EDITORIAL

Reverse Redistribution—"Part II": Occurrence after Thallium Reinjection

The development or enhancement of defects on thallium myocardial perfusion scintigrams obtained several hours after initial postexercise imaging, called "reverse redistribution," first was reported almost 20 yr ago (*1,2*). Nonetheless, the pathophysiologic and prognostic implications of this phenomenon remain speculative. Reverse redistribution occurring only after thallium reinjection, despite normal uptake on late postexercise imaging, first was reported only 4 yr ago (*3*), and its implications are even less well defined. With publication of their interesting article in the current issue of *JNM*, Marzullo et al. (*4*) have added knowledge in this area by relating reverse redistribution after thallium reinjection to coronary anatomy and regional ventricular performance in patients with remote myocardial infarction. If followed by appropriate additional research, their findings may lead to clinically useful inferences.

REVERSE REDISTRIBUTION AFTER STRESS

Reverse redistribution first was reported by Hecht et al. (*1*) in 1981, following an earlier preliminary report by Tanasescu et al. (*2*). The phenomenon was attributed to relatively higher thallium washout rate in the affected region than in adjacent regions. Although Hecht et al. found that most regions manifesting reverse redistribution were supplied by stenotic vessels, Tanasescu et al. indicated that the finding generally occurred in regions supplied by normal or only modestly stenotic arteries. The distinction is potentially important because normal uptake seen on immediate postexercise imaging generally is regarded as favoring the absence of functionally important coronary artery disease. Subsequent study revealed several situations commonly associated with reverse redistribution and led to plausible explanatory theories. Thus, the phenomenon is observed commonly when perfusion scintigraphy is performed in close proximity to thrombolytic therapy among patients who have suffered acute myocardial infarction. Based on the relation between reverse redistribution, coronary artery patency, regional ventricular performance, creatine kinase release and quantitatively defined regional thallium washout rates in infarcted patients studied 10 days after streptokinase therapy, Weiss et al. (*5*) suggested that reverse redistribution in this population is due to abnormally high washout rate in a segment containing some viable myocardium and supplied by a patent (successfully thrombolysed) coronary artery. To support this explanation, they postulated higher than normal blood flow to the noninfarcted tissue in the reperfused zone (masking the presence of subjacent poorly perfused tissue) which results, in turn, in relatively rapid washout rates in the hyperfused tissue. Touchstone et al. (*6*) confirmed Weiss's conclusions, finding that, like delayed redistribution, reverse redistribution indicates viability of myocardium within an infarcted zone which is supplied by a patent coronary artery.

Weiss et al. (*5*) suggested two additional possible explanations for reverse redistribution:

1. Normal blood flow in the noninfarcted region of the reperfused zone associated with subnormal flow in the infarcted region and resting hypoperfusion in the contralateral (possibly ischemic) myocardium.
2. Thallium uptake in the necrotic tissue and/or interstitium of the reperfused zone coupled with abnormally high washout rates from these tissues.

As experimental evidence accumulated, Beller (*7*) provided a plausible and more generalizable explanation for the former hypothesis, suggesting that delayed thallium uptake in the ischemic zone coupled with rapid washout from remote nonischemic but partially scarred tissue might result in an apparent delayed "defect" in the scarred zone.

Extrapolating from their results, Weiss et al. (*5*) speculated that reverse redistribution in patients with remote infarction might imply nontransmural infarct distribution within a region now supplied by a patent artery or graft or by well-developed collateral vessels. They correctly raised concern about extrapolation of their findings to other populations, noting that reverse redistribution may occur in patients without infarction or objective evidence of coronary artery disease.

REVERSE REDISTRIBUTION AFTER REINJECTION

The phenomenon of post-reinjection reverse redistribution first was reported by Dilsizian and Bonow (*3*) in a study of 50 patients with chronic stable coronary artery disease. Based on assessment of thallium washout rates and angiographic coronary anatomy, they concluded that regions supplied by totally occluded or severely stenotic arteries manifest relatively low thallium uptake early after reinjection, despite considerable uptake at standard 3–4-hr postexercise imaging. As a result, the early post-reinjection image reveals a defect relative to more normally perfused regions despite the apparent disappearance of the defect immediately prior to reinjection. Thus, after reinjection, the pathophysiologic implications of reverse redistribution may differ markedly from those drawn from late postexercise images obtained without reinjection. Direct comparison between the results of Marzullo and Dilsizian is not possible because the frequency of remote infarction was not reported for Dilsizian's population. The similarities, however, between the two populations appear to be sufficient such that additional research will be needed to resolve the apparent contradiction between Dilsizian's finding of total occlusion in most patients who manifest reverse redistribution only after reinjection and Marzullo's observation that mild-to-moderate stenoses are the norm in this subgroup.

