is to identify in patients with regional wall motion abnormalities those reversible defects that would improve with revascularization. Additional studies are required before this approach could be considered to be of benefit for evaluating ischemic heart disease.

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