Risk stratification of the normal perfusion scan: Does normal stress perfusion always mean very low risk?

Seth Dahlberg, MD, and Jeffrey Leppo, MD

See related articles, p 4 and 9

In the 1970s and 1980s several research groups studied the use of the coronary vasodilators adenosine and dipyridamole to generate hyperemic coronary flow in animals.[1-3] These researchers showed that vasodilators increase coronary flow 3 to 5 times above baseline in normally perfused myocardium and that creation of an experimental flow-limiting coronary stenosis prevents hyperemic flow in the stenotic territory. Further studies demonstrated that radiolabeled tracers such as thallium-201 could be used to image the flow heterogeneity between normal and abnormal territories noninvasively.[4] When specialized angioplasty guidewires later permitted the direct measurement of intracoronary flow or pressure during hyperemic flow in patients, impaired coronary flow reserve (CFR) was confirmed to show a high correlation with myocardial perfusion imaging (MPI) defects.[5,6]

CORONARY STEAL DURING VASODILATOR DIFFUSION

The development of coronary collaterals in the presence of severe stenoses provides important myocardial functional benefit by maintaining resting blood flow. However, experimental studies by Becker[7,8] showed that vasodilators can paradoxically cause ischemia in the territory of a significant coronary stenosis when the myocardium is dependent on collateral flow. Thus the term *coronary steal* was coined to describe the situation in which regional myocardial flow actually decreased below basal levels because of a vasodilator-induced fall in both arterial driving pressure and resistance in the conductance artery that supplies the collateral vessel flow. Additional experimental observations demonstrated that the subendocardial layer of the myocardium is the region that experiences this absolute decrease in blood flow because there is typically a much greater vasodilator capacity in the epicardium.[9] Therefore the endocardial-to-epicardial flow ratio, which is normally greater than 1, will typically decrease to less than 1 during vasodilator infusion, leading some investigators to call this a *relative coronary steal* phenomenon.

CLINICAL STUDIES OF CORONARY STEAL

Nishimura[10] showed that an ischemic electrocardiographic (ECG) response to adenosine infusion in patients with coronary disease and abnormal MPI had a high correlation with the presence of coronary collaterals. The development of quantitative blood flow studies with positron emission tomography further enhanced our ability to evaluate the relationship of coronary steal to collateral-dependent blood flow. Demer et al[11] showed a 15% relative decrease in regional myocardial tracer uptake in collateral-dependent myocardium with a vasodilator infusion. Akinboboye[12] measured regional myocardial blood flow with $^{13}NH_3$ (Nitrogen-13 ammonia) during dipyridamole infusion in 18 patients with multivessel coronary artery disease (CAD) and found evidence of coronary steal in 8. Ischemic ECG changes were significantly correlated with the presence of coronary steal. Although coronary steal in the presence of collaterals is one mechanism of ischemia during vasodilator infusion, ischemia may occur without an overall reduction in transmural flow. Araujo et al[13] found increased ^{18}FDG (Flourine-18 deoxyglucose) uptake during dipyridamole infusion in patients with single-vessel CAD and abnormal flow reserve. This evidence of ischemia occurred in patients both with and without collaterals, even without a reduction in transmural flow. This finding suggests that myocardial ischemia occurs in regions that have limited CFR, possibly due to a relative subendocardial steal, as discussed above. The complex relationship between vasodilators, coronary stenoses,

From Nuclear Medicine/Radiology Department and Cardiology/Medicine Department, University of Massachusetts Memorial Medical Center, Worcester, Mass.

Reprint requests: Jeffrey Leppo, MD, Nuclear Medicine/Radiology Department, University of Massachusetts Memorial Medical Center, 55 Lake Ave, Worcester, MA 01655; *jeffrey.leppo@umassmed.edu.*

J Nucl Cardiol 2003;10:87-91.

1071-3581/2003/$30.00 + 0
doi:10.1067/mnc.2003.6

collaterals, and CFR has also been assessed in intracoronary Doppler flow wire studies.[14]

Overall, these studies of regional coronary flow suggest that several physiologic mechanisms for ischemia with vasodilators are possible. One important implication is that myocardial segments (especially in the subendocardium) may experience an absolute decrease in blood flow that results in ischemic dysfunction that is not detected by imaging of regional transmural blood flow. It is also evident that an ischemic ECG response during vasodilator stress is often associated with multivessel coronary disease that has led to collateral development.

