Seminars in Nuclear Medicine

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Letter From the Editors

OUR GUEST editors have assumed the additional role of guest authors for this issue on the topic of Cardiovascular Nuclear Medicine. They have performed equally well, clearly defining the role of pharmacological stress testing in the assessment of cardiovascular disease. This alternative to standard treadmill exercise is achieving increased application with the availability of several agents that have significantly different pharmacological actions. As Drs. Wexler and Travin point out, approximately 60% of patients with suspected cardiovascular disease are stressed pharmacologically at our institution.

The remaining articles in this issue are equally informative. Dr. Berman has synthesized his prodigious contributions to the cardiovascular nuclear medicine literature and presents a cogent review of the role of cardiovascular nuclear medicine in clinical decision making. This article is essential for anyone who performs or uses these studies. The algorithms presented for cardiovascular nuclear medicine are well thought out and critical to our use of these tests. Cardiovascular nuclear medicine plays a powerful role in risk stratification, diagnosis, and therapy.

Another area of concern to many nuclear medicine physicians is the increasing use of stress echocardiography as a potential substitute for thallium and sestamibi studies. Dr. Verani defines for us the advantages and limitations of stress echocardiography in evaluating myocardial perfusion.

The introduction of hypoxia markers for myocardial imaging is discussed along with many other exciting developments. These agents, as discussed by Dr. Sinusas, have the potential to allow us to directly image myocardial tissue, which is hypoxic.

Thrombosis and atherosclerotic plaques are life-threatening problems that have obvious implications in the pathogenesis of heart disease. Unfortunately, therapy of thrombosis with anticoagulants also is not without risk. Dr. Cerqueira reviews newly introduced agents for thrombosis imaging and their potential application in clinical nuclear medicine. As he notes, "efforts in developing those modalities are important to expand the applications to new areas in nuclear cardiology."

Cardiovascular nuclear medicine continues to represent the single, most frequently performed, group of studies in most nuclear medicine departments. This and the previous issue of *Seminars in Nuclear Medicine* provide a comprehensive account of the state-of-the-art techniques in cardiovascular nuclear medicine by internationally recognized authorities.

Leonard M. Freeman, MD
M. Donald Blaufox, PhD

The Role of Nuclear Cardiology in Clinical Decision Making

Daniel S. Berman, Guido Germano, and Leslee J. Shaw

This review suggests that the field of nuclear cardiology is alive, well, and thriving, providing relevant information that aids in everyday clinical decision making for nuclear medicine and referring physicians alike. Despite the competition from other modalities, the clinically appropriate applications of nuclear cardiology techniques are likely to increase. The foundation of this optimism is based on the vast amount of data documenting cost-effective clinical applications for diagnosis, risk stratification, and assessing therapy in both chronic and acute coronary artery disease (CAD), the powerful objective quantitative analysis of perfusion and function provided by the technique, and the increasing general availability of the approach.

AMONG THE 5 million myocardial perfusion studies performed in the United States per year, approximately one half are still performed, at least in part, for purposes of simply establishing a diagnosis. Detection of coronary artery disease (CAD) remains important in certain patients with high-risk occupations, as well as in younger patients, for whom CAD detection, with its lifelong implications for therapy, may be important regardless of the likelihood of cardiac events over a 1- to 3-year period. The basis for the diagnostic application of nuclear testing lies in the concept of sequential Bayesian analysis of disease probability.[1] This analysis requires knowledge of the pretest likelihood of disease, as well as of the sensitivity and specificity of the test. The pretest likelihood of disease or prevalence of disease varies according to age, sex, symptoms, and risk factors, and can be derived directly from the work of Diamond and Forrester,[2] as well as other data bases.

One can consider this likelihood, for 50-year-old men, to be 5%, 20%, 50%, and 90% for asymptomatic, nonanginal chest pain, atypical angina, and typical angina, respectively. Values are scaled up or down depending on age. The likelihood values for women of 5%, 20%, 50%, and 90%, roughly apply just as they do with men, but starting 1 decade later. It has been shown that all imperfect noninvasive tests have their maximum diagnostic benefit when the pretest likelihood of disease is intermediate.[2,3] With well-performed gated myocardial perfusion single photon emission computed tomography (SPECT), we estimate the sensitivity to be 90% and the specificity to be 90%.[4] Given the 90% sensitivity and 90% specificity, it can be shown that a positive test result in the context of 50% pretest likelihood results in a 90% likelihood of CAD, and a negative test result in a 10% likelihood of CAD. This process can be seen in Figure 1.[3]

