Thallium-201 Myocardial Scintigraphy: Single Injection, Re-injection, or 24-Hour Delayed Imaging?

Discussion by: Pierluigi Pieri

Case Presentation: Pierluigi Pieri, Stephen A. Abraham, and Hisashi Katayama

Guest Editor: Tsunehiro Yasuda

From the case records of the Massachusetts General Hospital, Boston, Massachusetts and Harvard Medical School, Boston, Massachusetts

J Nucl Med 1990; 31:1390–1396

Forty days after an acute myocardial infarction a 60-yr-old man was referred for thallium-201 (^{201}Tl) scintigraphy to detect residual ischemia.

HISTORY

The patient had a long history of hypertension, controlled recently with calcium blockers but no other risk factors for coronary artery disease. At the time of hospitalization, he had chest pain radiating to both arms which, with decreasing intensity, persisted for 5–6 hr. The ECG revealed a normal sinus rhythm and a pattern of anteroseptal and high lateral myocardial infarction. Following acute therapy, his hospital course was uncomplicated. The patient remained free of angina and did not develop symptoms or signs of congestive heart failure. Serial ECGs showed Q-waves in V2-4 and progressive inversion of T-waves in I,AVL,V1-4 consistent with recent anteroseptal and high lateral myocardial infarction. The CPK rose to 2958 with a positive MB fraction. On the second hospital day, an echocardiogram showed normal left ventricular size with mild concentric left ventricular hypertrophy; akinesis to dyskinesis at the apex with hypokinesis to akinesis in the distal septum and distal free anterior wall. The ejection fraction was moderately reduced. On the ninth hospital day, prior to discharge, an exercise test was performed using the modified Bruce protocol. The patient exercised for 4.5 min without symptoms. The test was discontinued because the target heart rate of 120 was reached with a double product of 20,900. The ECG showed 1–2 mm horizontal S-T depression in leads III,AVF suggesting additional ischemia in an area remote from the infarction. The patient was discharged on the eleventh day on Beta-blockers and aspirin and was scheduled for an exercise thallium scan at a higher workload to determine whether the inferior wall changes represented ischemia at a distance. Forty days after discharge, while the patient was treated with beta-blockers and aspirin, a treadmill thallium stress test was performed. He exercised, according to the standard Bruce protocol, for a total of 7 min and 15 sec achieving a peak heart rate of 135 (84% of maximal predicted heart rate for age) with a double product of 20,250. The test was discontinued because of leg fatigue. Exercise ECG (Figs. 1–2) showed borderline positive ischemic changes with 1–1.5 mm of flat to upsloping S-T depression in II III AVF and 0.5 mm S-T depression in V6 at peak exercise. These changes occurred in the absence of chest pain and returned to baseline during early recovery.

The thallium scan was performed using a re-injection protocol where 105 MBq (2.8 mCi) of ^{201}Tl was injected at peak exercise with immediate imaging of the heart. Three hours later, 37 MBq (1 mCi) of ^{201}Tl were re-injected at rest with repetition of images starting 10 min after re-injection. The ^{201}Tl scan (Fig. 3) revealed a dilated left ventricle with increased lung uptake on the exercise images with normalization of size on the delayed images. These findings were consistent with exercise related left ventricular dysfunction. Diminished ^{201}Tl uptake was present in the anterior, anterolateral, and apical segments on the initial images with minimal improvement on the anterior and anterolateral seg-

Received May 17, 1990; revision accepted May 17, 1990.

For reprints contact: Tsunehiro Yasuda, MD, Massachusetts General Hospital, Nuclear Medicine Division, 32 Fruit St., Tilton 2, Boston, MA 02114.

Dr. Yasuda is a staff member in the Cardiac Unit and Assistant in Radiology at the Massachusetts General Hospital and an Assistant Professor of Radiology at the Harvard Medical School.

Drs. Pieri, Abraham, and Katayama are Fellows in Nuclear Medicine/Nuclear Cardiology at the Massachusetts General Hospital.

