Reverse Redistribution of Thallium-201

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The pattern of reverse redistribution of ^{201}Tl is defined as the appearance of a defect on the redistribution image in a region with normal or near normal initial uptake of ^{201}Tl. This pattern was initially reported in 1979 (*1*) and has since been studied by several investigators including the most recent study by Soufer et al. (*2*).

Initial reports described the phenomenon of ^{201}Tl reverse redistribution on exercise planar imaging of patients with chronic coronary artery disease (*1,3,4*). These studies demonstrated that the prevalence of the reverse redistribution pattern in these patients was low, but they did not agree on its clinical significance since the relationship of the reverse redistribution pattern to the underlying coronary artery disease was different in each case. Tanasescu et al. (*1*) found that reverse redistribution regions were supplied by the least stenotic coronary arteries. Hecht et al. (*3*) found that these areas were supplied by the most stenotic vessels, whereas Silberstein et al. (*4*) showed that the pattern of reverse redistribution may be observed in regions subtended by either normal or diseased coronary arteries and that in the diseased categories, stenosis was least or most severe.

In 1986, Weiss et al. (*5*) made several key observations about the phenomenon of reverse redistribution on rest-redistribution ^{201}Tl imaging. In 67 patients who received streptokinase thrombolytic therapy for acute myocardial infarction, they demonstrated early following reperfusion, that the pattern of ^{201}Tl reverse redistribution was: (1) common, occurring in 75% of these patients; (2) only noted in the reperfused myocardial region; (3) the result of a higher than normal washout rate of ^{201}Tl from the region manifesting the reverse redistribution pattern; (4) represented admixture of viable and nonviable myocardium; and (5) associated with patency of the infarct-related coronary artery. Published studies have shown that the pattern of ^{201}Tl reverse redistribution may be observed in different patient populations using rest-redistribution, exercise or pharmacologic stress-redistribution ^{201}Tl imaging protocols with either planar or SPECT imaging methods. Through these studies, five common denominators have emerged that characterize the clinical significance of this pattern.

ADMIXTURE OF VIABLE AND NONVIABLE TISSUE

The notion that myocardial regions showing the pattern of ^{201}Tl reverse redistribution contained an admixture of viable and nonviable tissue has been implied by several observations in two groups of patients. First, those who received thrombolytic therapy for acute nyocardial infarction and, second, patients with chronic coronary artery disease.

Weiss et al. (*5*) showed that reverse redistribution of ^{201}Tl was noted in regions that had evidence of myocardial salvage following reperfusion, as evidenced by improvement of ^{201}Tl defect from pre- to postreperfusion image. They further found that regions with ^{201}Tl reverse redistribution had improvement in regional wall motion by 10 days following reperfusion, suggesting that the viable myocardium in these regions were initially stunned. Fukuzawa et al. (*6*) similarly showed that at 3 wk following reperfusion, reverse redistribution regions had near normal regional wall motion. Langer et al. (*7*) reported that, in patients who received thrombolytic therapy, sublingual administration of nitroglycerin improved regional ejection fraction of segments with ^{201}Tl reverse redistribution to a greater degree, as compared to regions with fixed or reversible defects. This confirmed that reverse redistribution regions had stunned but viable myocardium. Touchstone et al. (*8*) showed that on predischarge exercise imaging of patients who underwent intravenous streptokinase therapy, reverse redistribution of ^{201}Tl was noted in areas with salvaged myocardium, defined by serial improvement in regional systolic function. Yamagishi et al. (*9*) studied patients 1 wk to 2 mo after myocardial infarction and showed that ^{201}Tl reverse redistribution correlated with improvement of regional wall motion on serial studies.

In patients with chronic coronary artery disease, Hecht et al. (*3*) and Pace et al. (*10*) showed that regions with ^{201}Tl reverse redistribution had impaired regional function, suggesting the presence of myocardial scarring in these areas. Marin-Neto et al. (*11*) studied 39 patients with chronic stable coronary artery disease who demonstrated reverse

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redistribution of ^{201}Tl on exercise-redistribution SPECT imaging. They concluded that regions with reverse redistribution contained viable myocardium since their ^{201}Tl uptake increased after ^{201}Tl reinjection and the incidence of Q-wave infarction and akinetic or dyskinetic wall motion was low. Furthermore, in 16 of 39 patients who were also assessed by PET for myocardial viability, all regions with reverse redistribution were found to have viable myocardium.