Our clinical algorithm for the purpose of simple detection of CAD is shown in Figure 2.[5] Patients with a low probability (<0.15) of having angiographically significant (>50% stenosis) CAD can be identified, even before the standard exercise tolerance test (ETT) is performed. Patients with a low pre-ETT likelihood of CAD do not require further diagnostic testing, although continued medical follow-up or a watchful waiting approach is recommended. Patients with a low-intermediate pre-ETT likelihood of CAD (0.15 to 0.50) would undergo standard ETT as the next diagnostic step. Those who continue to have an intermediate likelihood of CAD after ETT (or those with an indeterminate ETT) and those whose pre-ETT likelihood of CAD was in the 0.50 to 0.85 range (in these patients even a negative ETT would not result in a low likelihood of CAD) will benefit from exercise nuclear testing. Patients with a high pre-ETT likelihood of CAD (>0.85) are generally considered to have an established diagnosis of CAD, and nuclear stress testing is not needed for diagnostic purposes. Nevertheless, as described below, these noninvasive procedures may be very effective in risk stratification and may aid in consideration of invasive patient management strategies.

RISK STRATIFICATION AND PATIENT MANAGEMENT

The most rapidly growing area of application of nuclear cardiology techniques is risk stratification,

From the Departments of Medicine and Radiological Sciences, UCLA School of Medicine, the Departments of Nuclear Cardiology and Nuclear Medicine Physics, Cedars-Sinai Medical Center, Los Angeles, CA; and the Department of Medicine and Center for Outcomes Research, Emory University, Atlanta, GA.

Address reprint requests to Daniel S. Berman, MD, Director, Nuclear Cardiology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, A042N, Los Angeles, CA 90048.

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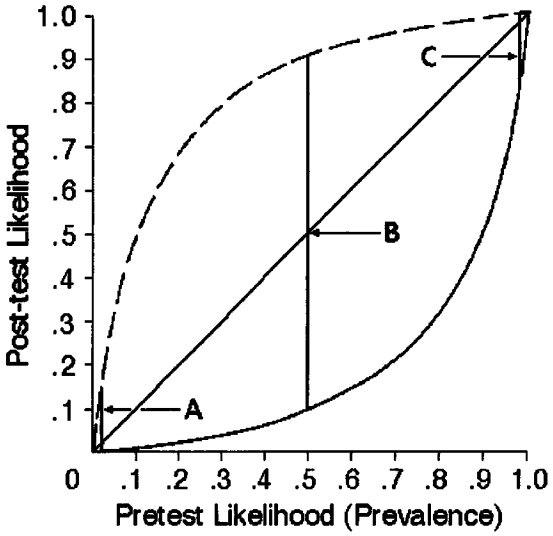


Fig 1. Relationship between pretest likelihood (X axis) and posttest likelihood (Y axis) of angiographically significant CAD for a test with 90% sensitivity and 90% specificity. The upper curve (*dashed*) depicts this relationship for the abnormal test results, and the lower curve (*solid*) for the normal test results. The center line is the line of identity. Vertical lines a, b, and c delineate three different pretest likelihoods of 0.01, 0.5, and 0.99, respectively. The length of these lines can be considered a measure of the diagnostic value of the test. Note that the longest line (greatest separation between the pretest and posttest likelihoods) is associated with the midrange of pretest likelihood. (Reprinted with permission.[15])

and this requires the acceptance of a new paradigm in patient management. A risk-based approach to patients with suspected CAD appears better suited to the modern environment of cost containment and dramatic improvements in medical therapy than the approach focusing on simple diagnosis, in which the patient with suspected disease typically undergoes coronary angiography and then frequently is revascularized. With the risk-based approach, the focus is not on predicting who has CAD, but on identifying and separating patients at risk for cardiac death, patients at risk for nonfatal myocardial infarction (MI), and patients at low risk for either event. The advantage of this prognostic end point in noninvasive testing is that it defines who has disease and who is at risk for an adverse event, thus needing to be treated. Another advantage for risk assessment is that it is not bound by many of the methodological limitations (eg, work-up bias) that hamper diagnostic assessments.

The basic concept in the use of nuclear tests for risk stratification is that they are best applied to patients with an intermediate risk of cardiac death, analogous to the optimal diagnostic application of noninvasive testing in patients with an intermediate likelihood of having CAD. For prognostic testing, patients known to be at high risk or low risk would not be appropriate subjects for cost-effective risk stratification because they are already risk stratified. The prognostic testing concept implies a need for a definition of risk categories. In a recent meta-analysis of randomized trials of bypass surgery,[6] definitions of low, intermediate, and high risk have been proposed. Low, intermediate, and high risk are defined as less than 1%, 1% to 3%, and greater than 3% cardiac mortality rate per year, respectively. Because the mortality risk for patients undergoing either coronary artery bypass grafting or angioplasty is greater than 1% per year,[7] patients with a less than 1% mortality rate would not be candidates for revascularization to improve survival, and would be appropriately classified by this rate as at a low risk of death.