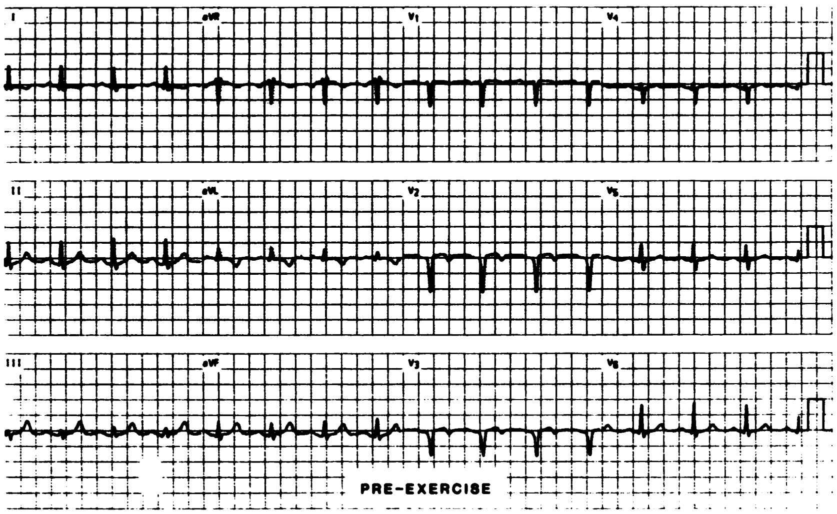

FIGURE 1
Baseline ECG, before exercise ^{201}Tl test, showing evidence of anterior myocardial infarction with residual T-waves inversion on the infarcted area.

ments after re-injection. Twenty-hour delayed images were obtained, without any additional administration of thallium, which showed better uptake in the anterior and anterolateral segments suggesting viable tissue in this territory. On the basis of the thallium scan, a coronary angiogram was performed which showed a near total occlusion of the left anterior descending coronary artery (LAD) after two large septal branches with visualization of the middle segment of the artery which had a second severe stenosis (Fig. 4). There was a severe stenosis in the diagonal artery adjacent to the proximal LAD stenosis and a 50% stenosis at the origin of the last marginal branch of left circumflex. There were collaterals from the right coronary artery and from the left circumflex (Cx) to the LAD. A successful PTCA was performed to both the proximal and middle segment lesions of the LAD (Fig. 5).

DISCUSSION

Early detection of residual ischemia in patients with previous myocardial infarction, especially in a coronary territory remote from the infarct site, is important to identify patients at higher risk for future cardiac events (*1–7*). While symptoms are important, relying on a history of chest pain to detect ischemia misses a significant number of patients due to the high frequency of silent ischemia (*8,9*). Exercise ^{201}Tl myocardial scintigraphy is more sensitive and specific than exercise ECG (*10–14*) and is more effective in stratifying the risk of further events in post-infarction patients (*1,7*). Particularly, in patients with recent uncomplicated myocardial infarction, ^{201}Tl myocardial scintigraphy appears superior to exercise ECG and even to the number of diseased vessels on coronary angiography at predicting future cardiac events (*1*). In this case, ^{201}Tl scintigraphy was performed for risk stratification after an uncomplicated myocardial infarction, to determine the significance of exercise ECG abnormalities and the site and extent of ischemia. The ^{201}Tl scan showed a large anteroapical perfusion defect with minimal improvement after re-injection. After a 20-hr delay, however, better uptake was seen in the infarcted area. This raises the

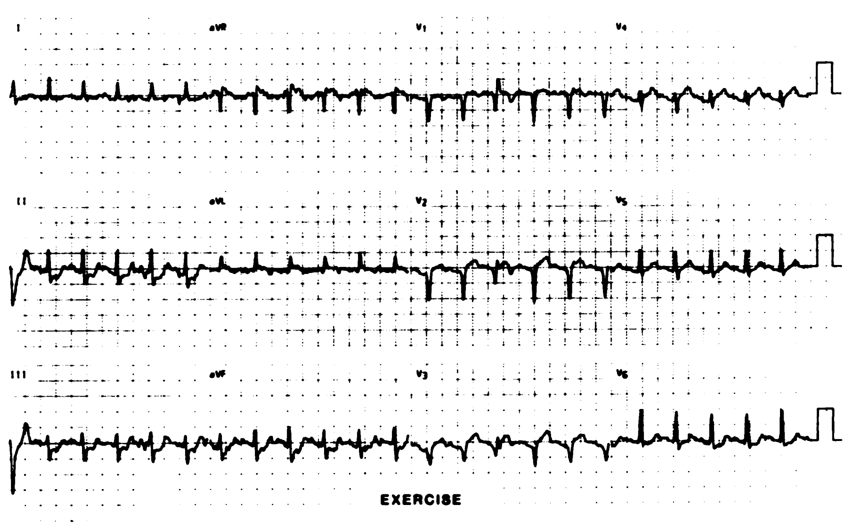

FIGURE 2
ECG recorded at peak exercise showing 1–1.5 mm S-T depression in II III aVF and 0.5 mm S-T depression in V6 suggesting ischemia in an area remote from the infarction.