Soufer et al.'s study (*2*) sheds additional light on the relationship between myocardial viability and regional wall motion in areas with ^{201}Tl reverse redistribution. They evaluated myocardial viability by PET in 32 patients with chronic coronary artery disease, who showed ^{201}Tl reverse redistribution on exercise planar imaging. Of the 50 segments with ^{201}Tl reverse redistribution, 72% showed evidence of viability by PET criteria, demonstrating either normal FDG uptake and flow or enhanced FDG uptake relative to flow (PET ischemia). It is of note that in this study, regions with concordant reduction of flow and FDG uptake below 50% of normal were classified as nonviable. Some of these regions, however, may be nontransmurally infarcted rather than entirely nonviable, especially when flow and FDG uptake are not markedly below 50% of normal. Therefore, it is likely that the true incidence of tissue viability in reverse redistribution regions is higher than 72%. An important observation of these investigators was in the 35 of 50 segments with reverse redistribution in which regional wall motion was analyzed by radionuclide angiography. The frequency of viability in reverse redistribution segments was highly different in the groups with and without abnormal wall motion. All but one of 17 segments with normal wall motion were viable by PET, whereas 7 of 18 segments with wall motion abnormality were viable by PET. These investigators concluded that the presence of moderate or severe hypokinesis in regions with ^{201}Tl reverse redistribution does not imply lack of viability in these areas.

Reverse redistribution of ^{201}Tl has also been reported with myocardial sarcoidosis (*12*) and chronic Chagas' disease (*13*). It is very likely that in both of these conditions, reverse redistribution of ^{201}Tl represents admixture of viable and nonviable myocardium in these areas.

PRESERVED REGIONAL FLOW

Another common denominator in the reported literature is that the reverse redistribution regions have preserved regional flow, either through patent coronary arteries or by collaterals when the corresponding coronary artery is totally occluded. In all studies conducted in patients following thrombolytic therapy (*5–8,14*), regions with reverse redistribution were found to be supplied by patent coronary arteries. In these reports, however, the severity of residual stenosis was variable. Similar results were also reported in patients with chronic coronary artery disease (*3,4,15*). Soufer et al.'s findings (*2*) are consistent with these results, showing that the arteries supplying the reverse redistribution regions were patent but significantly stenosed.

In two studies, the arteries supplying the reverse redistribution regions were reported to be totally occluded but supplied by collaterals. Pace et al. (*10*) showed that 46% of reverse redistribution segments were supplied by occluded coronary arteries, 58% of which were supplied by visible collaterals on angiography. Of note, despite lack of visible collaterals in the remaining 42% of regions, ^{201}Tl and ^{99m}Tc sestamibi were taken up by these areas suggesting preserved perfusion, presumably through collaterals not appreciated on angiography. Marin-Neto et al. (*11*) showed critically stenosed or totally occluded coronary arteries supplying 83% of reverse redistribution regions that showed evidence of viability after ^{201}Tl reinjection. In all but one of these regions, collateral circulation was detected to be present.

PROGNOSTIC SIGNIFICANCE

The stenotic coronary artery supplying the reverse redistribution segment may jeopardize the viable myocardial tissue in the region and pose a risk to the patient. Theoretically, the outcome of patients with the reverse redistribution pattern would depend on multiple parameters such as the size and severity of the reverse redistribution, the overall extent and severity of coronary disease, the presence and extent of ischemia and necrosis in other regions of the myocardium, global ventricular function and the clinical setting (chronic coronary artery disease versus post-thrombolysis). There are only a few studies that address the prognostic significance of the pattern of reverse redistribution (*2,14,16*). Sakata et al. (*14*) studied 50 patients, who received intracoronary thrombolysis, by simultaneous ^{99m}Tc-pyrophosphate and ^{201}Tl SPECT 3 days after first acute myocardial infarction. They showed that reverse redistribution or fixed defects on rest-redistribution ^{201}Tl images were less frequently associated with reinfarction during the hospital course than reversible defects. Preliminary observation in a group of patients in the thrombolysis in myocardial infarction (TIMI) trial indicated that reverse redistribution following thrombolysis is associated with a higher incidence of future cardiac events with substantial regional and global ventricular dysfunction (*16*).

