Myocardial Perfusion Imaging with Thallium-201

George A. Beller

Cardiovascular Division, University of Virginia Health Sciences Center, Charlottesville, Virginia

Over the past 15 yr, numerous clinical studies have validated the use of myocardial perfusion imaging with ^{201}Tl for detection and evaluation of coronary artery disease (CAD). In addition, ^{201}Tl scintigraphy plays a valuable role in the risk stratification of patients with suspected or known CAD to determine prognosis. Typical protocols involve a comparison of stress and rest images to locate regions of myocardial ischemia. Results are comparable from protocols that employ either exercise stress or pharmacologic stress. By combining ^{201}Tl scintigraphic criteria with electrocardiographic (ECG) data, the sensitivity for detection of ischemia may be increased by as much as 25%–30%. The introduction of quantitative interpretation and SPECT has increased the accuracy of myocardial perfusion imaging with ^{201}Tl. With respect to prognosis, several ^{201}Tl scan variables, such as multiple perfusion defects and abnormal ^{201}Tl lung uptake, are associated with high risk. Even when cardiac catheterization findings are known, ^{201}Tl scintigraphy provides important supplementary information for identifying high-risk subgroups of patients with CAD.

Key Words: myocardial perfusion imaging; thallium-201

J Nucl Med 1994; 35:674–680

Myocardial ^{201}Tl perfusion imaging has been chiefly employed for: (1) detection of CAD in patients presenting with chest pain; (2) risk stratification of patients with suspected or known CAD to determine prognosis; and (3) assessment of myocardial viability in patients with left-ventricular dysfunction. In this review, the diagnostic and prognostic applications of ^{201}Tl stress perfusion imaging will be discussed.

DIAGNOSIS OF CAD

A review by Gianrossi et al. of 147 consecutively published reports comparing exercise-induced ST-segment depression with coronary angiography, revealed a mean sensitivity of 68% and specificity of 77% for CAD detection (*1*). When planar ^{201}Tl scintigrams are interpreted based solely on visual analysis, sensitivity and specificity for CAD detection are approximately 80%–85% and 85%–90%, respectively. Kotler and Diamond found an average sensitivity of 84% and specificity of 87% for CAD detection in pooled data from 33 published studies that employed qualitative assessment of ^{201}Tl scintigrams (*2*).

Quantitative planar ^{201}Tl scintigraphy provided an average sensitivity of 91% and specificity of 89% for CAD detection as assessed from a review of four studies comprising 682 patients (*3*). Quantitative scintigraphy has significantly enhanced detection of individual coronary artery stenoses in patients with multivessel CAD (*4*). Some patients demonstrate abnormal segmental washout of ^{201}Tl by quantitative criteria as well as ^{201}Tl defects that are not observed visually.

Perhaps one of the greatest perfusion imaging advances in the past decade is SPECT. Several studies have shown that sensitivity for CAD detection can be improved by using SPECT instead of planar imaging, with perhaps some loss of specificity (*5–10*). Table 1 summarizes pooled data on sensitivity (92%), specificity (68%), and normalcy (84%) for SPECT ^{201}Tl imaging from 147 patients in six published studies.

Displaying SPECT data in the form of a polar map, or "bull's-eye plot," has enhanced the interpretation of tomographic images. This technique employs the circumferential maximal count profiles of the short-axis slices from the left ventricle and converts them into polar coordinate profiles. These data are then displayed as a series of concentric circles, with the apex at the center and the base at the outer edge, resulting in a two-dimensional representation of three-dimensional tomographic perfusion data. New computer methods can now subtract the stress image data from delayed image data to display areas of ^{201}Tl redistribution.

Pharmacologic Stress

Pharmacologic stress with dipyridamole, adenosine, or dobutamine can substitute for exercise stress in myocardial perfusion studies for detection of CAD, particularly in patients with peripheral vascular disease who are unable to exercise to their target heart rates or workloads. Studies indicate that sensitivities and specificities of pharmacologic stress imaging, with either the vasodilator agents or dobutamine, for CAD detection are comparable to those of exercise ^{201}Tl scintigraphy (*11–13*). This finding is not unexpected since both exercise stress and pharmacologic stress

Received Jan. 3, 1994; revision accepted Jan. 18, 1994.
This paper was presented in part at the Annual Meeting of the Society of Nuclear Medicine on June 8, 1993, as part of a Continuing Medical Education Seminar organized by the Cardiovascular Council.
For correspondence or reprints contact: George A. Beller, MD, Cardiovascular Division/Box 158, University of Virginia Health Sciences Center, Charlottesville, VA 22908.

TABLE 1
Detection of CAD with Exercise ^{201}Tl SPECT

Authors	No. of patients	Sensitivity (%)	Specificity (%)	Normalcy rate (%)
Maddahi et al. (*10*)	183	96	55	86
Van Train et al. (*9*)	318	94	44	82
Tamaki et al. (*5*)	104	98	91	—
DePasquale et al. (*6*)	210	95	71	—
Mahmarian et al. (*8*)	360	87	87	—
Iskandrian et al. (*7*)	272	82	62	—
Total	1,447	92	68	84

Reprinted with permission from *Current Problems in Cardiology*, 1991;16:449.

induce flow heterogeneity, and ^{201}Tl administered at peak pharmacologic stress will be taken up by the myocardium in proportion to blood flow.