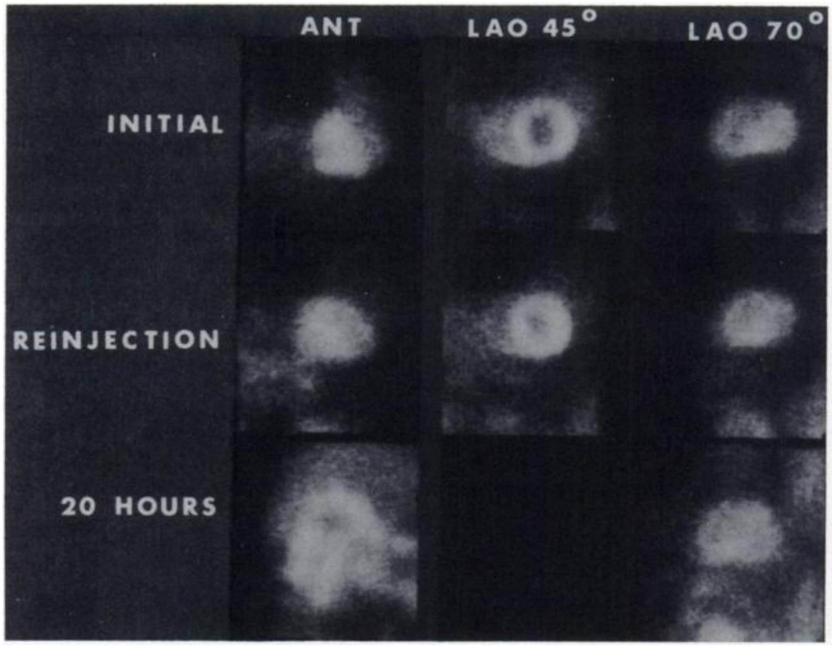

FIGURE 3
Thallium-201 myocardial scintigraphy (before PTCA). The comparison between the initial (stress) images and images collected after re-injection shows a reversible dilation of the left ventricle and increased lung uptake. There is a large ^{201}Tl defect involving the antero-lateral, anterior, and apical segments with minimal improvement after re-injection. The images collected 20 hr after re-injection (bottom) show further improvement on the anterior and antero-lateral segments compared to the images after re-injection.

question of the best method to detect residual ischemic viable myocardium after acute myocardial infarction.

Thallium-201 Myocardial Scintigraphy: Different Approaches

At present ^{201}Tl myocardial scintigraphy is performed, in the majority of institutions, according to the stress/redistribution approach introduced by Pohost et al. in 1977 (*15*) where, after a single injection of ^{201}Tl at peak exercise, two sets of images are collected: the initial after exercise and the delayed, 3–4 hr later. A reversible abnormality between the initial and delayed images is considered ischemia while a persistent defect is considered as scar. With the stress/redistribution approach two different phenomena are studied: perfusion with the initial images (*16*); the potassium pool within the myocardium, as an indication of myocardial viability, with the delayed images (*15*). This approach simplified the original method for ^{201}Tl scintigraphy, which was done with two separate injections, the first at peak exercise and the second, at rest, after an interval of several days. Ritchie (*17*) compared stress/4–5 hr redistribution with rest injection, given 1 wk later, in 41 patients. In 37% of them, the defect size on the redistribution images was larger than on the rest images and 7% of fixed defects "filled in" after the rest injection. Similar findings were reported by Blood (*18*): in 16/87 patients, defects were present in the redistribution scan but not in the rest study. Ritchie concluded that the "extent or presence of prior myocardial infarc-