VASODILATOR INFUSIONS TO DETECT CAD AND RISK ASSESSMENT

Early clinical studies of MPI in combination with vasodilators assessed its diagnostic accuracy compared with coronary angiography. Despite issues of referral bias and evidence that catheterization was not a true "gold standard" for diagnosing CAD, coronary angiography remained a benchmark for comparison with other diagnostic techniques partly because it gave powerful prognostic information. Studies by Schulman et al[15] and other authors showed that the number of diseased coronary vessels predicted survival during long-term follow-up. Randomized studies such as the Veterans Administration Cooperative Study of Coronary Artery Surgery,[16] CASS,[17] and European Coronary Surgery trials[18] demonstrated that the effectiveness of medical treatment and benefit of coronary artery bypass surgery in patients with coronary disease could be predicted with coronary angiography.

Initial studies to assess the use of vasodilator MPI for prognosis in patients with CAD focused on the presence of thallium redistribution. The presence of Tl-201 redistribution after dipyridamole stress was shown to identify a high risk of cardiac death or myocardial infarction (CD/MI) in patients with recent myocardial infarction[19] and in patients undergoing vascular surgery.[20,21] Studies of perioperative risk assessment showed that clinical variables such as age, diabetes mellitus, and a history of coronary disease or congestive heart failure were independent risk factors for CD/MI. Ischemic ECG changes after adenosine or dipyridamole infusion also predicted an adverse outcome. These risk factors could be combined with MPI data, such as thallium redistribution, left ventricular cavity size, and thallium lung uptake, to give an improved overall multivariate assessment of risk.

With an additional important finding, Eagle et al[22] found that the patients at highest clinical risk remained at high risk even in the absence of thallium redistribution. In this study thallium redistribution was shown to stratify perioperative mortality in vascular surgery patients with 1 to 2 clinical risk factors, whereas the highest-risk patients with multiple clinical risk factors still had a high event rate even in the absence of thallium redistribution. The current American College of Cardiology/American Heart Association "Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery" supports the concept that MPI is most useful in risk-stratifying patients with intermediate predictors of risk rather than major predictors of high risk.[23]

The assessment of prognosis with MPI has been advanced by the development of single photon emission computed tomography (SPECT) imaging and quantitation of abnormal perfusion defect size. Many studies show a risk of CD/MI that is lowest in patients with normal MPI, moderate in those with mildly abnormal MPI, and highest in those with a large area of abnormal perfusion.[24-29] Patients with a normal exercise MPI have a combined rate of CD/MI of less than 1% per year, even in the presence of an abnormal stress electrocardiogram or coronary angiography that shows significant CAD.[30-32]

However, patients who undergo vasodilator stress testing cannot perform an exercise test, and the inability to perform an exercise test has been shown to identify patients at higher risk.[33] In a study of 10,407 patients treated with thrombolysis for myocardial infarction, the 6-month total mortality rate was 0.9% in patients with a normal maximal exercise test and 1.5% in patients with an abnormal maximal test, whereas it was markedly increased, at 7.1%, in those patients who could not perform exercise stress testing.[34] Patients with coronary disease who cannot exercise and who undergo vasodilator stress testing are a group at moderate to high pretest risk for CD/MI. Although normal vasodilator stress MPI predicts a relatively benign prognosis, the rate of CD/MI in this higher-risk group is 2 to 3 times that for patients with normal exercise MPI.[35-39]

In this issue of *Journal of Nuclear Cardiology*, studies by Abbott et al[40] and Klodas et al[41] address the prognosis of patients with normal MPI and ischemic ECG changes after vasodilator infusion. The patients studied by Abbott et al underwent adenosine stress followed predominantly by technetium-99m sestamibi SPECT imaging; some underwent planar imaging, and some were imaged with Tl-201 or Tc-99m tetrofosmin. The patients studied by Klodas et al underwent adenosine or dipyridamole stress followed by Tl-201 or Tc-99m sestamibi SPECT imaging. Both groups found similar results. The patients were predominantly elderly women with angina, diabetes, and other risk factors for CAD or established coronary heart disease. Although an ischemic ECG response to vasodilator stress with normal MPI was uncommon, occurring in 0.9% to 2% of

patients, these patients were found to be at increased risk for cardiac events. During a mean follow-up of 2 to 3 years, the rate of CD/MI was 4% to 5% per year. In contrast to this moderate to high event rate, Abbott et al[40] found age- and gender-matched patients with normal stress ECG and MPI to have a CD/MI rate of less than 1% per year. Approximately 20% to 25% of the patients with ischemic vasodilator stress electrocardiograms in these two studies underwent coronary angiography; most of these were found to have significant CAD, and many underwent late revascularization. Two questions raised by these studies are as follows: why was MPI normal despite significant CAD, and why was the prognosis of this subset of patients with normal MPI worse than expected?