In the study by Varma et al. from our laboratory, segmental ^{201}Tl uptake and washout were comparable in quantitative exercise scintigraphy and quantitative dipyridamole scintigraphy performed two weeks apart (*14*). Agreement between the two tests was observed in 92% of the coronary supply regions evaluated. In the 21 patients studied, both exercise and dipyridamole ^{201}Tl scintigraphy could detect 61% of stenotic vessels. Figure 1 shows the prevalence of normal and abnormal segments for the exercise and dipyridamole scans. Note that more reversible defects were detected by dipyridamole-^{201}Tl than by exercise ^{201}Tl imaging.

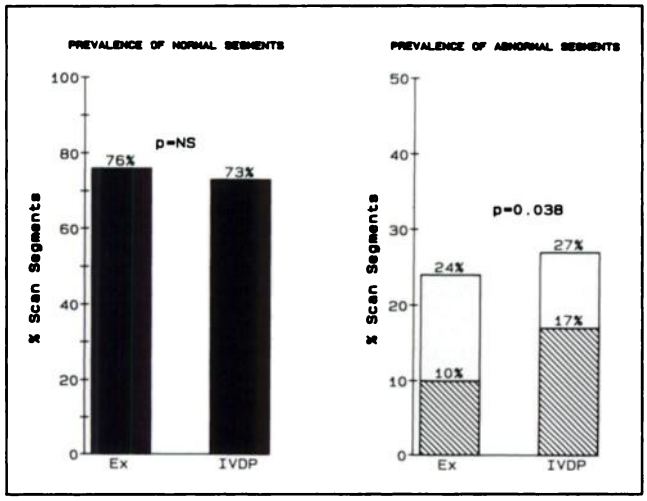

FIGURE 1. Prevalence of normal segments (left) and abnormal segments (right) in 21 patients who underwent exercise (Ex) and dipyridamole (IVDP) ^{201}Tl scanning several weeks apart. The cross-hatched portion of the bars in the right panel reflect the percentage of abnormal scan segments showing initial defects with delayed redistribution. Reprinted with permission from the American College of Cardiology (*Journal of the American College of Cardiology* 1989; 64:871).

Factors Influencing Sensitivity

Several factors can increase or decrease the sensitivity of ^{201}Tl scintigraphy for detecting CAD (*15*). It is more difficult to resolve stenoses of the left circumflex coronary artery than stenoses of the left anterior descending (LAD) or right coronary arteries (RCA). It is more difficult to detect branch stenoses of the LAD and circumflex vessels than more proximal lesions in those arteries. SPECT, however, is more accurate than the planar imaging method for detection of left circumflex stenosis and branch stenoses of coronary arteries. Perfusion abnormalities are more likely to be observed in the supply zone of vessels with severe stenoses (>90%) than in that of vessels with more moderate stenoses (50%–90%).

The level of exercise achieved during stress testing influences the exercise electrocardiogram (ECG) more than the ^{201}Tl scintigram. Esquivel et al. found that throughout the range of achieved exercise workloads or peak heart rates, ^{201}Tl scan abnormalities were more prevalent than exercise-induced ST-segment depression (Fig. 2) (*16*). It is likely that flow heterogeneity is induced earlier during the course of exercise stress than the myocardial cellular alterations that mediate ST-segment depression or anginal chest pain.

As expected, patients with prior myocardial infarction (MI) have a higher frequency of positive scintigrams than patients without prior MI.

Certain drugs may potentially affect the accuracy of ^{201}Tl scintigraphy. However, in clinical practice, the influence of drugs on ^{201}Tl scan results does not seem to cause a major problem. One study showed that pretreatment with isosorbide dinitrate increased ^{201}Tl uptake on exercise scintigrams, thus diminishing sensitivity for CAD (*17*). In our experience, neither beta blockers nor calcium antagonists seem to significantly affect the sensitivity or specificity of ^{201}Tl scintigraphy for CAD detection. It is usually our

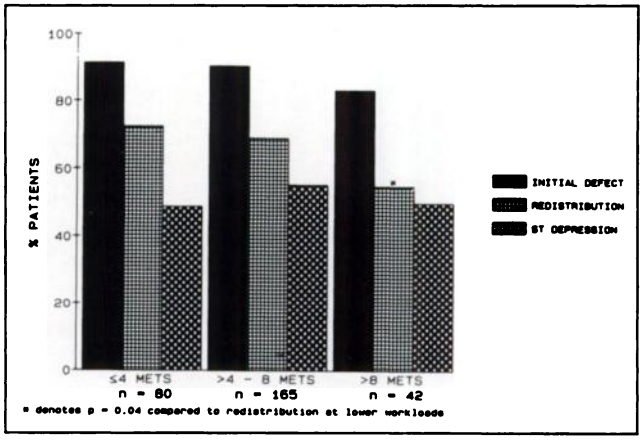

FIGURE 2. Prevalence of initial defects, delayed redistribution, and ischemic ST-segment depression relative to exercise workload achieved (METS). Note that prevalence of ^{201}Tl defects was higher than the prevalence of ST-segment depression at all workloads. Reprinted with permission from the American College of Cardiology, (*Journal of the American College of Cardiology* 1989;63:160).

practice not to discontinue beta blockers or other cardioactive drugs prior to exercise testing.