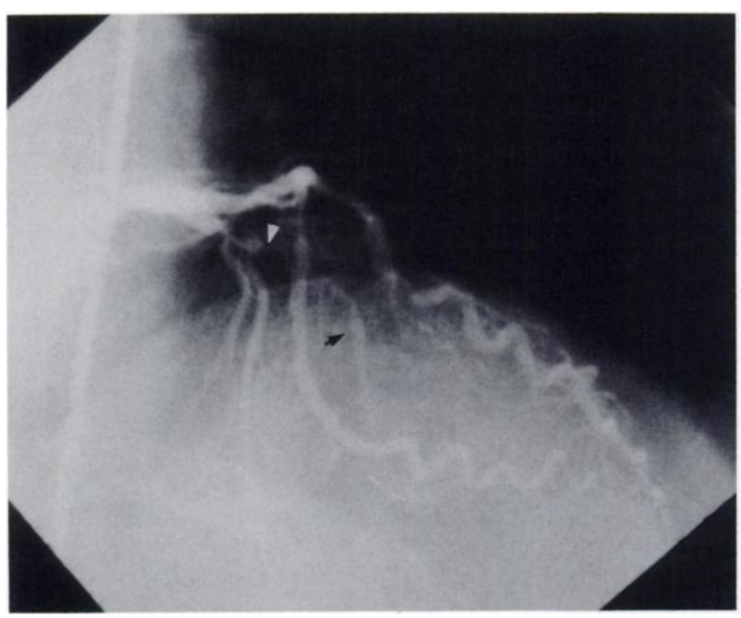

FIGURE 4
Left coronary angiogram (before PTCA), which shows near total occlusion of the LAD (white arrow) after two septal branches with visualization of the middle segment of the artery (black arrow).

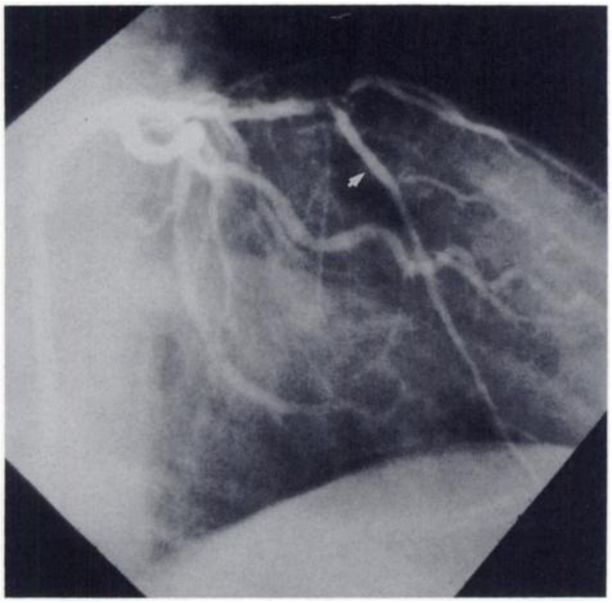

FIGURE 5
Left coronary angiogram (after PTCA), performed in a slightly different projection, which shows a patent LAD (arrow) and a severe stenosis in the diagonal artery adjacent to the previous LAD sub-total occlusion. There is also a 50% stenosis of the marginal branch of left Cx.

tion is often overestimated by the redistribution technique and, especially if ^{201}Tl scintigraphy is performed to assess myocardial viability, a rest image should be done." However, in spite of this, the single injection approach has been preferred for its simplicity and is still widely used.

Recently, Gibson reported that after by-pass surgery normal thallium uptake was demonstrated in 45% of persistent defects on the 4-hr delayed images (*19*). Liu et al. reported that 75% of fixed defects detected in patients before angioplasty of their single vessel LAD lesion, improved or became normal after PTCA (*20*).

Furthermore Gutman et al. (*21*) reported that the time to complete redistribution after stress injection appeared related to the severity of the stenosis in the coronary artery supplying the defect. In this study, 21% of ^{201}Tl defects, persistent after 4 hr, redistributed after 18–24 hr.

Based on this observation, they introduced the 24-hr ^{201}Tl delayed imaging as a more accurate method to detect viable myocardium. Further confirmation of these observations have been provided by studies performed with positron emission tomography (PET). Shelbert and coworkers reported that 47% of fixed defects showed significant uptake of ^{18}Fluorodeoxyglucose as evidence of viable myocardium (*22*). Similar results were reported by Tamaki et al. (*23*).

All these observations emphasize the limits of stress/3–4-hr redistribution ^{201}Tl myocardial scintigraphy for detecting viable ischemic myocardium.

