The Role of Stress Redistribution Thallium-201 Myocardial Perfusion Imaging in Evaluating Coronary Artery Disease and Perioperative Risk

Kenneth A. Brown

Cardiology Unit, Department of Medicine, University of Vermont College of Medicine, Burlington, Vermont

Thallium-201 myocardial perfusion imaging can provide prognostic information on the risk of future cardiac events in patients with known or suspected chronic coronary artery disease (CAD). In addition, patients at risk for cardiac events during surgery can be risk-stratified preoperatively with myocardial perfusion studies. The presence or absence of transient defects on perfusion images is a strong predictor of subsequent cardiac events. The extent of transient defects, which reflects the extent of jeopardized yet viable myocardium, is useful to predict patient outcome. Myocardial perfusion imaging with ^{201}Tl adds significant prognostic value to standard ECG and clinical data.

Key Words: myocardial perfusion imaging; thallium-201; coronary artery disease; perioperative risk; stress redistribution

J Nucl Med 1994; 35:703–706

Clinical studies have shown that ^{201}Tl myocardial perfusion imaging is a powerful predictor of cardiac events for a wide spectrum of patients with known or suspected coronary artery disease (CAD). In addition, studies have found myocardial perfusion images to be of value for determining cardiac risk in patients undergoing noncardiac surgery.

KNOWN OR SUSPECTED CHRONIC CAD

The two most consistent predictors of cardiac events among ^{201}Tl myocardial perfusion imaging variables in patients with known or suspected CAD have been: (1) the presence and extent of transient (reversible) defects as a marker of jeopardized, viable myocardium (*1–8*) and (2) increased lung uptake as an index of left-ventricular dysfunction (*9,10*).

Received Dec. 8, 1993; revision accepted Dec. 21, 1993.
This paper was presented in part at the Annual Meeting of the Society of Nuclear Medicine on June 9, 1993, as part of a Continuing Medical Education Seminar organized by the Cardiovascular Council.
For correspondence or reprints contact: Kenneth A. Brown, MD, Cardiology Unit, Department of Medicine, University of Vermont College of Medicine, Medical Center Hospital of Vermont, Burlington, VT 05401.

Transient Defects

In 1983, our group analyzed the predictive value of myocardial perfusion imaging in relation to other known predictors (*2*). We studied 100 patients with chest pain but no history of myocardial infarction (MI). Over a 4-yr follow-up, patient outcomes were correlated with several factors, including clinical data, exercise ^{201}Tl results, exercise electrocardiogram (ECG) results and catheterization data. The predictive values of these variables were compared with logistic regression analysis.

The only significant predictor of cardiac death or MI was the number of ^{201}Tl myocardial segments with transient defects (Fig. 1). The risk of subsequent cardiac events increased as the number of transient defects increased, indicating that the extent, more than simply the presence, of jeopardized, viable myocardium was the most important predictor of outcome. Other clinical studies have now confirmed and expanded these observations, showing a direct relation between the presence and extent of jeopardized, viable myocardium and cardiac death or MI (*3–5,7*).

The prognostic value of transient defects is maintained when dipyridamole is used as a pharmacologic substitute for exercise (*6,7*). The report from Younis et al. (*6*) is representative of these studies. Patients with normal dipyridamole-thallium scans or with fixed defects had benign outcomes. However, patients with transient defects had an increased risk of cardiac death or MI, and those with a combination of transient and fixed defects had the worst outcomes.

Lung Uptake

Increased lung uptake of ^{201}Tl during exercise myocardial perfusion imaging is another marker of adverse outcome in patients with known or suspected CAD. Two studies, using multivariate analysis, found that increased lung uptake was the best predictor of cardiac events among clinical, ^{201}Tl and exercise data (*9,10*). The prognostic value of ^{201}Tl lung uptake presumably reflects its relation to left ventricular dysfunction and extensive CAD (*11–14*).