The study of Soufer et al. (*2*) provides new information with respect to the outcome of patients with chronic coronary artery disease and the pattern of reverse redistribution. During 14-mo follow-up, 10/32 patients developed unstable angina (nine patients) or myocardial infarction (one patient). Of the 13 patients who had severe reverse redistribution, all who had PET viability had a cardiac event, compared to those who had PET scarring of whom none had an event. In this small population, other standard predictors of outcome such as exercise time, ECG changes or chest pain did not predict outcome. Furthermore, adjacent myocardial ischemia alone did not predict a poor outcome. This study, therefore, suggests that PET assessment of viability may be helpful in identifying a subgroup of patients who are at higher risk for subsequent cardiac events and require closer follow-up. This preliminary find-

ing, however, requires additional large-scale studies as pointed out by these investigators.

MECHANISM OF REVERSE REDISTRIBUTION

Despite concordance of data demonstrating that reverse redistribution is the result of faster regional washout of ^{201}Tl, the mechanism for such enhanced washout of ^{201}Tl is not well understood and remains speculative. In patients undergoing early thrombolytic therapy, Weiss et al. (*5*) proposed two likely mechanisms for faster than normal washout of ^{201}Tl: (1) higher than normal blood flow to the noninfarcted tissue in the reperfused zone and (2) initial ^{201}Tl uptake by the necrotic tissue or the interstitial component in the reperfused zone and subsequent faster washout. One or both of these explanations were supported by subsequent studies.

OTHER CAUSES OF THALLIUM-201 REVERSE REDISTRIBUTION

In patients with a low pretest likelihood of coronary artery disease, reverse redistribution of ^{201}Tl may be observed as a normal variant or may be artifactual. Kaul et al. (*17*) found significant variability in regional myocardial washout of ^{201}Tl in normal subjects. Brown et al. (*18*) showed that rapid washout of ^{201}Tl in the region with reverse redistribution may be artifactually caused by interpolative background subtraction of planar ^{201}Tl images. Lear et al. (*19*) used a mathematical model and showed that in myocardial regions with ischemia or infarction, the measured myocardial washout of ^{201}Tl depended on the degree of background oversubtraction, the difference between myocardial and pulmonary washout of ^{201}Tl, and on initial myocardial ^{201}Tl uptake. The conclusions of the latter two studies, however, do not apply to SPECT imaging. Shifting of breast and diaphragmatic attenuation artifacts between the initial and the redistribution image may also appear as reverse redistribution defects. Furthermore, reinjection of ^{201}Tl may accentuate regional myocardial count differences on the redistribution images and result in artifactual appearance of reverse redistribution of ^{201}Tl (*20*).

The phenomenon of reverse redistribution of ^{201}Tl has been the focus of several studies since its initial description about a decade and a half ago. In patients with a low pretest likelihood of coronary artery disease, reverse redistribution of ^{201}Tl may be observed as a normal variant or may be artifactual. In patients with chronic coronary artery disease and those with prior thrombolytic therapy for acute myocardial infarction, the pattern of reverse redistribution of ^{201}Tl indicates presence of an admixture of viable and nonviable myocardium in a region that is being perfused by either a patent coronary artery or by collateral circulation. The recent report by Soufer et al. (*2*) confirms this notion and further raises the possibility that evaluation of myocardial viability by PET may identify a subgroup of patients who are at a high risk for development of subsequent unstable angina.