Thallium-201 Re-injection After 4-Hr Delayed Images

On the basis of these observations suggesting that a dual injection approach could be more sensitive to detect ischemia, Rocco et al. recently described a method of ^{201}Tl re-injection (*24*) using a second, smaller, dose of 37 MBq (1 mCi) of ^{201}Tl injected at rest (re-injection) immediately after the redistribution images instead of several days later as in the early seventies. In this fashion, instead of comparing flow-related images (initial) to redistribution images (delayed), two different flow-related images were compared reflecting different conditions of flow (at peak exercise and at rest). Rocco et al. studied a group of 41 patients selected on the basis of fixed ^{201}Tl defects on 3-hr delayed images and reported that 30% of fixed defects "filled in" after re-injection. This percentage increased to 49% if a higher risk subgroup of these patients, undergoing coronary angiography, was analyzed. Other studies have been performed that confirmed the superiority of the re-injection technique compared with the single injection stress/redistribution imaging (*25–27*).

In 37 patients selected on the basis of recent myocardial infarction, suspected or known residual ischemia and one or more fixed defects on 3-hr delayed images, we found that 40% of fixed defects "filled-in" after re-injection (*25*). This percentage increased to 71% in a group of patients undergoing revascularization studied by Dilsizian et al. (*26*). It is noteworthy that all of them had normal ^{201}Tl uptake and improved wall motion after revascularization. A comparison between 24-hr delayed imaging and re-injection was done by Kayden et al., who re-injected patients after their 24-hr delayed images (*27*). They reported that 37% of views with fixed defects on the 24-hr images showed significant or total reversibility after re-injection.

These results are consistent with previous data of Kiat et al. (*28*) which demonstrated that 37% of fixed defects which did not show late reversibility on 24-hr delayed images improved after revascularization. These data suggest that, even if the 24-hr delayed imaging increases the ability to detect viable myocardium, it is possible that nonreversible defects on 24-hr imaging may actually be viable. Furthermore, these images are sometimes difficult to interpret because of poor image quality due to the low residual content of ^{201}Tl within the myocardium.

A comparison between ^{201}Tl re-injection and ^{18}Fluorodeoxyglucose study, by PET, was done by Bonow et al. in patients with coronary artery disease and left ventricular dysfunction. They reported that ^{201}Tl re-injection identified 54% of viable myocardial segments detected by PET (*29*). Moreover, for the defects with more than 50% reduction of ^{201}Tl uptake, myocardial viability was detected basically in the same number of segments by both PET and ^{201}Tl re-injection.

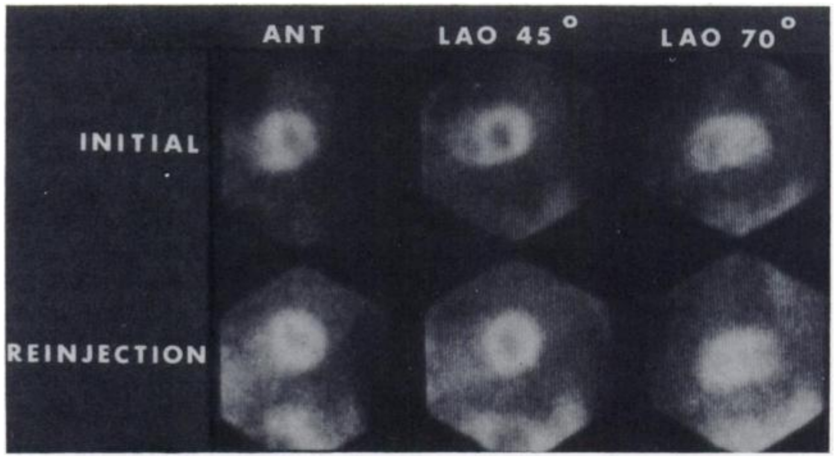

FIGURE 6
Exercise ^{201}Tl scintigraphy (after PTCA). There is normal lung uptake and no left ventricular cavity dilation; moderate, reversible defects in the antero-apical and septal segments. Contrary to the thallium scan performed before PTCA, these normalize competely after re-injection.

(Bonow RO, *personal communication*, 1990) However, even though ^{201}Tl re-injection is useful for detection of viable jeopardized myocardium and is probably superior to 24-hr delayed imaging, in some cases it may fail to identify ischemia. In this patient, the lesion remained basically fixed following re-injection and only the images taken 20 hr after rest re-injection identified a significant amount of viable jeopardized myocardium.

This is consistent with the results of clinical (*30–31*) and experimental studies (*32*), which reported that ^{201}Tl defects after rest injection may disappear several hours later when associated with severe coronary artery stenosis with persistent reduction of flow at rest.