The basis for the power of nuclear testing for risk stratification is found in the fact that the major

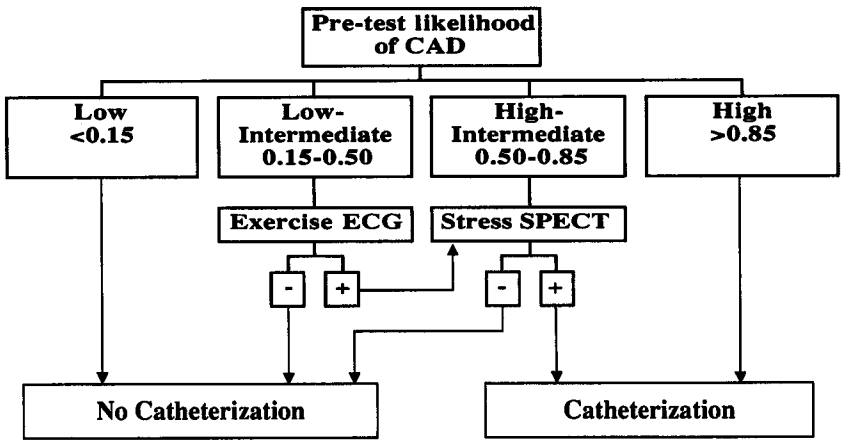


Fig 2. Role of nuclear testing in CAD diagnosis.

determinants of prognosis in CAD can be assessed by measurements of stress-induced perfusion or function. These measurements include the amount of infarcted myocardium, the amount of jeopardized myocardium (supplied by vessels with hemodynamically significant stenosis), and the degree of jeopardy (tightness of the individual coronary stenosis). An additional important factor in prognostic assessment is the stability (or instability) of the CAD process. This last consideration may help explain an apparent paradox: Nuclear tests, which in general are expected to be positive only in the presence of hemodynamically significant stenosis, are associated with a very low risk of either cardiac death or nonfatal MI when normal; in contrast, it has been observed that most MIs occur in regions with pre-MI lesions causing less than 50% stenosis.[8,9] This paradox may be explained by the different response to stress of mild stenoses associated with stable and unstable plaque. It has been shown that unstable plaque is associated with abnormal endothelial function, resulting in vasoconstriction in response to acetylcholine stimulation, whereas stable mild coronary lesions respond with vasodilation.[10] It is possible that factors released during exercise or vasodilator stress may be similar to acetylcholine in stimulation of a differential endothelial response in stable and unstable plaque. Thus, nuclear tests (by virtue of their physiological assessments) might be able to discern abnormalities of endothelial function associated with high risk, even in the absence of significant stenosis. This interesting hypothesis, however, requires further testing.

To maximally extract the information regarding these prognostic determinants in CAD, it is necessary to consider the full extent and severity of abnormality, either quantitatively[11,12] or semiquantitatively,[13] rather than simply determining that the nuclear study is normal or abnormal. Furthermore, there appears to be incremental value in measuring both perfusion and function for the purposes of risk stratification, thus leading to gated cardiac SPECT's increased prognostic use over standard myocardial perfusion SPECT.

SUSPECTED CHRONIC CAD

Ladenheim et al, from our group,[14] documented that the extent and severity of ischemia, as reflected by nuclear variables, are independent prognostic markers. Data from Staniloff et al,[15] also from our laboratory, showed that the prognostic content of nuclear tests is present even in the subset of patients who have not undergone catheterization, ie, in patients with no known CAD. This work showed that patients with mild or no perfusion defects had an excellent 1-year prognosis, with less than 1% of these patients having hard events (MI or death) or soft events (revascularization procedures occurring at more than 60 days after testing). That nuclear testing provided incremental prognostic information was first documented by Ladenheim et al using planar thallium-201 scintigraphy.[16] Exercise thallium-201 SPECT was subsequently shown by Iskandrian et al[17] to provide significant information over clinical information alone or clinical plus exercise information. Furthermore, these investigators showed that, once the SPECT information was known, there was no further incremental prognostic information provided by catheterization data (Fig 3).[17]

The early demonstration that the extent and severity of ischemia measured by nuclear variables are independent prognostic markers was carried over into the development of prognostic applications of myocardial perfusion SPECT. The approach we have advocated uses a 20-segment, 5-point semiquantitative analysis. To optimally determine the level of risk from the extent and severity of perfusion abnormalities, we have developed a number of summed or global scores derived from the 20 individual segment scores (Table 1). Summed indices provide single numbers representing global perfusion, analogous to ejection fraction's role in representing global function. Specifically, the summed stress score (SSS) represents the extent and severity of stress perfusion defects, analogous to a peak exercise ejection fraction, and the summed rest score (SRS) provides the perfu-