Normal Thallium-201 Perfusion Studies

An important corollary to these observations is that a normal ^{201}Tl study predicts a benign outcome, even in the

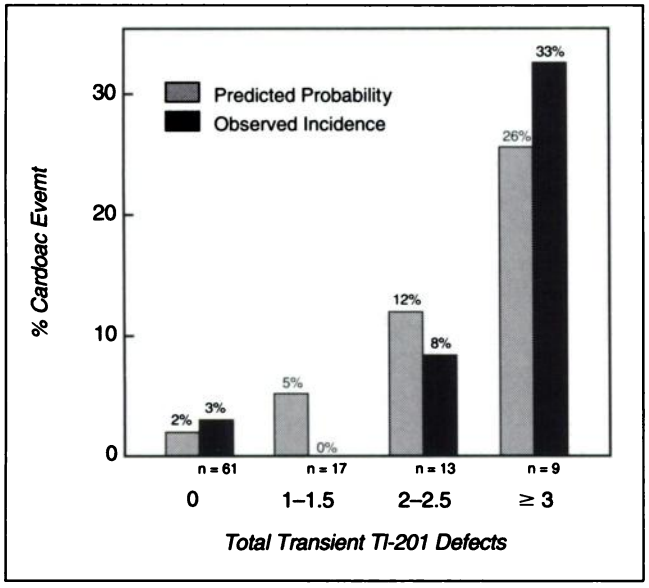

FIGURE 1. Probability of a cardiac event (cardiac death or MI) as a function of the number of myocardial segments with transient ^{201}Tl defects in 100 patients without prior MI. Reprinted with permission from the Annals of Internal Medicine, 1989;110:859.

setting of angiographic CAD (*1*). Such a normal ^{201}Tl result can be valuable in making patient management decisions. A review of 16 clinical trials, comprising more than 3500 patients, indicates that the annual rate of cardiac death or MI in CAD patients with normal ^{201}Tl perfusion studies is <1% (*1*).

Patients with angiographic evidence of CAD and normal ^{201}Tl perfusion studies could present a clinical dilemma: since both ^{201}Tl images and angiographic data have important prognostic value, which should one trust?

In a clinical report, the outcomes of 75 patients with normal myocardial perfusion scans and CAD documented by catheterization (approximately half with multivessel disease) were compared with 101 patients with normal ^{201}Tl scans and no evidence of CAD (*15*). Over a 2-yr follow-up period, both patient groups had very benign outcomes. The annual rate of cardiac death or MI for the patients with angiographic evidence of CAD was <1%, not significantly different than the cardiac event rate for the patients with no evidence of CAD.

Given such a very low event rate, it would be difficult to improve prognosis with any kind of revascularization intervention in the vast majority of such patients.

Incremental Value

An important question to ask is whether ^{201}Tl myocardial perfusion imaging adds significant incremental predictive value to simpler, and less expensive, clinical and ECG data. Pollack et al. (*16*) showed that clinical data alone are not a good predictor of outcome in patients with CAD (Fig. 2). When clinical data are combined with stress ECG results, the ability to predict cardiac events increases significantly. Adding ^{201}Tl imaging to ECG and clinical data almost doubles the predictive value. When catheterization data are added, however, there is very little improvement in predictive value. In addition, there is no significant difference in predictive value between ^{201}Tl and clinical data versus catheterization and clinical data.

The important conclusion from this and several other studies (*1*) is that ^{201}Tl myocardial perfusion imaging has significant incremental prognostic value, above and beyond clinical and stress ECG results. Invasive angiographic data, on the other hand, do not appear to add any significant predictive value beyond myocardial perfusion imaging.

PERIOPERATIVE CARDIAC EVENTS

Because patients with peripheral vascular disease have a high prevalence of underlying—often asymptomatic—CAD, perioperative ischemic cardiac events are an important concern for such patients undergoing vascular surgery. Therefore, it is logical to apply risk stratification using myocardial perfusion imaging to patients scheduled for peripheral vascular surgery.

In 1985, Boucher and colleagues examined a group of 48 patients who underwent dipyridamole-thallium studies before vascular surgery (*17*). In patients whose ^{201}Tl scans showed transient defects, half experienced perioperative cardiac events. In contrast, no patient with a normal study or only fixed defects had a perioperative cardiac event. Thus, test results suggested that myocardial perfusion imaging can provide important discriminatory value for patients at risk of perioperative cardiac events. Subsequently, a number of studies have now confirmed and expanded these observations (*18–25*).