The majority of these patients with an ischemic stress electrocardiogram had significant CAD that was not detected by MPI. Although most patients with severe multivessel or left main CAD have abnormal MPI, several studies have shown that 8% to 21% have normal imaging results.[42-46] Klodas et al[41] speculate that balanced ischemia might result in an ischemic stress electrocardiogram but normal MPI. It is also possible that diffusely abnormal CFR might cause a falsely normal perfusion scan. Sambuceti et al[47] used positron emission tomography imaging to show that CFR was impaired in angiographically normal vessels in the presence of single-vessel CAD. Uren at al[48,49] also demonstrated reduced CFR in normal vessels after single-vessel myocardial infarction. This impaired CFR could reduce the image contrast between normal and ischemic territories needed to detect CAD.

Even if diffuse ischemia did not result in a discrete perfusion scan defect, perhaps other imaging information might suggest the presence of ischemia. A dilated left ventricular cavity on planar Tl-201 imaging has been shown to be a strong predictor of cardiac events,[50] and reduced left ventricular ejection fraction or increased end-systolic volume calculated from gated SPECT imaging has been shown to have prognostic value.[51] Increased Tl-201 lung uptake is a marker of pulmonary congestion and may suggest a poor prognosis even in the absence of myocardial perfusion scan defects.[52] The utility of such additional imaging data was not assessed in the present studies.

NEED TO BALANCE PERFUSION "PICTURE" WITH CLINICAL RISK

In this group of elderly patients with clinical risk factors such as angina and diabetes, an ischemic ECG response to vasodilator stress indicated moderate to high cardiac risk despite normal MPI. As discussed above, the data from Eagle et al[22] also indicate that patients at highest clinical risk remain at significant risk despite benign results of MPI. Other more recent studies also support the concept that high-risk patients with normal MPI remain at moderate cardiac risk. Hachamovitch et al[53] found that patients with normal exercise MPI had a less than 0.3% annual rate of CD/MI with low or intermediate Duke treadmill scores compared with a rate of 2.3% per year in the small number of patients with high-risk treadmill scores and normal MPI. In another study Hachamovitch et al[35] also showed that yearly risk for CD/MI in patients with normal MPI ranged from 0.5% in the absence of CAD or angina up to approximately 2.5% with a combination of CAD, angina, or resting ECG abnormalities. Calnon et al[54] studied patients who underwent dobutamine stress MPI predominantly because of obstructive lung disease. These high-risk patients with normal stress MPI and ECG results had a cardiac event rate of 1.5% per year, whereas the event rate in the small group of patients ($n = 23$) with normal MPI but an ischemic ECG response to dobutamine stress was much higher, at 7.8% per year.

CLINICAL IMPLICATIONS

What are the clinical implications of these two current studies?[40,41] Both show a consistent moderate to high event rate in a small subset of patients with an ischemic vasodilator stress ECG result and normal MPI. The stress ECG result is an important part of the study that should alert the physician to the presence of significant coronary disease. The physician interpreting the study should use all available information, including clinical risk factors, stress ECG results, left ventricular size and systolic function, and if available, lung uptake. MPI should not be interpreted in isolation from these other data. When all other combined information indicates high cardiac risk, normal MPI may still be associated with moderate to high risk. Because the high event rates in these studies occurred despite catheterization and revascularization for many patients, the optimal treatment of this high-risk group remains to be established.

In summary, these studies remind us that a single image is not the whole picture. Although normal stress perfusion scans usually imply a favorable prognosis, an ischemic ECG response to vasodilator stress should alert the interpreting physician to appropriately consider the full clinical situation and details. Although it appears true that a normal stress perfusion scan lowers the risk of cardiac events, the end result of this prognostic evaluation is quite dependent on the value of the pretest starting point.