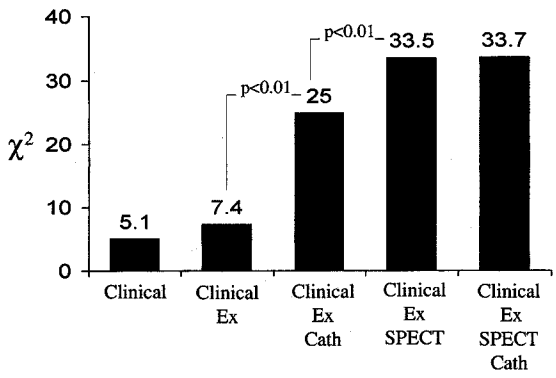


Fig 3. Incremental prognostic information provided by clinical, exercise, catheterization, and SPECT variables, shown by global χ^2. (Reprinted with permission from the American College of Cardiology [*Journal of the American College of Cardiology*, 1993, 22, 665-670].)

Table 1. Definition of Scintigraphic Indices

Summed scores	
SSS*: sum of stress scores of the 20 segments	
SRS*: sum of rest scores of the 20 segments	
SDS*: SSS − SRS	
Degree of abnormality by SSS category	
<4	Normal
4-8	Mildly abnormal
9-13	Moderately abnormal
>13	Severely abnormal

Abbreviations: SSS, summed stress score; SRS, summed rest score; SDS, summed difference score.
*Incorporates extent and severity of defects.

sion analogue of the resting ejection fraction. The degree of reversibility, or summed difference score (SDS), can then be calculated by subtracting the SRS from the SSS, providing a measurement that is the perfusion analogue to the change in ejection fraction during stress. Based on our work, SSS values are divided into four categories: normal (0–3), mildly abnormal (4–8), moderately abnormal (9–13), and severely abnormal (greater than 13).

A series of manuscripts has documented the prognostic value of this semiquantitative analysis with either technetium-99m sestamibi or T1-201 SPECT. In a study of 1,702 patients, of whom 1,131 had normal scan results, we showed that a normal technetium-99m sestamibi scan was associated with a very low (0.2%) likelihood of cardiac death or MI over a 20-month period (Fig 4).[18] This study documented that the greatest separation in event rates between the patients with normal and abnormal test results occurred in patients with high

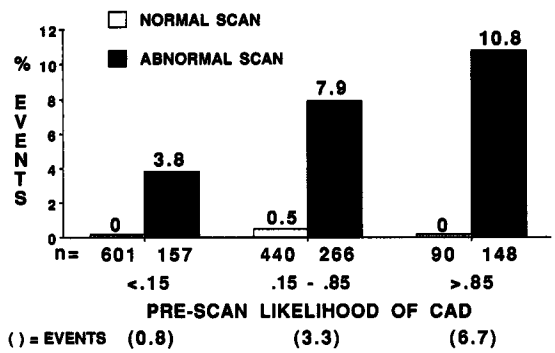


Fig 4. Rate of cardiac events (cardiac death or nonfatal MI) throughout the follow-up period (≥20 ± 5 months) as a function of SPECT results and prescan likelihood of CAD (<0.15, low likelihood; 0.15-0.85, intermediate likelihood; >0.85, high likelihood). *Solid bars,* abnormal scan results; *open bars,* normal scan results. (Adapted and reprinted with permission from the American College of Cardiology [*Journal of the American College of Cardiology,* 1995, 26, 639-647].)

pretest likelihood of CAD, supporting the use of prognostic testing in this large patient subset. Significant stratification occurred in patients with low, intermediate, and high likelihoods of CAD. When cost was taken into account, however, it was found that patients with a low likelihood of CAD could not be studied cost-effectively for prognostic purposes, despite the stratification in this group (Fig 5). Because low-risk patients have so few events, the costs or resource use expended to identify risk becomes excessive. On the basis of this prognostic data, we devised an optimized nuclear strategy for the assessment of prognosis (Fig 6). With this approach, patients with a low pretest likelihood of CAD would not be tested because their risk was observed to be low (0.8% likelihood of death or MI over a 20-month follow-up). The remaining patients would be divided on the basis of their resting electrocardiogram (ECG). If the ECG could not be interpreted for purposes of stress testing (eg, LBB, LVH, digoxin, WPW), direct nuclear testing was highly effective in prognostic stratification. Although the overall 20-month event rate in this patient group was 5%, the 50% of the patients who had normal scan results enjoyed a 0% event rate over 20 months; the remaining 50% with abnormal scan results had an 11% event rate over the same period.