These observations have clinical implications for the management of residual stenosis of an infarct-related coronary artery. Some investigators recommend early revascularization, while others prefer a conservative approach with antiplatelet or anticoagulant drugs (*33*, *34*). The results of TIMI-IIB have demonstrated, at one year follow-up, no difference in cumulative mortality (6.9% versus 7.5%) and myocardial infarction (8.9% versus 9.5%) for patients treated with angioplasty and with a conservative approach, respectively (*35*). The most important factor that may orient the decision towards one of these two choices is the detection of substantial amount of residual ischemia (*36*). Particularly, detection of rest ischemia, as in our patient, may identify a group of patients at higher risk for whom PTCA should be recommended if indicated (*37*). In a considerable number of cases, residual ischemic viable myocardium may or may not be detected depending on the methodology used for ^{201}Tl scintigraphy. In the case discussed here, this was clearly detected only by additional imaging performed 24 hr after re-injection. To prove these findings, a thallium stress test and a gated blood-pool scan were scheduled three months after PTCA.

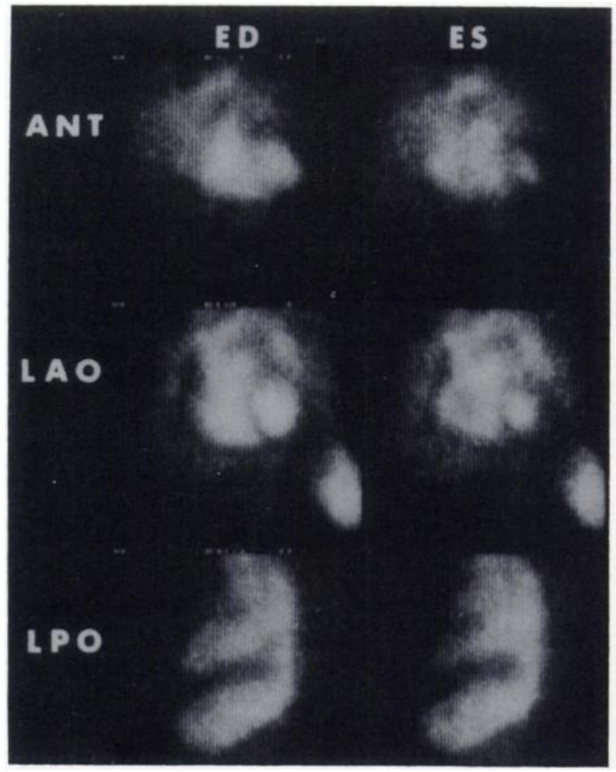

FIGURE 7
Gated blood-pool scan (after PTCA), performed on anterior (ANT), left anterior oblique 45° (LAO) and left posterior oblique 30° (LPO) views which show normal global and regional left ventricular wall motion in all views.

Follow-Up

The patient remained free of symptoms after PTCA and, three months later, a second exercise ^{201}Tl scintigraphy was performed on beta-blockers, calcium-blockers, and nitrates. The patient exercised, according to the standard Bruce protocol, for 10 min and 30 sec, achieving a peak heart rate of 149 (93% of predicted maximum heart rate). The double product was 23,840. The test was discontinued because of leg fatigue. The ECG was negative for ischemic changes and arrhythmias. Thallium-201 myocardial scintigraphy, performed with the re-injection protocol, did not show evidence of increased lung uptake nor of cavity dilation on stress images. There were moderate reversible defects in the anteroapical and septal segments that, contrary to the ^{201}Tl scan performed before PTCA, normalized completely after re-injection (Fig. 6).

The following day a gated blood-pool scan was performed, which showed normal global and regional left ventricular wall-motion with an ejection fraction of 56% (Fig. 7). It is noteworthy that even the apex, which was akinetic to dyskinetic on the echocardiogram performed during hospitalization, had normal wall motion. This confirmed previous observations (*38–41*), reporting that even severe wall motion abnormalities may disappear after reperfusion when related to a chronic reduction of flow at rest.

CONCLUSION

This case and references (*24–27,29*) show that ^{201}Tl re-injection is superior to single injection to detect ischemia and myocardial viability. However, even ^{201}Tl re-injection may fail to identify the total extent of ischemic viable myocardium and delayed images may be required. Detection of this myocardium is very important because, as in this case, function could be completely restored after revascularization.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr. Kenneth A. McKusick for his review of the manuscript and his suggestions. They also thank Mr. Frank Maltais and John Hergenrotter for their technical assistance.