Factors Influencing Specificity

There are several factors that can diminish the specificity of both planar and SPECT ^{201}Tl scintigraphy. If one is not knowledgeable of image artifacts or variants of normal studies, interpretation of ^{201}Tl scintigrams can be difficult. Such knowledge is mandatory in order to decrease false-positive interpretations of the following: overlying breast shadow; altered position of the left ventricle's inflow or outflow tracts; abnormally high degree of apical thinning; overlying diaphragm, resulting in diminished relative activity of the inferior wall; or enlarged right-ventricular blood pool overlying the inferior wall on the anterior planar image. The major cause of false-positive ^{201}Tl scan interpretations in women is breast tissue attenuation.

Patients with left-bundle-branch block and normal coronary arteries can exhibit septal perfusion abnormalities on exercise scintigraphy (*18–20*). In some instances, reversible septal defects can be observed in such patients in the absence of angiographically confirmed epicardial coronary artery stenoses. Recent data indicate that the frequency of abnormal scans in the absence of CAD is reduced when vasodilator stress imaging is employed instead of exercise stress (*21*).

Recognition of image artifacts and variants of normal scans will reduce unnecessary referrals for coronary angiography in patients with false-positive ^{201}Tl scan results. In a study from our institution by Desmarais et al., only four of 93 (4%) patients with ^{201}Tl abnormalities judged to be artifactual were ultimately referred for coronary angiography (Fig. 3) (*22*). The remaining 89 (96%) patients with artifactually abnormal scars who did not undergo cardiac catheterization experienced no cardiac events during the follow-up period. On the other hand, 96% of the patients with ^{201}Tl scans judged to be truly abnormal (nonartifactual) had documented CAD when referred for coronary angiography. This study shows the importance of rendering unequivocal interpretations of ^{201}Tl scans that do not "hedge" with respect to the type of abnormality identified. When attenuation artifacts are identified, the scan report should not be ambiguous; i.e., the scan should be interpreted as not demonstrating perfusion abnormalities attributed to CAD.

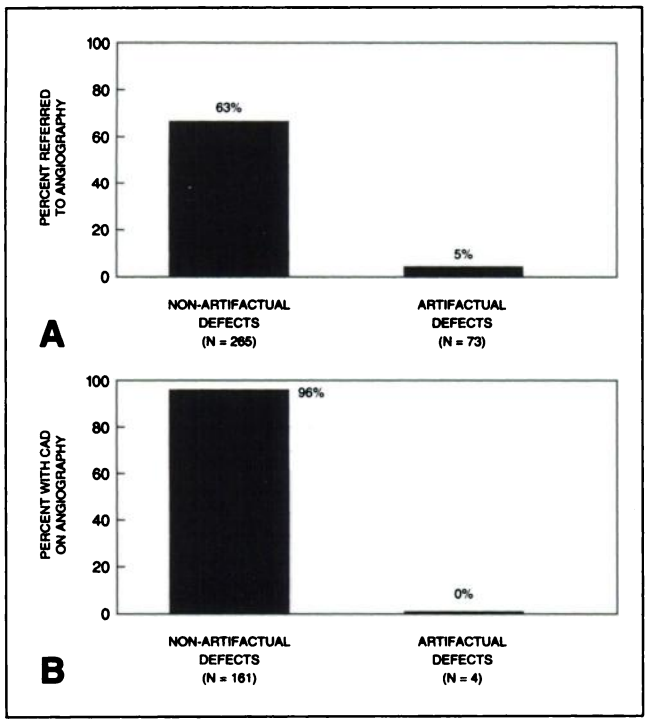

FIGURE 3. (A) Percentage of patients referred for cardiac catheterization who had either nonartifactual or artifactual ^{201}Tl defects on exercise imaging. (B) Percentage of patients with significant CAD on coronary angiography who had either artifactual or nonartifactual ^{201}Tl scan abnormalities. Reprinted with permission from the American College of Cardiology (*Journal of the American College of Cardiology* 1993; 21:1058).

TABLE 2
Advantages of Myocardial Perfusion Imaging for Identifying High-Risk CAD Patients with Exercise Stress Testing

1. More sensitive than exercise ST-segment depression for detection of myocardial ischemia.
2. Better localization of ischemia to the supply regions of the three major coronary arteries than exercise ECG.
3. Enhancement of identification of patients with multivessel or left-main CAD than with exercise ECG testing alone.
4. Prognostic value of supplementary scintigraphic markers of high risk (e.g., increased lung ^{201}Tl uptake and exercise left ventricular dilation).
5. Detection of myocardial viability in regions of abnormal wall motion with or without Q-waves.
6. Identification of high-risk CAD in patients with abnormal resting ECG abnormalities (e.g., left ventricular hypertrophy and strain).