The overall event rate was lower for patients with an interpretable exercise ECG, but still in the intermediate category (3.3% over the 20-month

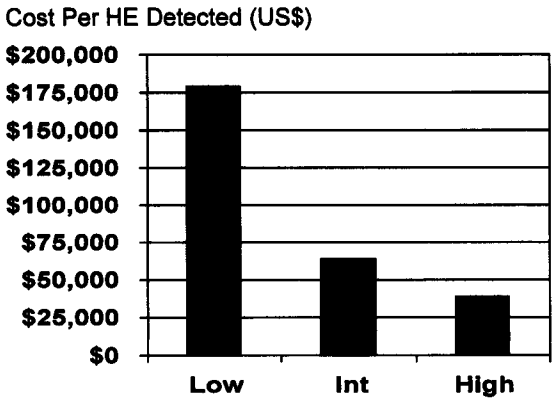


Fig 5. Cost-benefit of nuclear testing: the cost per hard event detected in patients with a low prescan likelihood of CAD is prohibitive. Low, intermediate, and high prescan likelihood of CAD, respectively. Assumptions: nuclear cost, $840, catheterization cost, $2,800; all abnormal scans referred to catherization. Int, intermediate. (Adapted and reprinted with permission from the American College of Cardiology [*Journal of the American College of Cardiology,* 1995, 26, 639-647].)

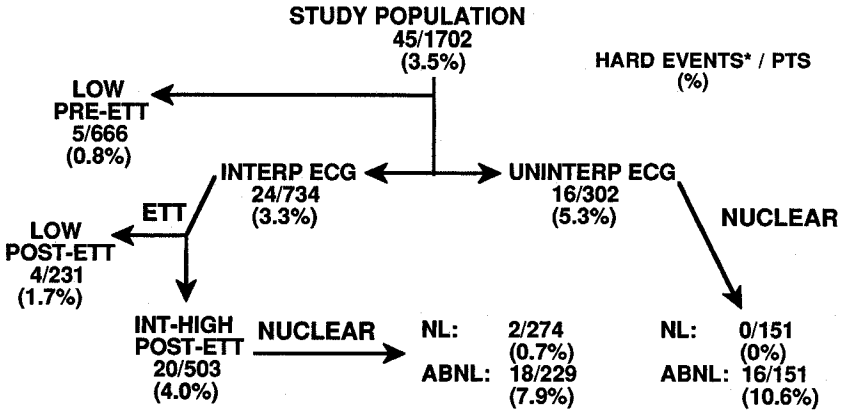


Fig 6. Optimized nuclear strategy for prognostic purposes. Low pre-ETT, low pre–exercise tolerance test likelihood of CAD; interp ECG, interpretable ECG for exercise purposes; uninterp ECG, uninterpretable ECG for exercise purposes; low post-ETT, low post–exercise tolerance test likelihood of CAD (<15%); INT-high post-ETT, intermediate to high post-ETT likelihood of CAD (≥15%); NL, normal; ABNL, abnormal. (Adapted and reprinted with permission from the American College of Cardiology [*Journal of the American College of Cardiology*, 1995, 26, 639-647].)

follow-up period). In patients with a low likelihood of CAD after exercise testing, the event rate was also low (1.7% over 20 months), suggesting these patients did not need further nuclear testing. When a patient's likelihood of CAD was intermediate to high after exercise ECG, the overall event rate was 4%. The study population was stratified on a nearly 50:50 basis into patients with normal scan results, in whom the event rate was low (0.7%), and patients with abnormal scan results, in whom the event rates were intermediate to high (7.9%).

In an expanded patient population, our group examined the differences in the prognostic value of technetium-99m sestamibi perfusion SPECT in women versus men. Nuclear information added substantially more information in women than in men, representing the first demonstration of the superiority of a noninvasive test for CAD in women compared with CAD in men. Furthermore, women were risk stratified more efficiently than men, suggesting the potential for a more cost-efficient strategy in women using myocardial perfusion SPECT.[19]

What was yet to be documented was whether this stratification had an effect on patient outcome. We and others thought that documentation of the post–nuclear testing catheterization rate, which governs the rate of revascularization, could be considered an indication of the effect of testing on patient outcome. After initially describing a low catheterization rate in patients with normal scans,[18] we then evaluated a population of 2,203 patients with no known CAD.[20] The follow-up was of 18 ± 7 months duration. In this population, nuclear scanning added dramatically to the prediction of subsequent hard cardiac events. By multivariate analysis, the nuclear result was the overwhelmingly dominant factor determining the subsequent referral to catheterization. The study showed that myocardial perfusion SPECT was effective in risk stratification and in governing management across the spectrum of clinical risk. In this regard, the data were analyzed as a function of the Duke treadmill score, a composite clinical variable of documented prognostic importance including exercise duration, exertional chest pain, and ST segment depression.[21] As illustrated in Figure 7, the SSS stratified patients with respect to subsequent heart event rates in all categories of risk according to Duke treadmill scores. The subsequent catheterization rates (Fig 8) more closely paralleled the nuclear score results than the Duke treadmill score results. Closer analysis of these data reveals that the patients with a low Duke treadmill score had a hard event rate of less than 1%, perhaps not needing nuclear testing.