ARTIFACTS

Finally, Lear et al. (*8*) used sophisticated mathematical modeling to find that interpolative background subtraction techniques commonly used during quantitative assessment of myocardial perfusion scintigrams can result in artifactually apparent reverse redistribution in the postinfarction patient. This is not surprising: thallium imaging does not lend itself readily to absolute quantitation of flow and identification of defects depends on the relative abundance of isotope uptake in different myocardial regions, none of which need be normal. As a result, kinetics of distribution in regions of differing ischemia severity and tissue composition can result in image patterns which cannot be interpreted unequivocally. Interposition of reinjection in this process increases the number of potential interpretations by increasing the time during which the effects of differential regional kinetics

Received Feb. 27, 1996; accepted Mar. 6, 1996.
For correspondence or reprints: Jeffrey S. Borer, MD, The New York Hospital-Cornell Medical Center, 525 E. 68th St., New York, NY 10021.

can be observed and by adding a new input function prior to return to baseline.

CLINICAL INFERENCES

The plethora of plausible explanations for reverse redistribution provides a basis for a variety of clinically useful conclusions. Our inability to identify the mechanism involved in any given situation, however, mitigates the clinical utility of the phenomenon by minimizing its specificity. Importantly, previously published studies almost exclusively involved patients with recent myocardial infarction. The exceptions, including Lear's computer modeling study (*8*) and Dilsizian's assessment of chronic stable coronary patients (*3*), suggest that the finding of reverse redistribution cannot be unequivocally interpreted without information in addition to that available from the scan itself. It would seem highly imprudent, then, to extrapolate from the available data to populations that have not yet been studied. For example, it is not possible, with any reasonable certainty, to interpret reverse redistribution in a patient with suspected but not otherwise documented coronary artery disease. Therefore, the most defensible conclusion from the data of Marzullo et al. (*4*) is that which is consistent with the data of Dilsizian (*3*): reverse redistribution in patients with known chronic stable coronary artery disease frequently is associated with a hemodynamically important coronary artery stenosis (severity unspecified) in the affected region.

Marzullo et al. (*4*) go beyond this, suggesting that the presence of reverse redistribution after reinjection is an indicator of collateral-dependent myocardial dysfunction and preserved tissue viability. This inference is not consistent with the findings of Marin-Neto et al. (*9*), who used post-reinjection imaging to differentiate subgroups among those manifesting reverse redistribution after stress alone (i.e., Marzullo's Group 1 patients). Marzullo et al. reported a preponderance of viable myocardium and good collaterals among those whose defects diminished (rather than developed) after reinjection and the relative absence of these characteristics among those who did not. Unfortunately, detection of the differences separating Marin-Neto's subgroups requires a degree of precision which is probably not achievable in single studies performed clinically. Most importantly, though, the neat separation reported by Marin-Neto et al. was not apparent in Marzullo's data. Partly because of the study design they used, the conclusions reported by Marzullo et al. (*4*) seem to run beyond their data. Almost half the regions showing reverse redistribution were akinetic, half the regions were supplied by totally occluded arteries, only one-third of these regions were supplied by "efficient" collaterals and less than half the segments manifested "viability" according to the authors' quantitative thallium uptake criterion. From these data, it would seem that most of the regions manifesting reverse redistribution following reinjection may *not* be collateral-dependent *or* viable, although it is possible that the *relative* likelihood of these associations is greater than if reverse redistribution were absent. Thus, while their interesting data [as well as their apparent disagreement with Marin-Neto et al. (*9*)] suggest the appropriateness of further study, it is not yet reasonable to conclude that any specific physiological correlate necessarily can be inferred from post-reinjection reverse redistribution.