Reprinted with permission from the American College of Cardiology (*Journal of the American College of Cardiology* 1991;16:449).

PROGNOSIS OF CAD

Myocardial perfusion imaging with ^{201}Tl can provide useful information for determining prognosis in patients with CAD.

Advantages of ^{201}Tl Data Over ECG Results

Myocardial scintigraphy with ^{201}Tl is valuable when performed in conjunction with exercise ECG to identify patients who are at increased risk for adverse cardiac events (*23*). In addition to enhancing the diagnostic accuracy of conventional ECG, myocardial perfusion imaging provides information related to the extent and severity of stress-induced ischemia, which has prognostic significance. In fact, demonstration of multiple reversible defects may be more important for risk stratification than mere delineation of the extent of coronary stenoses on angiography.

Table 2 summarizes the potential advantages of combining myocardial perfusion imaging and exercise ECG for identifying high-risk CAD:

First, as mentioned previously, sensitivity for detection

of ischemia may be increased by as much as 25%–30% by combining scintigraphic criteria with ST-segment depression in patients with underlying CAD (*1–4*). This enhanced sensitivity is more evident in patients who fail to achieve >85% of their maximum predicted heart rates (*16*).

Second, myocardial perfusion imaging is superior to exercise ECG for locating the site(s) of stress-induced ischemia. This diagnostic advantage is important because defects observed in the anterior wall and septum are almost always caused by a coronary stenosis in the LAD. Because prognosis in patients with multivessel disease is, in part, related to the existence of a proximal LAD stenosis, it is important to identify such proximal lesions by a noninvasive technique.

Third, multivessel ischemia is better identified by perfusion imaging than by exercise ECG; i.e., defects observed simultaneously in the inferior wall and the anterior septal region indicate the presence of ischemia in the distributions of the RCA and LAD vessels, respectively. This ^{201}Tl defect pattern is associated with a worse outcome than perfusion abnormalities localized to the supply zone of only one of the three major coronary vessels (*24*). An increase in the number of segments with perfusion abnormalities increases the probability of left-main or multivessel disease (*25*) and worsens the prognosis with medical therapy (*26*).

Fourth, an important role of ^{201}Tl perfusion imaging for risk stratification is the differentiation between ischemia and scar in hypoperfused myocardial segments. In patients with prior infarction, ischemia is more easily demonstrated with perfusion imaging than with exercise ECG. Resting ST-T wave abnormalities in association with Q-waves may preclude accurate interpretation of exercise ST-segment responses in post-MI patients.

Thallium-201 Variables Associated with High Risk

There are several ^{201}Tl scintigraphic variables that indicate functionally important underlying CAD and which are associated with high risk, including: (1) multiple ^{201}Tl defects and/or washout abnormalities in one or more coronary supply regions, (2) increased ^{201}Tl lung uptake, determined by quantifying the lung/heart ratio of ^{201}Tl uptake, and (3) exercise-induced cardiac dilatation, with the left-ventricular cavity size appearing enlarged on the stress image when compared with the subsequent redistribution image.

Nygaard et al., from the University of Virginia, found that 67% of patients with left-main CAD had a multivessel ^{201}Tl scan pattern (defects identified in more than one coronary supply region) (*25*). In addition, 42% of patients with left-main CAD had abnormal ^{201}Tl lung uptake. Although SPECT provides better defect contrast and improved resolution of small defects, the anterior planar image should initially be acquired to evaluate pulmonary ^{201}Tl activity and left-ventricular cavity size. These scintigraphic variables supplement the evaluation of defect extent and severity for separation of high- and low-risk subsets of patients with CAD. Figure 4 shows postexercise and delayed ^{201}Tl planar images in patients with marked increase in ^{201}Tl lung activity with reversible defects in the apex, anterolateral wall and septum.

Since multiple reversible perfusion defects, increased lung ^{201}Tl uptake and transient left ventricular cavity dilatation are markers of high-risk CAD, it stands to reason that one or more of these scintigraphic variables would be associated with an increased rate of subsequent cardiac events in medically treated patients. Many studies in the literature have investigated the prognostic utility of exercise scintigraphy in patients with chest pain who are referred for noninvasive evaluation (*26–40*).