REFERENCES

1. Tanasescu D, Berman D, Staniloff H, et al. Apparent worsening of thallium-201 myocardial defects during redistribution—what does it mean [Abstract]? *J Nucl Med* 1979;20:688.
2. Soufer R, Dey HM, Lawson AJ, Wackers FJT, Zaret BL. Relationship between reverse redistribution on planar thallium scintigraphy and regional myocardial viability: a correlative positron emission tomography study. *J Nucl Med* 1995;36:180–187.
3. Hecht HS, Hopkins JM, Rose JG, Blumfield DE, Wong M. Reverse redistribution: worsening of thallium-201 myocardial images from exercise to redistribution. *Radiology* 1981;140:177–181.
4. Silberstein EB, DeVries DF. Reverse redistribution phenomenon in thallium-201 stress tests: angiographic correlation and clinical significance. *J Nucl Med* 1985;26:707–710.
5. Weiss AT, Maddahi J, Lew AS, Shah PK, Ganz W, Swan JH, Berman DS. 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. Fukuzawa S, Ozawa S, Nobuyoshi M, Inagaki Y. Reverse redistribution on Tl-201 SPECT images after reperfusion therapy for acute myocardial infarction: possible mechanism and prognostic implications. *Heart Vessels* 1992; 7:141–147.
7. Langer A, Burns RJ, Freeman MR, Liu P, Morgan CD, Wilson R, Armstrong PW. Reverse redistribution on exercise thallium scintigraphy: relationship to coronary patency and ventricular function after myocardial infarction. *Can J Cardiol* 1992;8:709–715.
8. 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.
9. Yamagishi H, Itagane H, Akioka K, et al. Implications of delayed image on simultaneous thallium-201 single-photon emission computed tomography in patients with acute myocardial infarction. *Jpn Circ J* 1993;57:27–36.
10. Pace L, Cuocolo A, Maurea S, et al. Reverse redistribution in resting thallium-201 myocardial scintigraphy in patients with coronary artery disease: relation to coronary anatomy and ventricular function. *J Nucl Med* 1993;34:1688–1692.
11. Marin-Neto JA, Dilsizian V, Arrighi JA, et al. Thallium reinjection demonstrates viable myocardium in regions with reverse redistribution. *Circulation* 1993;88:1736–1745.
12. Fields CL, Ossorio MA, Roy TM, Denny DM, Varga DW. Thallium-201 scintigraphy in the diagnosis and management of myocardial sarcoidosis. *South Med J* 1990;83:339–342.
13. Marin-Neto JA, Marzullo P, Marcassa C, et al. Myocardial abnormalities in chronic Chagas' disease as detected by thallium-201 scintigraphy. *Am J Cardiol* 1992;69:780–784.
14. Sakata K, Yoshida H, Ono N, et al. Implications of delayed image on simultaneous thallium-201/technetium-99m pyrophosphate dual emission computed tomography early after acute myocardial infarction. *Jpn Circ J* 1993;57:27–36.
15. Popma JJ, Smitherman TC, Walker BS, Simon TR, Dehmer GJ. Reverse redistribution of thallium-201 detected by SPECT imaging after dipyridamole in angina pectoris. *Am J Cardiol* 1990;65:1176–1180.
16. Wackers FJT, Zaret BL, Chatman B, Wassermann A, Thompson B. The prognostic significance of reverse redistribution in thallium-201 stress testing after thrombolytic therapy for acute infarction [Abstract]. *J Am Coll Cardiol* 1992;22.
17. Kaul S, Chesler DA, Newell JB, Pohost GM, Okada RD, Boucher CA. Regional variability in the myocardial clearance of thallium-201 and its importance in determining the presence or absence of coronary artery disease. *J Am Coll Cardiol* 1986;8:95–100.
18. Brown KA, Benoit L, Clements JP, Wackers FJ. Fast washout of thallium-201 from area of myocardial infarction: possible artifact of background subtraction. *J Nucl Med* 1987;28:945–949.
19. Lear JL, Raff U, Jain R. Reverse and pseudo redistribution 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.
20. van Eck-Smith BLF, van der Wall EE, Kuijper AF, Zwinderman AH, Pauwels EK. Immediate thallium-201 reinjection following stress imaging: a time-saving approach for detection of myocardial viability. *J Nucl Med* 1993;34:P737–P743.