In addition to these concerns, however, this article serves as a basis for more general consideration of the relation between published data and mandates for action by clinicians. Marzullo et al. (*4*) studied a retrospectively defined cohort of 29 patients with post-reinjection reverse redistribution, almost all of whom also had prior infarction. Their aim was to define pathophysiologic correlates from which to draw clinically useful conclusions. The authors also compared the subgroup of their 29 patients who evidenced reverse redistribution on 4-hr postexercise imaging with the subgroup manifesting normal thallium uptake 4 hr after exercise. No comparison was made with patients who lacked post-reinjection reverse redistribution. As in any retrospective study, there was considerable potential for unintentional bias in selecting patients for study. Moreover, even if the sample were statistically representative of the larger cohort from which it was drawn, the small population size would preclude sufficient power to identify any but extraordinarily consistent group patterns or subgroup differences. Finally, no follow-up data are presented to indicate the predictive value of the findings.

CONCLUSION

Given these observations, especially in these cost-conscious times, the authors legitimately might be asked to justify their suggestion that their work "expands the indication for thallium reinjection." As compared with standard thallium exercise-redistribution imaging, reinjection involves greater radiation exposure, higher cost for materials and more camera, patient and personnel time. Reinjection may be appropriate when a clinical decision will be based on the presence or absence of tissue viability as judged from thallium images. Expansion of the indication, however, for any test requires evidence that the result of its new application will affect management decisions and, through them, will beneficially alter outcome compared with decisions reached without the test. To expand the indication for reinjection imaging, it would be necessary to show that therapy based on the finding of reverse redistribution is more effective than therapy selected without knowledge of this phenomenon. Marzullo et al. (*4*) have provided no data relevant to these issues, and none are available from the literature in the field. Without such data, the present interesting and important study represents a mandate for additional research, not additional costly procedures.

ACKNOWLEDGMENT

Supported by a grant from The Howard Gilman Foundation, New York, NY.

Jeffrey S. Borer
Cornell University Medical College
The New York Hospital-Cornell Medical Center
New York, New York

REFERENCES

1. Hecht HS, Hopkins JM, Rose JG, Blumfield DE, Wong M. Reverse redistribution: worsening of ^{201}Tl myocardial images from exercise to redistribution. *Radiology* 1981;140:177–181.
2. Tanasescu D, Berman D, Staniloff H, Brachman M, Rammana L, Waxman A. Apparent worsening of ^{201}Tl defects during redistribution: what does it mean? [Abstract]. *J Nucl Med* 1979;20:688.
3. Dilsizian V, Bonow RO. Differential uptake and apparent ^{201}Tl washout after thallium reinjection: options regarding early redistribution imaging before reinjection and late redistribution imaging after reinjection. *Circulation* 1992;85:1032–1038.
4. Marzullo P, Gimelli A, Cuocolo A, et al. Thallium-201 reverse redistribution at reinjection imaging correlated with coronary lesion wall motion abnormality and tissue viability. *J Nucl Med* 1996;37:735–741.
5. Weiss AT, Maddahi J, Lew AS, et al. Reverse redistribution of thallium-201: a sign of nontransmural myocardial infarction with patency of the infarct-related coronary artery. *J Am Coll Cardiol* 1986;7:61–67.
6. Touchstone DA, Beller GA, Nygaard TW, Watson DD, Tedesco C, Kaul S. Functional significance of predischarge exercise thallium-201 findings following intravenous streptokinase therapy during acute myocardial infarction. *Am Heart J* 1988;116:1500–1507.
7. Beller GA. Myocardial perfusion imaging with thallium-201. In: Marcus ML, Schelbert HR, Skorton DJ, Wolf GL, eds. *Cardiac imaging*. Philadelphia: WB Saunders; 1991:1047–1073.
8. Lear JL, Raff U, Jain R. Reverse and pseudoredistribution of thallium-201 in healed myocardial infarction and normal and negative thallium-201 washout in ischemia due to background oversubtraction. *Am J Cardiol* 1988;62:543–550.
9. Marin-Neto JA, Dilsizian V, Arrighi JA, et al. Thallium reinjection demonstrates viable myocardium in regions with reverse redistribution. *Circulation* 1993; 88:1736–1745.