In 1987, Leppo et al. took the next sequential step by using multivariate analysis to compare the relative predictive value for dipyridamole-thallium imaging and other variables, including clinical data, ECG results, and ST-segment depression, in a series of 89 patients undergoing peripheral vascular surgery (*18*). They found that the only significant multivariate predictor of cardiac death or MI was the presence of transient defects on myocardial perfu-

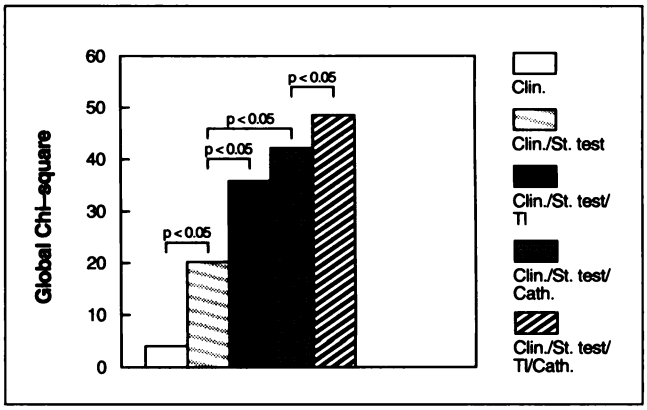

FIGURE 2. Bar graphs illustrate prognostic value (depicted by x^2 value on y-axis) of tests performed in hierarchical order. Reprinted with permission from the American Heart Association (*Circulation* 1992;85:237).

sion scans. In patients who had transient defects, about 33% experienced perioperative events compared with only 2% of patients without transient defects.

Clinical Risk Stratification

Eagle et al. examined whether clinical risk factors could be used to identify a subgroup of patients who would be most likely to benefit from the expense and inconvenience of performing myocardial perfusion imaging (*19*). Among 61 patients undergoing peripheral vascular surgery and preoperative dipyridamole-thallium imaging, 32 had a clinical risk factor, including a history of angina, MI, congestive heart failure, diabetes mellitus or Q-waves on ECG. Among patients with clinical risk factors, about half had transient defects on their ^{201}Tl images and about half of those patients experienced a perioperative cardiac event; none of the patients in this group without transient defects had a perioperative event. In patients without risk factors, only approximately 10% had transient defects on their ^{201}Tl images. These results suggested that clinical risk factors may be useful for selecting patients most likely to benefit from preoperative evaluation with dipyridamole-thallium imaging.

More recently, Eagle and colleagues examined 200 patients who underwent planned noncardiac vascular surgery, in which 30 patients experienced a perioperative cardiac event, including 15 cases with hard end-points of cardiac death or MI (*21*). Outcomes were related to clinical data and dipyridamole-thallium perfusion imaging results. Univariate analysis showed that predictors of cardiac death or MI included angina, heart failure, diabetes mellitus, age and Q-waves on ECG. The significant univariate predictors from ^{201}Tl imaging were ST-segment depression and the presence of transient defects. Using multivariate regression analysis to compare the relative predictive value of clinical and imaging variables, the authors found that ^{201}Tl reversibility had the highest predictive value of perioperative cardiac events.

The investigators devised an algorithm (Fig. 3) to determine which patients to select for risk stratification by myocardial perfusion imaging. Patients with no clinical risk factors had a low rate (3%) of perioperative cardiac events, whereas patients with three or more clinical risk factors had a high rate (50%) of perioperative cardiac events. Such patients probably do not need to be risk-stratified further with myocardial perfusion imaging. Patients in the middle group (which accounted for approximately 60% of the total), with one or two clinical risk factors, had an intermediate risk and appeared to benefit most from risk-stratification. In this group, patients with transient defects on ^{201}Tl images had a 30% risk for perioperative cardiac events, a ten-fold increase compared to patients without transient defects who had only a 3% risk.

