EDITORIAL

Differential Myocardial Washout of Technetium-99m-Teboroxime: Mechanism and Significance

The paper by Stewart et al. (*1*) in this issue of the *Journal* indicates that myocardial washout of teboroxime is flow-dependent and that regions of myocardium presumed to have reduced myocardial blood flow exhibit delayed tracer clearance in comparison with regions of enhanced myocardial perfusion. Although myocardial blood flow was not measured in these experiments, the model and interventions employed are straightforward and it is likely that flow changes occurred in the direction anticipated by the authors. Quantitative data relating teboroxime washout to levels of myocardial blood flow have been reported previously by Stewart et al. (*2*) and more recently from our laboratory (*3*). An inverse, generally linear, relationship exists such that retention of teboroxime in the heart declines as myocardial blood flow increases (*3*). As a result, in cases of nonuniform blood flow, teboroxime scans of the myocardium exhibit a definite tendency for defects present in early images (1–2 min postinjection) to resolve over time (7–10 min postinjection) (*3,4*). Therein lies the rub. How is the clinician to deal with the fact that teboroxime scan defects may disappear very quickly from view, and even more importantly what significance should be attached to the phenomenon?

WHAT TO DO?

The answer to this question is simple. Scan early and often. Imaging should be commenced within 1–2 min of tracer injection and an effort should be made to obtain at least two 40–60-sec scans in each of three sequential views for planar imaging. SPECT imaging may be possible, especially with multidetector cameras, but acquisition time should be limited to less than 10 min and preferably to 5–7 min (*5*). Even at scan times of 5–7 min, it is possible that defects may be missed. This is especially likely to be a problem if imaging following pharmacologic hyperemia with dipyridamole is performed. Dipyridamole effects on myocardium may persist for sometime [~15 min (*6*)] and could greatly accelerate teboroxime washout from non-stenotic regions. The problem may be overcome, however, by reversing dipyridamole's effect with aminophylline just before imaging is begun. Alternatively, pharmacologic vasodilation could be induced with adenosine whose effects on the coronary circulation abate very rapidly after it is discontinued (*7*). It should be noted, however, since teboroxime washout is flow-dependent (*3*) that eliminating regional disparities in myocardial blood flow could result in equalization of washout rates and hence persistence of initial defects in serial planar scans.

The more important issue raised by the current report and others (*3,4*) concerns the physiological and diagnostic significance of differential teboroxime washout from the myocardium. Specifically, does "redistribution" observed in serial teboroxime scans following stress injection of the tracer carry the same diagnostic meaning as redistribution observed in thallium scans of the myocardium? In order to answer this question, it is useful to briefly consider the mechanism of thallium uptake and washout from the myocardium, particularly as it relates to scans obtained under clinical conditions of chronic, stable ischemic heart disease.

THALLIUM MYOCARDIAL KINETICS

Although often considered to be a simple analog of potassium, it is important to note that thallium differs from it in a number of respects. First, in two studies showing very prominent effects, only half of thallium uptake by myocardial cells could be inhibited by metabolic poisons (*8,9*). In other studies, interventions such as ischemia with reperfusion (*10–12*), ouabain (*10,11,13*), and hypoxia (*10–11,13*) had only modest effects on thallium uptake and retention by the myocardium. Further, under clinically relevant conditions the principle factor determining the rate of thallium washout from the myocardium appears to be the rate of decline in thallium levels in the blood (*14–16*). Marked changes in myocardial blood flow (up or down) occurring more than 10–15 min after injection (i.v.) have little or no effect on net loss of isotope from the heart (*12,17*). Redistribution occurs in clinical scans because zones with normal perfusion lose thallium faster than zones in which flow is reduced (relative or absolute). The difference in net rate of loss is related to the fact that reduced initial concentration in the low flow area permits the region to extract and retain thallium longer against rapidly declining levels in the blood (*14–16*). In contrast, a normally perfused zone obtains an higher initial concentration of the tracer and thus is less able to maintain those levels as blood activity falls. The end result is differential thallium washout from the myocardium, more commonly known as redistribution.

Although thallium redistribution is widely regarded as evidence of myocardial viability, lack of redistribution of course does not prove lack of myocardial viability (*18–20*). Indeed, viability information is largely related to the capacity of myocytes to retain thallium which in turn is a reflection of intact cell membranes and the ability to maintain a negative resting membrane potential (*21,22*). Both

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For reprints contact: Henry Gewirtz, MD, Director, Cardiac Research Laboratory, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903.

factors (i.e., cell membrane integrity and potential) in the chronic steady-state are dependent on a minimal level [~20% of normal basal values (*23*)] of myocardial blood flow. Thus, leaving aside unsteady conditions such as acute myocardial infarction with reperfusion, myocardial viability may be infered from evidence of thallium uptake. More detailed metabolic studies, however, may be required to determine if low flow zones are likely to improve function after revascularization.

SIGNIFICANCE OF DIFFERENTIAL TEBOROXIME WASHOUT

The implications of the above analysis for interpretation of serial teboroxime images of the myocardium is as follows. Teboroxime is a neutral, highly lipophilic molecule whose uptake by and washout from the myocardium is largely diffusional in nature and is closely related to myocardial blood flow. As shown in the present report (*1*) and others (*2,3*), differential washout of teboroxime from the myocardium reflects differences in regional myocardial flow reserve as well as ongoing differences in regional blood flow during imaging (*3*). Accordingly, teboroxime "redistribution" implies a persistent flow deficit and thus may be seen with myocardial ischemia (acute), myocardial hibernation [chronic (*24,25*)], or even scar. The intensity and extent of the defect likely will be useful in distinguishing between hibernating myocardium and scar as is the case with thallium (*19,20*). Finally, it should be recognized that a persistent teboroxime defect on serial planar scans may reflect the fact that flow differences have resolved quickly after discontinuing stress. Thus, in contrast to thallium, persistent teboroxime defects suggest myocardial viability since the phenomenon implies equality of flow between ischemic and normal zones post-stress.

CONCLUSION

Teboroxime is a promising myocardial perfusion agent that is capable of providing good estimates of relative coronary flow reserve. Its utility may be enhanced by obtaining serial myocardial images after stress injection in order to detect evidence of differential tracer washout which is an indicator of more persistent disparities in regional coronary flow. Such disparities may reflect viable regions with persistently reduced flow [myocardial hibernation (*24,25*)] or scar. The extent and intensity of the initial uptake abnormality should be helpful in making the distinction. A second injection of teboroxime with the patient at rest will be helpful in delineating the stress-induced component of the defect, but may not be helpful in distinguishing scar from hibernation. As noted above, the extent and intensity of the initial uptake abnormality may be most helpful in this regard. It is also important to recognize that persistence of a defect, especially if only mild/moderate in intensity, in serial teboroxime images obtained after exercise or pharmacological stress testing implies equalization of post-stress flows and hence the presence of *viable* myocardium in the defect zone. Images acquired after rest-injection of the tracer should be obtained to confirm the presence of viable myocardium in the region (i.e., resolution of the stress defect). Finally, in interpreting the results of these studies it is crucial to be aware of technical limitations of conventional gamma camera imaging when inferring viability from apparent myocardial tracer uptake.

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Henry Gewirtz
Rhode Island Hospital
Brown University Program in Medicine
Providence, Rhode Island

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