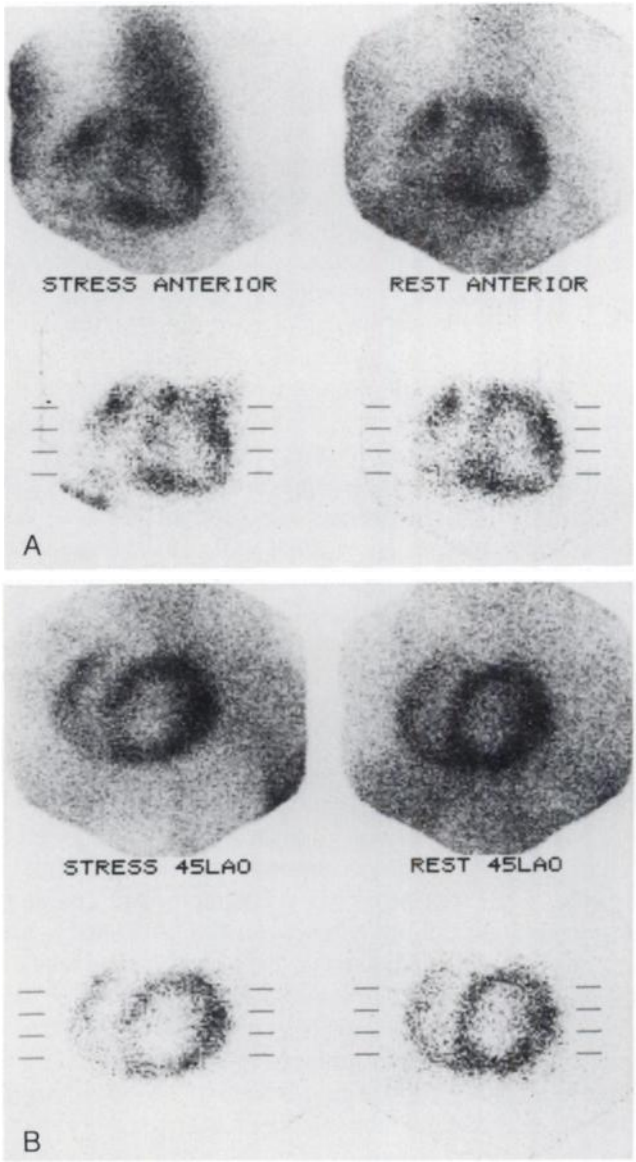

FIGURE 4. (A) Stress and rest anterior projection images in a patient with increased lung ^{201}Tl uptake and defects in the anterolateral wall apex and inferior wall showing delayed redistribution on the rest images. (B) The stress and rest 45° left anterior oblique (LAO) images in the same patient showing septal and inferoapical defects with redistribution.

In one of the first published studies evaluating the prognostic utility of exercise ^{201}Tl scintigraphy, Brown et al. showed that the number of reversible ^{201}Tl defects was the best predictor of future cardiac events as determined by logistic regression analysis in CAD patients without prior infarction (*27*). Although the number of coronary vessels with significant stenoses was a univariate predictor of events, it added no significant prognostic value to the ^{201}Tl assessment of the extent of hypoperfused myocardium.

In a similar study by Ladenheim et al., stepwise logistic regression analysis identified the number of myocardial regions with redistribution defects, the maximum magnitude of hypoperfusion and the exercise heart rate as the only independent predictors of cardiac events in 1,689 patients with CAD and no prior infarction (*28*). In another report, Staniloff et al. found that the event rate increased in proportion to the magnitude of hypoperfusion (*29*). The probability of an event also increased with the number of abnormal vascular scan territories.

Iskandrian et al. also found that the number of myocardial scan segments with abnormal perfusion (reversible or fixed defects) was the single best predictor of future cardiac events (*30*). In a subsequent study by Iskandrian et al., three ^{201}Tl variables offered significant univariate prediction for cardiac death or nonfatal MI: the presence of reversible defects, the extent of perfusion abnormalities and a multivessel scan pattern (*31*). This study comprised a cohort of patients who were age 65 or older. Multivariate analysis identified abnormal ^{201}Tl images and a multivessel ^{201}Tl scan pattern as independent predictors of events.

Hilton et al. assessed the prognostic value of exercise ^{201}Tl scintigraphy in patients age 70 or older who were followed for approximately three years after testing (*32*). Multivariate logistic regression analysis identified the combination of peak exercise less than stage one and any ^{201}Tl perfusion defect as the most powerful predictor of subsequent events. Patients with a normal ^{201}Tl scan had a 2% event rate compared with 18% in patients with a fixed or reversible defect.

Comparison of ECG, ^{201}Tl and Angiographic Data

From the University of Virginia, Kaul et al. reported a follow-up study of 382 patients who were evaluated with exercise ECG, exercise ^{201}Tl scintigraphy and coronary angiography (*33*). Of these patients, 83 (22%) had bypass surgery within three months of testing and were excluded from further analysis. Of the remaining 299 patients, 210 (70%) had no events and 89 (30%) had events (41 deaths, 9 nonfatal MIs and 39 late coronary bypass procedures after three months) during medically treated follow-up. When all clinical, exercise, scintigraphic and catheterization variables were analyzed by Cox regression analysis, the number of diseased vessels emerged as the single most important predictor of subsequent events. When the number of diseased vessels was excluded from analysis, the number of segments with ^{201}Tl redistribution became the single best variable for predicting future events. Other variables that