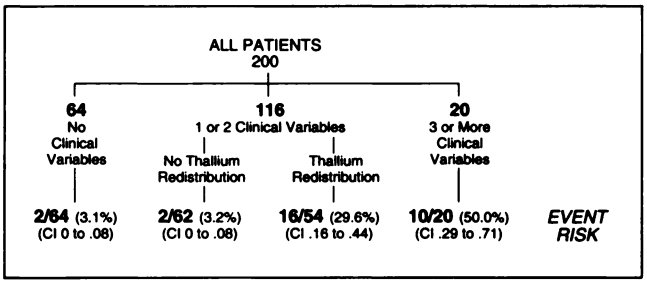

FIGURE 3. Flow-chart relating perioperative cardiac risk, clinical risk factors and presence or absence of ^{201}Tl redistribution. Reprinted with permission from the *Annals of Internal Medicine*, 1989; 110:859.

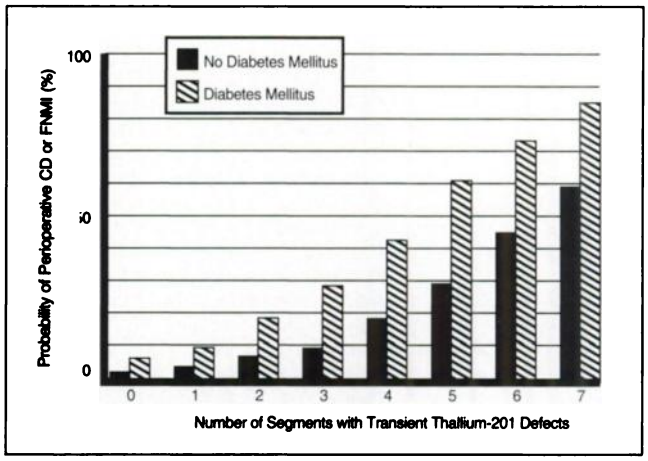

FIGURE 4. Risk of perioperative cardiac death or MI as a function of the number of myocardial segments with transient defects and history of diabetes mellitus. Reprinted with permission from the American College of Cardiology (*Journal of Cardiology*, 1993;21: 325).

Presence and Extent of Transient Defects

Beyond the simple presence or absence of transient defects, the extent of jeopardized, viable tissue has an important impact on perioperative risk. In a study of 231 patients who underwent noncardiac surgery after dipyridamole-thallium imaging, Brown and Rowen compared the ability of clinical, ECG and imaging variables to predict perioperative cardiac death or MI (*26*). Using multivariate analysis, the only two significant predictors of perioperative cardiac events were: (1) the number of myocardial segments with transient defects and (2) a history of diabetes mellitus.

As the number of myocardial segments with transient defects increases, reflecting the extent of jeopardized, viable myocardium, the probability of a perioperative cardiac event increases (Fig. 4). Furthermore, for any given number of segments with transient defects, a history of diabetes mellitus increases the perioperative risk significantly.

CONCLUSION

Myocardial perfusion imaging with ^{201}Tl is a noninvasive, routinely available procedure that provides valuable prognostic information regarding the risk of future cardiac events in patients with known or suspected CAD. Furthermore, myocardial perfusion images can provide important

information regarding perioperative cardiac risk in patients scheduled for noncardiac surgery.