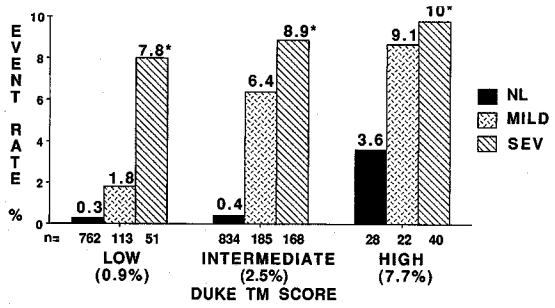


Fig 7. Duke treadmill (TM) score category and nuclear scan result versus hard event rate. Rates of hard events (MI or cardiac death) over the follow-up period in patients in low, intermediate, and high Duke treadmill score categories with normal (NL), mildly abnormal (MILD), and severely abnormal (SEV) nuclear scans. Parentheses under Duke treadmill subgroups show hard event rates in these groups. *$P < .05$ across scan results. (Adapted and reprinted with permission from 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 93:905-914, 1996.)

Those with a high Duke treadmill score (representing less than 5% of the population) overall had a high event rate of 7.7% over the 18-month follow-up, and could have been directly catheterized. However, 55% of the patients fell into the category of an intermediate Duke treadmill score with an intermediate event rate of 2.5%. Within this category, those patients with a normal scan had a very low event rate and were infrequently catheterized. Those with moderately abnormal scans had intermediate event rates and an intermediate rate of catheterization, and those with moderately to severely abnormal scans had higher event rates with higher rates of catheterization. Thus, the nuclear tests were able to stratify patients who could not be differentiated according to risk by Duke treadmill score alone. Similar strong relationships between the results of myocardial perfusion SPECT and subsequent catheterization rates have been reported by Bateman et al[22] and Nallamothu et al.[23]

In more recent studies, we have found that patients with mildly abnormal scans also have a low risk of cardiac death. Hachamovitch et al[24] analyzed 5,183 patients undergoing stress perfusion SPECT testing in our laboratory. Approximately one third of these patients underwent adenosine stress, and two thirds underwent exercise stress. The follow-up duration was 646 ± 226 days, and 158 nonfatal MIs and 119 cardiac deaths were observed in this group. The most important result from this study is shown in Figure 9, which separately analyzes the nonfatal MI and cardiac death rates as a function of the summed stress perfusion scores. Patients with normal scans had relatively low risk for cardiac events, and patients with moderately and severely abnormal scans were at intermediate risk for both cardiac death and MI. Importantly, however, patients with mildly abnormal summed stress scores were at intermediate risk for MI (2.7% risk of MI per year of follow-up), but were at low risk for subsequent mortality (0.8% cardiac death rate per year of follow-up). These latter results have major implications for therapeutic intervention in these patients.

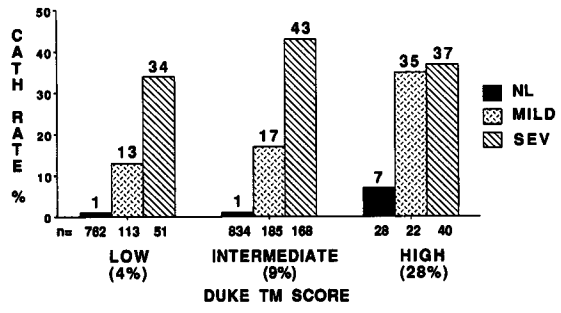


Fig 8. Duke treadmill (TM) score category and nuclear scan result versus rate of referral to catheterization. Rates of referral to early catheterization (within 60 days after nuclear testing) in patients with low, intermediate, and high Duke treadmill score categories with normal (NL), mildly abnormal (MILD), and severely abnormal (SEV) nuclear scans. Parentheses under Duke treadmill subgroups show hard event rates in these groups. *$P < .05$ across scan results. (Adapted and reprinted with permission from 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 93:905-914, 1996.)