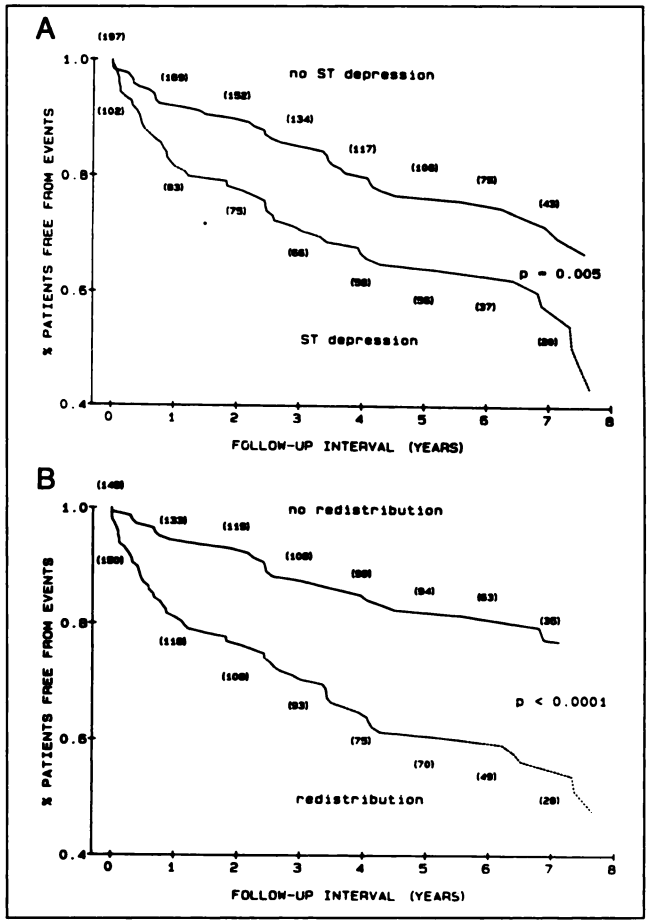

FIGURE 5. (A) Event-free survival in patients with and without exercise-induced ischemic ST-segment depression. (B) Event-free survival in the same patient cohort relative to the presence or absence of exercise-induced ^{201}Tl redistribution. Note that the separation of high- and low-risk subgroups was better achieved with ^{201}Tl redistribution compared with ST-segment depression as the ischemic variable. Reprinted with permission from the American Heart Association (*Circulation* 1988;77:745).

independently predicted future events included: the change in heart rate from rest to exercise, ST-segment depression and ventricular ectopy recorded during stress. As shown in Fig. 5, the separation of high- and low-risk subgroups was better achieved with ^{201}Tl redistribution as a marker of ischemia than with ST-segment depression. Thus, these results show that data derived from coronary angiography and noninvasive ^{201}Tl scintigraphy are complementary in identifying high-risk CAD patients.

Incremental Prognostic Value

The data from the study by Kaul et al. (*33*) was reanalyzed by Pollock et al. to assess the incremental prognostic value of information obtained in succession (clinical exam, exercise ECG, ^{201}Tl scintigraphy and coronary angiography) (*34*). When the additional value of sequentially performed tests was analyzed, the exercise ECG data added significant prognostic information to the clinical data. The inclusion of the number of segments showing ^{201}Tl redistribution improved the prognostic information beyond that

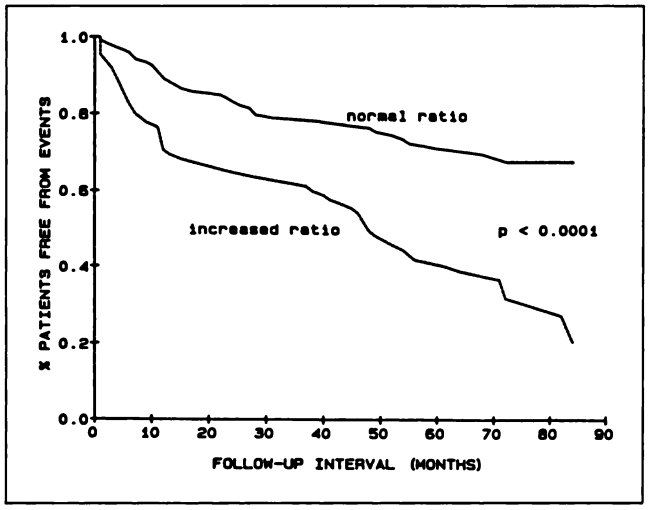

FIGURE 6. Event-free survival in patients with normal versus abnormal lung-to-heart ^{201}Tl ratios. Reprinted with permission from the American College of Cardiology (*Journal of the American College of Cardiology* 1988;12:25).

provided by clinical and exercise stress test data alone. Coronary angiography was of significant additional prognostic value when added to clinical, exercise ECG, and ^{201}Tl scintigraphic data. Interestingly, more than 75% of the prognostic information could be obtained from the combination of clinical data, ECG stress test data and the number of ^{201}Tl redistribution segments.

Increased lung uptake of ^{201}Tl was not evaluated as a variable in the Pollock et al. study (*34*). Several other follow-up studies in patients with CAD who underwent exercise ^{201}Tl scintigraphy have indicated abnormal ^{201}Tl lung uptake is perhaps an even better prognostic variable for assessing outcome than the number of reversible defects (*35,36*). In a study from Massachusetts General Hospital, Kaul et al. found that a lung/heart ^{201}Tl uptake ratio ≥0.52 was the single best predictor of subsequent cardiac events (*36*). Of the 20 patients who died during follow-up, 17 (85%) had an abnormal lung/heart ^{201}Tl uptake ratio. Figure 6 shows the survival curves in patients with normal versus increased lung/heart ^{201}Tl uptake ratios. Interestingly, although the number of diseased coronary vessels by angiography was a significant univariate predictor of events in this study (*36*), it does not add to the overall ability of the exercise perfusion scan to predict future events (*34*).