References

1. Gould KL, Hamilton GW, Lipscomb K, Ritchie JL, Kennedy JW. A method for assessing stress induced regional malperfusion during coronary arteriography: experimental validation and clini-

cal application. Am J Cardiol 1974;34:557-64.
2. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. I. Physiologic basis and experimental validation. Am J Cardiol 1978;41:267-78.
3. Okada RD, Leppo JA, Boucher CA, Pohost GM. Myocardial kinetics of thallium-201 after dipyridamole infusion in normal canine myocardium and in myocardium distal to a stenosis. J Clin Invest 1982;69:199-209.
4. Leppo J, Boucher CA, Okada RD, et al. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. Circulation 1982;66:649-57.
5. Miller DD, Donohue TJ, Younis LT, et al. Correlation of pharmacological ^{99m}Tc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. Circulation 1994;89: 2150-60.
6. Heller LI, Cates C, Popma J, et al. Intracoronary Doppler assessment of moderate coronary artery disease: comparison with ^{201}Tl imaging and coronary angiography. Circulation 1997;96:484-90.
7. Becker LC. Effect of nitroglycerin and dipyridamole on regional left ventricular blood flow during coronary artery occlusion. J Clin Invest 1976;58:1287-96.
8. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57:1103-10.
9. Leppo JA, Simons M, Hood WB Jr. Effect of adenosine on transmural flow gradients in normal canine myocardium. J Cardiovasc Pharmacol 1984;6:1115-9.
10. Nishimura S, Kimball KT, Mahmarian JJ, Verani MS. Angiographic and hemodynamic determinants of myocardial ischemia during adenosine thallium-201 scintigraphy in coronary artery disease. Circulation 1993;87:1211-9.
11. Demer LL, Gould KL, Goldstein RA, Kirkeeide RL. Noninvasive assessment of coronary collaterals in man by PET perfusion imaging. J Nucl Med 1990;31:259-70.
12. Akinboboye OO, Idris O, Chou RL, et al. Absolute quantitation of coronary steal induced by intravenous dipyridamole. J Am Coll Cardiol 2001;37:109-16.
13. Araujo LI, McFalls EO, Lammertsma AA, Jones T, Maseri A. Dipyridamole-induced increased glucose uptake in patients with single-vessel coronary artery disease assessed with PET. J Nucl Cardiol 2001;8:339-46.
14. Seiler C, Fleisch M, Meier B. Direct intracoronary evidence of collateral steal in humans. Circulation 1997;96:4261-7.
15. Schulman SP, Achuff SC, Griffith LSC, et al. Prognostic cardiac catheterization variables in survivors of acute myocardial infarction: a five year prospective study. J Am Coll Cardiol 1988;11: 1164-72.
16. Peduzzi P, Hultgren H, Thomsen J, Detre K. Ten-year effect of medical and surgical therapy on quality of life: Veterans Administration Cooperative Study of Coronary Artery Surgery. Am J Cardiol 1987;59:1017-23.
17. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS Registry study. J Am Coll Cardiol 1995;25:1000-9.
18. Varnauskas E, European Coronary Surgery Study Group. Twelve-year follow-up of survival in the randomized European Coronary Surgery study. N Engl J Med 1988;319:332-7.
19. Leppo JA, O'Brien J, Rothendler JA, Getchell JD, Lee VW. Dipyridamole-thallium-201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. N Engl J Med 1984;310:1014-8.
20. Leppo J, Plaja J, Gionet M, et al. Noninvasive evaluation of cardiac risk before elective vascular surgery. J Am Coll Cardiol 1987;9: 269-76.
21. 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;64:276-81.
22. 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;110:859-66.
23. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 2002;39:542-53.
24. Brown KA. Prognostic value of myocardial perfusion imaging: state of the art and new developments. J Nucl Cardiol 1996;3:516-37.
25. Zaret BL, Wackers FJ. Nuclear cardiology (second of two parts). N Engl J Med 1993;329:855-63.
26. Zaret BL, Wackers FJ. Nuclear cardiology (first of two parts). N Engl J Med 1993;329:775-83.
27. Kozma C, Macklin W, Cummins LM, Mauer R. Anatomy, physiology, and biochemistry of the rabbit. In: Weisbroth SH, Flatt RE, Kraus AL, editors. The biology of the laboratory rabbit. New York: Academic Press; 1974. p. 50-70.
28. Gibbons RJ, Hodge DO, Berman DS, et al. Long-term outcome of patients with intermediate-risk exercise electrocardiograms who do not have myocardial perfusion defects on radionuclide imaging. Circulation 1999;100:2140-5.
29. Zafrir N, Dahlberg ST, Villegas BJ, Leppo JA. Prognostic utility of increased pulmonary thallium uptake in patients without ischemia. J Nucl Cardiol 1996;3:301-7.
30. Brown KA, Rown M. Prognostic value of a normal exercise myocardial perfusion imaging study in patients with angiographically significant coronary artery disease. Am J Cardiol 1993;71: 865-7.
31. Fattah AA, Kamal AM, Pancholy S, et al. Prognostic implications of normal exercise tomographic thallium images in patients with angiographic evidence of significant coronary artery disease. Am J Cardiol 1994;74:769-71.
32. Platia EV, Griffith LSC, Watkins L Jr, et al. Treatment of malignant ventricular arrhythmias with endocardial resection and implantation of the automatic cardioverter-defibrillator. N Engl J Med 1986;314:213-6.
33. Froelicher VF, Perdue S, Pewen W, Risch M. Application of meta-analysis using an electronic spread sheet to exercise testing in patients after myocardial infarction. Am J Med 1987;83:1045-54.
34. Villella A, Maggioni AP, Villella M, et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: the GISSI-2 data-base. Lancet 1995;346: 523-9.
35. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998;97:535-43.
36. Hachamovitch R, Berman DS, Kiat H, et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. Am J Cardiol 1997;80:426-33.