REFERENCES

1. Gibson RS, Watson DD, Craddock GB, et al. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. *Circulation* 1983; 68:321–336.
2. Gibson RS, Beller GA, Gheorghiade M, et al. The prevalence and clinical significance of residual myocardial ischemia 2 weeks after uncomplicated non-Q wave infarction: a prospective natural history study. *Circulation* 1986; 73:1186–1198.
3. Boden WE, Gibson RS, Kleiger RE, et al. Importance of early recurrent ischemia on one-year survival after non-Q-wave acute myocardial infarction. *Am J Cardiol* 1989; 64:799–801.
4. Schuster EH, Bulkley BH. Early post-infarction angina: ischemia at a distance and ischemia in the infarct zone. *N Engl J Med* 1981; 305:1101–1105.
5. Gimple LW, Hutter AM Jr, Guiney TE, Boucher CA. Prognostic utility of pre-discharge dipyridamole-thallium imaging compared to pre-discharge submaximal exercise electrocardiography and maximal exercise thallium imaging after uncomplicated acute myocardial infarction. *Am J Cardiol* 1989; 64:1243–1248.
6. Brown KA, O'Meara J, Chambers CE, Plante DA. Ability of dipyridamole thallium-201 imaging one to four days after acute myocardial infarction to predict in-hospital and late recurrent myocardial ischemic events. *Am J Cardiol* 1990; 65:160–167.
7. Wilson WW, Gibson RS, Nygaard TW, et al. Acute myocardial infarction associated with single vessel coronary artery disease: an analysis of clinical outcome and the prognostic importance of vessel patency and residual ischemic myocardium. *J Am Coll Cardiol* 1988; 11:223–234.
8. Pepine CJ: Silent myocardial ischemia: definition, magnitude and scope of the problem. *Cardiol Clin* 1986; 4:557–581.
9. Epstein SE, Quyyumi AA, Bonow RO. Myocardial ischemia silent or symptomatic. *N Engl J Med* 1988; 1038–1043.
10. Bailey IK, Griffith LSC, Rouleau J, Strauss HW, Pitt B. Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* 1977; 55:79–87.
11. Pohost GM, Alpert NM, Ingwall JS, Strauss HW. Thallium-201 redistribution: mechanism and clinical utility. *Semin Nucl Med* 1980; 10:70–93.
12. Guiney TE, Pohost GM, Beller GA, et al. Differentiating false-positive from true positive stress test by single dose Tl-201 stress scanning. *Am J Cardiol* 1977; 39:321.
13. Ritchie JL, Zaret BL, Strauss HW, et al. Myocardial imaging with thallium-201: a multicenter study in patients with angina pectoris or acute myocardial infarction. *Am J Cardiol* 1978; 42:345.
14. Ritchie JL, Trobaugh GB, Hamilton GW, et al. Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* 1977; 56:66–71.
15. Pohost GM, Zir LM, Moore RH, McKusick KA, Guiney TE, Beller GA. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 1977; 55:294–302.
16. Strauss HW, Harrison K, Langan JK, Lebowitz E, Pitt B. Thallium-201 for myocardial imaging. Relation of thallium-201 to regional myocardial perfusion. *Circulation* 1975; 51:641–645.
17. Ritchie JL, Albro PC, Caldwell JH, Trobaugh GB, Hamilton GW. Thallium-201 myocardial imaging: a comparison of the redistribution and rest images. *J Nucl Med* 1979; 20:477–483.
18. Blood DK, McCarthy DM, Sciacca RR, Cannon PJ. Comparison of single-dose and double-dose thallium-201 myocardial perfusion scintigraphy for the detection of coronary artery disease and prior myocardial infarction. *Circulation* 1978; 58:777–788.
19. Gibson RS, Watson DD, Taylor GJ, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. *J Am Coll Cardiol* 1983; 1:804–815.
20. Liu P, Kiess MC, Okada RD, et al. The persistent defect on exercise Tl-201 scintigraphy and its fate after myocardial revascularization: does it represent scar or ischemia? *Am Heart J* 1985; 110:996.
21. Gutman J, Berman DS, Freeman M, et al. Time to complete redistribution of thallium-201 in exercise myocardial scintigraphy: relationship to the degree of coronary artery stenosis. *Am Heart J* 1983; 989–995.
22. Brunken RC, Kottou S, Nienaber CA, et al. PET detection of viable tissue in myocardial segments with persistent defects at Tl-201 SPECT. *Radiology* 1989; 172:65–73.
23. Tamaki N, Yonekura Y, Yamashita K, et al. Relation of left ventricular perfusion and wall motion with metabolic activity in persistent defects on thallium-201 tomography in healed myocardial infarction. *Am J Cardiol* 1988; 62:201–208.
24. Rocco T, Dilsizian V, Maltais F, Strauss HW, Boucher CA, McKusick KA. Thallium-201 re-injection after delayed imaging demonstrate fill-in to regions with "fixed defects" [Abstract]. *J Nucl Med* 1988; 29:769.
25. Pieri PL, McKusick KA, Tisselli A, Acito P, Strauss HW. Detection of ischemia after myocardial infarction: comparison of thallium-201 re-injection vs. redistribution in a high