Travin et al. more recently reviewed the exercise ^{201}Tl test results of 268 patients from Massachusetts General Hospital who had unequivocal ^{201}Tl redistribution (*37*). At a follow-up of 25 months, occurrence of MI was most closely associated with the extent and severity of ischemia demonstrated by ^{201}Tl scintigraphy, whereas cardiac death was associated with abnormal ^{201}Tl lung uptake and an inability to exercise to 9.6 METS. These data suggest that cardiac death is best predicted by variables that reflect poor left-ventricular function, whereas nonfatal MI is best predicted by variables indicative of ischemia.

Finally, several reports have indicated that patients with chest pain who have normal myocardial exercise perfusion scans on symptom-limited testing have an excellent prognosis during follow-up (*38–40*). In a study from the University of Virginia, Pamelia et al. found that the yearly mortality rate in 345 patients with chest pain and a normal quantitative planar ^{201}Tl perfusion scan was 0.5% (*38*). Brown et al. undertook a pooled analysis of all studies published in the literature and found a yearly rate of 0.9% for cardiac death or nonfatal MI in 3,594 patients with normal ^{201}Tl scintigrams who were followed for an average of 29 months (*40*). Even patients with angiographic CAD and normal exercise ^{201}Tl perfusion scans have an excellent prognosis (*40*).

An overall view of the prognostic studies cited above suggests that even when cardiac catheterization findings are known, myocardial perfusion imaging provides important supplementary physiologic information for identifying high-risk subgroups of patients with CAD. Conversely, patients with a normal ^{201}Tl perfusion scan have an excellent prognosis, regardless of angiographic results.

CONCLUSION

Over the past 15 years, clinical studies published in the literature indicate that myocardial perfusion imaging with ^{201}Tl is a valuable tool for detection and evaluation of CAD, as well as for risk stratification of patients with suspected or known CAD to determine prognosis.

Results are comparable from protocols that employ either exercise stress or pharmacologic stress. By combining scintigraphic criteria and ST-segment depression in patients with underlying CAD, the sensitivity for detection of ischemia may be increased by as much as 25% to 30%. The use of quantitative interpretation and SPECT has increased the accuracy of myocardial perfusion imaging with ^{201}Tl. There are several factors that influence the sensitivity and specificity of ^{201}Tl scintigraphy; the most common cause of false-positive results is failure to identify artifacts.

With respect to prognosis, several ^{201}Tl scan variables, such as multiple perfusion defects and abnormal ^{201}Tl lung uptake, are associated with high risk. Thallium-201 scintigraphy provides important supplementary information for identifying high-risk subgroups of patients with CAD. Conversely, patients with a normal ^{201}Tl perfusion scan have an excellent prognosis, regardless of angiographic results.

REFERENCES

1. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation* 1989;80:87–98.
2. Kotler TS, Diamond GA. Exercise thallium-201 scintigraphy in the diagnosis and prognosis of coronary artery disease. *Ann Intern Med* 1990;113:684–702.
3. Beller GA. Current status of nuclear cardiology techniques. *Curr Probl Cardiol* 1991;16:449–535.
4. Berger BC, Watson DD, Taylor GJ, et al. Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease. *J Nucl Med* 1981;22:585–593.
5. Tamaki N, Yonekura Y, Mukai T, et al. Stress thallium-201 transaxial