37. Heller GV, Herman SD, Travin MI, et al. Independent prognostic value of intravenous dipyridamole with technetium-99m sestamibi tomographic imaging in predicting cardiac events and cardiac-related hospital admissions. J Am Coll Cardiol 1995;26:1202-8.
38. Stratmann HG, Tamesis BR, Younis LT, Wittry MD, Miller DD. Prognostic value of dipyridamole technetium-99m sestamibi myocardial tomography in patients with stable chest pain who are unable to exercise. Am J Cardiol 1994;73:647-52.
39. Lette J, Bertrand C, Gossard D, et al. Long-term risk stratification with dipyridamole imaging. Am Heart J 1995;129:880-6.
40. Abbott BG, Afshar M, Berger AK, Wackers FJTh. Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging. J Nucl Cardiol 2002;9.
41. Klodas EM, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prognostic significance of ischemic electrocardiographic changes during vasodilator stress testing in patients with normal SPECT images. J Nucl Cardiol 2003;10.
42. Ficaro EP, Fessler JA, Shreve PD, et al. Simultaneous transmission/emission myocardial perfusion tomography: diagnostic accuracy of attenuation-corrected ^{99m}Tc-sestamibi single-photon emission computed tomography. Circulation 1996;93:463-73.
43. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Noninvasive identification of severe coronary artery disease using exercise tomographic thallium-201 imaging. Am J Cardiol 1992;70:14-20.
44. Mahmarian JJ, Boyce TM, Goldberg RK, et al. Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. J Am Coll Cardiol 1990;15:318-29.
45. Tamaki N, Yonekura Y, Mukai T, et al. Segmental analysis of stress thallium myocardial emission tomography for localization of coronary artery disease. Eur J Nucl Med 1984;9:99-105.
46. Hendel RC, Berman DS, Cullom SJ, et al. Multicenter clinical trial to evaluate the efficacy of correction for photon attenuation and scatter in SPECT myocardial perfusion imaging. Circulation 1999; 99:2742-9.
47. Sambuceti G, Parodi O, Marcassa C, et al. Alteration in regulation of myocardial blood flow in one-vessel coronary artery disease determined by positron emission tomography. Am J Cardiol 1993;72:538-43.
48. Uren NG, Marraccini P, Gistri R, De Silva R, Camici PG. Altered coronary vasodilator reserve and metabolism in myocardium subtended by normal arteries in patients with coronary artery disease. J Am Coll Cardiol 1993;22:650-8.
49. Uren NG, Crake T, Lefroy DC, et al. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994;331:222-7.
50. Emlein G, Villegas B, Dahlberg S, Leppo J. Left ventricular cavity size determined by preoperative dipyridamole thallium scintigraphy as a predictor of late cardiac events in vascular surgery patients. Am Heart J 1996;131:907-14.
51. Sharir T, Berman DS, Lewin HC, et al. Incremental prognostic value of rest-redistribution ^{201}Tl single-photon emission computed tomography. Circulation 1999;100:1964-70.
52. Jain D, Thompson B, Wackers FJTh, Zaret BL. Relevance of increased lung thallium uptake on stress imaging in patients with unstable angina and non-Q wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI)-IIIB study. J Am Coll Cardiol 1997;30:421-9.
53. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation 1996;93:905-14.
54. Calnon DA, McGrath PD, Doss AL, et al. Prognostic value of dobutamine stress technetium-99m-sestamibi single-photon emission computed tomography myocardial perfusion imaging: stratification of a high-risk population. J Am Coll Cardiol 2001;38: 1511-7.