risk population [Abstract]. *J Nucl Med* 1990; 31:743.
26. Dilsizian V, Swin J, Dextras R, Almagor Y, Bonow R. Prediction of viable myocardium by thallium-201 re-injection at rest after stress-redistribution imaging: a pre- and post-revascularization study [Abstract]. *Circulation* 1989; 80:II-367.
27. Kayden DS, Sigal SL, Soufer R, Zaret BL, Wackers FJ. 24-hour planar thallium-201 delayed imaging: is re-injection necessary? [Abstract]. *Circulation* 1989; 80:II-377.
28. Kiat H, Berman D, Maddahi J, Rozanski A. Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability. *J Am Coll Cardiol* 1988; 12:1456-1463.
29. Bonow RC, Bacharach SL, Cuocolo A, Dilsizian V. Myocardial viability in coronary artery disease and left ventricular dysfunction: thallium-201 re-injection vs. fluorodeoxyglucose [Abstract]. *Circulation* 1989; 80:II-377.
30. Gewirtz H, Beller GA, Strauss HW, et al. Transient defects of resting thallium scans in patients with coronary artery disease. *Circulation* 1979; 59:707-713.
31. Wackers FJ, Lie KI, Liem KL, et al. Thallium-201 scintigraphy in unstable angina pectoris. *Circulation* 1978; 57:738.
32. Pohost GM, Okada RD, O'Keefe DD, et al. Thallium redistribution in dogs with severe coronary artery stenosis of fixed caliber. *Circ Res* 1981; 48:439-446.
33. Chandler J, Nath H, Rogers W. Heparin and antiplatelet drugs following streptokinase in acute myocardial infarction: what are their effects on vessel patency? [Abstract]. *J Am Coll Cardiol* 1984; 3:600.
34. Swan HJC. Thrombolysis in acute MI: treatment of the underlying coronary artery disease [Editorial]. *Circulation* 1982; 66:914-16.
35. Williams DO, Braunwald E, Knatterud G, et al. The thrombolysis in myocardial infarction (TIMI) trial: outcome at one year in patients randomized to either invasive or conservative management [Abstract]. *Circulation* 1989; 80(suppl II):II-519.
36. Weiss TA, Maddahi J, Shah PK, et al. Exercise-induced ischemia in the streptokinase-reperfused myocardium: relationship to extent of salvaged myocardium and degree of residual coronary stenosis. *Am Heart J* 1989; 118:9-16.
37. Berman DS, Kiat H, Maddahi J, Shah PK. Radionuclide imaging of myocardial perfusion and viability in assessment of acute myocardial infarction. *Am J Cardiol* 1989; 64:9B-16B.
38. Bodenheimer MM, Banka VS, Fooshee C, Hermann GA, Helfant RH. Relationship between regional myocardial perfusion and the presence, severity and reversibility of asynergy in patients with coronary heart disease. *Circulation* 1978; 58:789-795.
39. Breisblatt WM, Brown DL, Weiland FL. Reversibility of longstanding left ventricular aneurysm predicted by Tl-201 imaging. *J Am Coll Cardiol* 1986; 7:1162-1166.
40. Brundage BH, Massie BM, Botvinick EH. Improved left ventricular function after successful surgical revascularization. *J Am Coll Cardiol* 1984; 3:902-908.
41. Braunwald E, Rutherford MB. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium." *J Am Coll Cardiol* 1986; 8:1467-1470.