emission computed tomography: Quantitative versus qualitative analysis for evaluation of coronary artery disease. *J Am Coll Cardiol* 1984;4:1213–1221.
6. DePasquale EE, Nody AC, DePuey EG, et al. Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease. *Circulation* 1988;77:316–327.
7. Iskandrian AS, Heo J, Kong B, Lyons E. Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients. *J Am Coll Cardiol* 1984;14:1477–1486.
8. Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS. Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. *J Am Coll Cardiol* 1990;15:318–329.
9. Van Train RF, Maddahi J, Berman DS, Kiat H, Areeda J, Prigent F, Friedman J. Quantitative analysis of tomographic stress thallium-201 myocardial scintigrams: a multicenter trial. *J Nucl Med* 1990;31:1168–1179.
10. Maddahi J, Van Train K, Prigent F, et al. Quantitative single photon emission computed thallium-201 tomography for detection and localization of coronary artery disease: optimization and prospective validation of a new technique. *J Am Coll Cardiol* 1989;14:1689–1699.
11. Gupta N, Esterbrooks DJ, Hilleman DE, Mohiuddin SM. Comparison of adenosine and exercise thallium-201 single-photon emission computed tomography (SPECT) myocardial perfusion imaging. *J Am Coll Cardiol* 1992; 19:248–257.
12. Leppo JA. Dipyridamole-thallium imaging: the lazy man's stress test. *J Nucl Med* 1989;30:281–287.
13. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol* 1993;21:1583–1590.
14. Varma SK, Watson DD, Beller GA. Quantitative comparison of thallium-201 scintigraphy after exercise and dipyridamole in coronary artery disease. *Am J Cardiol* 1989;64:871–877.
15. Beller GA, Gibson RS. Sensitivity, specificity and prognostic significance of noninvasive testing for occult or known coronary disease. *Prog Cardiovasc Dis* 1987;29:241–270.
16. Esquivel L, Pollock SG, Beller GA, Gibson RS, Watson DD, Kaul S. Effect of the degree of effort on the sensitivity of the exercise thallium-201 stress test in symptomatic coronary artery disease. *Am J Cardiol* 1989;63:160–165.
17. Tono-oka I, Satoh S, Kanaya T, et al. Alterations in myocardial perfusion during exercise after isosorbide dinitrate infusion in patients with coronary disease: assessment by thallium-201 scintigraphy. *Am Heart J* 1986;111: 525–533.
18. DePuey EG, Guertler-Krawczynska E, Robbins WL. Thallium-201 SPECT in coronary artery disease patients with left bundle branch block. *J Nucl Med* 1988;29:1479–1485.
19. Rothbart R, Beller GA, Watson DD, Nygaard TW, Gibson RS. Diagnostic accuracy and prognostic significance of quantitative thallium-201 scintigraphy in patients with left bundle branch block. *Am J Noninvas Cardiol* 1987;1:197–205.
20. Larcos G, Gibbons RJ, Brown ML. Diagnostic accuracy of exercise thallium-201 single-photon emission computed tomography in patients with left bundle branch block. *Am J Cardiol* 1991;68:756–760.
21. O'Keefe JH Jr, Bateman TM, Barnhart CS. Adenosine thallium-201 is superior to exercise thallium-201 for detecting coronary artery disease in patients with left bundle branch block. *J Am Coll Cardiol* 1993;21:1332–1338.
22. Desmarais RL, Kaul S, Watson DD, Beller GA. Do false positive thallium-201 scans lead to unnecessary catheterization? Outcome of patients with perfusion defects on quantitative planar thallium-201 scintigraphy. *J Am Coll Cardiol* 1993;21:1058–1063.
23. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age. *Circulation* 1991;83:363–381.
24. 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.
25. Nygaard TW, Gibson RS, Ryan JM, Gascho JA, Watson DD, Beller GA. Prevalence of high-risk thallium-201 scintigraphic findings in left main coronary artery stenosis: comparison with patients with multiple- and single-vessel coronary artery disease. *Am J Cardiol* 1984;53:462–469.
26. Harris PJ, Harrell FE Jr, Lee KL, Behar VS, Rosati RA. Survival in medically-treated coronary artery disease. *Circulation* 1979;60:1259–1269.
27. 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.
28. Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1986;7:464–471.
29. Staniloff HM, Forrester JS, Berman DS, Swan HJ. Prediction of death, myocardial infarction, and worsening chest pain using thallium scintigraphy and exercise electrocardiography. *J Nucl Med* 1986;27:1842–1848.
30. Iskandrian AS, Hakki AH, Kane-Marsch S. Prognostic implications of exercise thallium-201 scintigraphy in patients with suspected or known coronary artery disease. *Am Heart J* 1985;110:135–143.
31. Iskandrian AS, Heo J, Decoskey D, Askenase A, Segal BL. Use of exercise thallium-201 imaging for risk stratification of elderly patients with coronary artery disease. *Am J Cardiol* 1988;61:269–272.
32. Hilton TC, Shaw LJ, Chaitman BR, Stocke KS, Goodgold HM, Miller DD. Prognostic significance of exercise thallium-201 testing in patients aged ≥70 years with known or suspected coronary artery disease. *Am J Cardiol* 1992;69:45–50.
33. Kaul S, Lilly DR, Gascho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization. *Circulation* 1988;77:745–758.
34. Pollock SG, Abbott RD, Boucher CA, Beller GA, Kaul S. Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease. validation of models based on these tests. *Circulation* 1992;85:237–248.
35. 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;317:1486–1489.
36. 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.
37. Travin MI, Boucher CA, Newell JB, LaRaia PJ, Flores AR, Eagle KA. Variables associated with a poor prognosis in patients with an ischemic thallium-201 exercise test. *Am Heart J* 1993;125:335–344.
38. Pamelia FX, Gibson RS, Watson DD, Craddock GB, Sirowatka J, Beller GA. Prognosis with chest pain and normal thallium-201 exercise scintigrams. *Am J Cardiol* 1985;55:920–926.
39. Wackers FJ, Russo DJ, Russo D, Clements JP. Prognostic significance of normal quantitative planar thallium-201 stress scintigraphy in patients with chest pain. *J Am Coll Cardiol* 1985;6:27–30.
40. Brown K. Critical assessment of prognostic applications of thallium-201 myocardial perfusion imaging. In: Zaret BL, Beller GA, eds. *Nuclear cardiology: state of the art and future directions*. St. Louis: Mosby; 1993:155–169.