REFERENCES

1. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. *Circulation* 1991;83:363–381.
2. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. *J Am Coll Cardiol* 1983;1:994–1001.
3. Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial reperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1986;7:464–471.
4. Staniloff HM, Forrester JS, Berman DS, Swan HJC. Prediction of death, myocardial infarction, and worsening chest pain using thallium scintigraphy and exercise electrocardiography. *J Nucl Med* 1986;27:1842–1848.
5. Kaul S, Lilly DR, Gasho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain. *Circulation* 1988;77:745–748.
6. Younis LT, Byers S, Shaw L, Barth G, Goodgold H, Chaitman BR. Prognostic importance of silent myocardial ischemia detected by intravenous dipyridamole-thallium myocardial imaging in asymptomatic patients with coronary artery disease. *J Am Coll Cardiol* 1989;14:1635–1641.
7. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole-thallium scintigraphy for evaluation of ischemic heart disease. *J Am Coll Cardiol* 1990;15:109–116.
8. Stratman HG, Mark AL, Walter KE, Williams GA. Prognostic value of atrial pacing and thallium-201 scintigraphy in patients with stable chest pain. *Am J Cardiol* 1989;64:985–990.
9. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. *N Engl J Med* 1987;317:1485–1489.
10. Kaul S, Finkelstein DM, Homma S, Leavitt M, Okada RD, Boucher CA. Superiority of quantitative exercise thallium-201 variables in determining long-term prognosis in ambulatory patients with chest pain: a comparison with cardiac catheterization. *J Am Coll Cardiol* 1988;12:25–34.
11. Boucher CA, Zin LM, Beller GA, et al. Increased lung uptake of thallium-201 during exercise myocardial imaging: clinical, hemodynamic and angiographic implications in patients with coronary artery disease. *Am J Cardiol* 1980;46:189–196.
12. Brown KA, Boucher CA, Okada RD, Strauss HW, Pohost GM. Quantification of pulmonary thallium-201 activity following upright exercise in normal subjects: importance of peak heart rate and propranolol usage in defining normal values. *Am J Cardiol* 1984;53:1678–1682.
13. Gibson RS, Watson DD, Carabello BA, Holt NA, Beller GA. Clinical implications of increased lung uptake of thallium-201 during exercise scintigraphy 2 weeks after myocardial infarction. *Am J Cardiol* 1982;49:1586–1593.
14. Levy R, Rozanski A, Berman DS, et al. Analysis of the degree of pulmonary thallium washout after exercise in patients with coronary artery disease. *J Am Coll Cardiol* 1983;2:719–728.
15. Brown KA, Rowen M. Prognostic value of a normal exercise myocardial perfusion imaging study in patients with angiographically significant coronary artery disease. *Am J Cardiol* 1993;71:865–867.
16. Pollack SW, Abbott RD, Boucher CA, et al. Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease. *Circulation* 1992;85:237–248.
17. Boucher CA, Brewster DC, Darling RC, Okada RD, Strauss HW, Pohost GM. Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med* 1985;312:389–394.
18. Leppo J, Plaja J, Gionet M, Tumolo J, Paraskos JA, Cutler BS. Noninvasive evaluation of cardiac risk before elective vascular surgery. *J Am Coll Cardiol* 1987;9:269–276.
19. Eagle KA, Singer DE, Brewster DC, Darling RC, Mulley AG, Boucher CA. Dipyridamole-thallium scanning in patients undergoing vascular surgery: optimizing preoperative evaluation of cardiac risk. *JAMA* 1987;257:2185–2189.
20. Sachs RN, Tellier P, Larmignat P, et al. Assessment of dipyridamole-thallium-201 myocardial scintigraphy of coronary risk before peripheral vascular surgery. *Surgery* 1988;103:584–587.
21. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* 1989;110:859–866.
22. Lette J, Waters D, Lassonde J, et al. Postoperative myocardial infarction and cardiac death. *Ann Surg* 1990;211:84–90.
23. Lane SE, Lewis SM, Pippin JJ, et al. Predictive value of quantitative dipyridamole-thallium scintigraphy in assessing cardiovascular risk after vascular surgery in diabetes mellitus. *Am J Cardiol* 1989;64:1275–1239.
24. Lette J, Waters D, Lapointe J, et al. Usefulness of the severity and extent of reversible perfusion defects during thallium-dipyridamole imaging for cardiac risk assessment before noncardiac surgery. *Am J Cardiol* 1989;64:276–281.
25. Brown KA, Rimmer J, Haisch C. Noninvasive cardiac risk stratification of diabetic and nondiabetic uremic renal allograft candidates using dipyridamole-thallium-201 imaging and radionuclide ventriculography. *Am J Cardiol* 1989;64:1017–1021.
26. Brown KA, Rowen M. Extent of jeopardized viable myocardium determined by myocardial perfusion imaging best predicts perioperative cardiac events in patients undergoing non-cardiac surgery. *J Am Coll Cardiol* 1993;21:325–330.