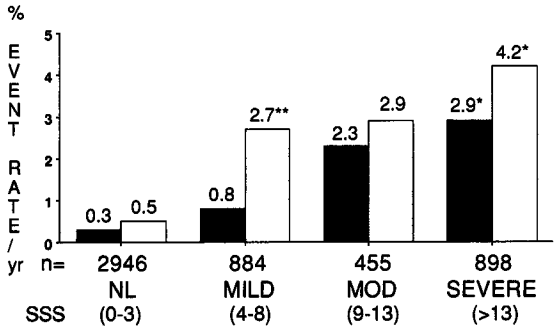


Fig 9. Rates of cardiac death (*solid bars*) and MI (*open bars*) per year, as a function of scan result. The numbers of patients within each scan category are shown underneath each pair of columns. *Statistically significant increase as a function of scan result. **Statistically significant increase in rate of MI versus cardiac death with scan category. NL, normal; MILD, mildly abnormal; MOD, moderately abnormal; SEVERE, severely abnormal. (Reprinted with permission from 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 97:535-543, 1998.)

Based on the results of this study, a modification of the approach to management of patients with known or suspected CAD using nuclear testing can be proposed (Fig 10). Concordant with the previously validated strategy (Fig 6), patients with an intermediate-to-high likelihood of CAD would be candidates for testing. Those with normal test results would have a low risk of MI or death, and would require primary preventive measures. Those with moderately to severely abnormal scans would have an intermediate risk of MI or death, and would be candidates for catheterization with consideration of revascularization (of course, to be accompanied by medical therapy). As indicated by the results of the recent study of Hachamovitch et al,[24] patients with a mildly abnormal scan (SSS = 4-8) could be considered as having CAD and intermediate risk of

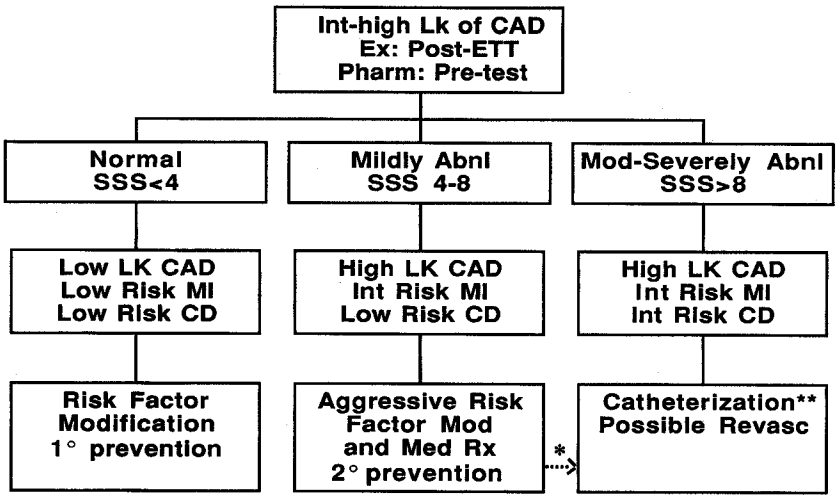


Fig 10. Strategy for management of CAD based on the results of myocardial perfusion SPECT. INT-high LK of CAD, intermediate to high likelihood of CAD (≥0.15). For exercise, this represented the post-ETT likelihood; for pharmacological stress, the pretest likelihood; SSS, summed stress score; CD, cardiac death; MOD, moderately; ABNL, abnormal; SX, symptoms; PT, patient. (Data from 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 97:535-543, 1998.)

MI, but low risk of cardiac death. In the absence of refractory symptoms or another compelling reason for catheterization, these patients would be candidates for aggressive risk factor modification without catheterization, using secondary prevention guidelines. Thus, maximal medical therapy would be indicated because a variety of medical therapies have been shown by randomized trials to reduce the risk of MI.[25-34] Further analysis of the patients in our recent study indicates that the use of nuclear testing for selection of patients for revascularization is associated with an expected effect on mortality rates (Fig 11). When patients undergoing

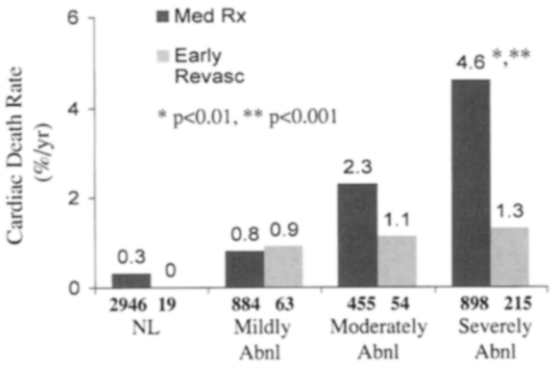


Fig 11. Rates of cardiac death per year as a function of scan result and type of therapy. *Dark gray bars,* patients undergoing initial medical therapy after SPECT; *light gray bars,* patients undergoing revascularization early after SPECT. *$P <$ .01 versus patients undergoing revascularization early after SPECT; **$P <$ .001 within patients treated with medical therapy after SPECT. (Reprinted with permission from 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 97:535-543, 1998.)

medical management were compared with patients undergoing early revascularization in our study, the mortality rates were found to be lower in the latter group when the SSS was moderately to severely abnormal. The medical and surgical groups, however, had equal mortality rates in the presence of normal or mildly abnormal SSS.

These promising data are based on a single-center study. In a recent preliminary communication,[35] a new collaborative study by the TriCOR Foundation (involving over 20,000 patients from Cedars-Sinai Medical Center and the Mid America Heart Institute) resulted in findings very similar to those observed in the single-center study, with respect to the relationship between SSS and subsequent nonfatal MI and cardiac death rates.

In the era of cost containment, it becomes increasingly important to determine whether noninvasive test results can be cost effective. To this end, Shaw et al[36] evaluated a patient population of 11,249 consecutive stable angina patients, gathered in a large multicenter trial comprising many laboratories around the United States, including our own. The study was designed to answer the question of whether stress myocardial perfusion SPECT of stable angina patients reduces the cost of care compared with direct catheterization, and was structured as a matched cohort study, with a direct catheterization group chosen from the Duke databank and a myocardial perfusion SPECT group chosen from the multiple center cohorts. Patients chosen from the Duke databank were matched to SPECT patients with respect to their pretest risk of CAD, the objective being that of determining whether there could be cost minimization through

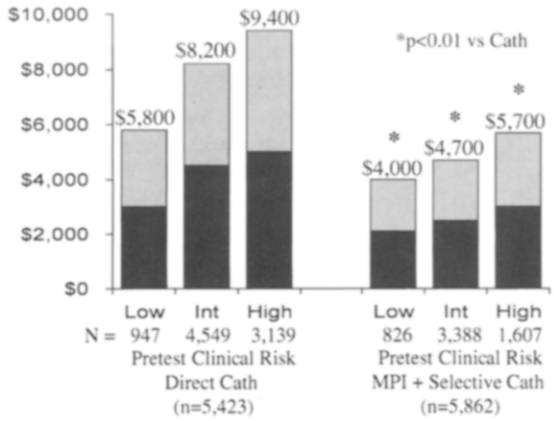


Fig 12. Comparative cost between screening strategies using direct catheterization (Cath) and myocardial perfusion imaging (MPI) with selective catheterization. Low, Int, and High represent low-, intermediate-, and high-risk subsets of the patients with stable angina. Shown are the initial diagnostic costs (*solid bars*) and follow-up costs including costs of revascularization (*gray bars*). A 30% to 41% reduction in costs was noted in each category. (Adapted and reprinted with permission from the American College of Cardiology [*Journal of the American College of Cardiology*, 1999, 33, 661-669].)

the use of SPECT, at equal mortality risk. Costs included the early diagnostic costs of SPECT and catheterization, as well as the follow-up (late) costs of angioplasty and surgery.

Figure 12 shows the comparative costs of (1) the direct catheterization and (2) the myocardial perfusion imaging with selective catheterization screening strategies. For all levels of pretest clinical risk, there was a substantial reduction (31% to 50%) in costs using the myocardial perfusion SPECT plus selective catheterization approach. This cost reduction was seen in both the diagnostic (early) and follow-up (late) costs. This information alone, of course, shows cost savings but not cost effectiveness, because documentation of cost effectiveness requires consideration of event rates (ie, cost per life year saved). The event rates from this trial are shown in Figure 13. The rates of subsequent nonfatal MI and cardiac death were virtually identical in all risk subsets for the catheterization and myocardial perfusion imaging approaches. What was significantly different was the rate of revascularization, which was reduced by nearly 50% in the myocardial perfusion imaging with selective catheterization cohort. Thus, when event rates are considered, the substantial cost savings and equivalent outcomes translate into cost-effective care when myocardial perfusion imaging is used as an initial test for patients with stable chest pain symptoms. Cost effectiveness is achieved through its role in helping avoid the "oculostenotic reflex."

Assessing patients by noninvasive testing at one particular point in time does not imply that no follow-up testing is necessary. There can be progression of coronary disease over time, particularly in the absence of aggressive medical therapy. In that regard, our group has preliminarily evaluated the "warranty period" for a normal scan. It appears that for patients who are appropriately referred to testing (patients with intermediate to high likelihood of CAD), a normal scan result is associated with a very low risk for approximately 2 years. After that time the risk increases, suggesting that repeat testing after 2 years should be considered in most patients for prognostic purposes.[37]

The foregoing information provides compelling

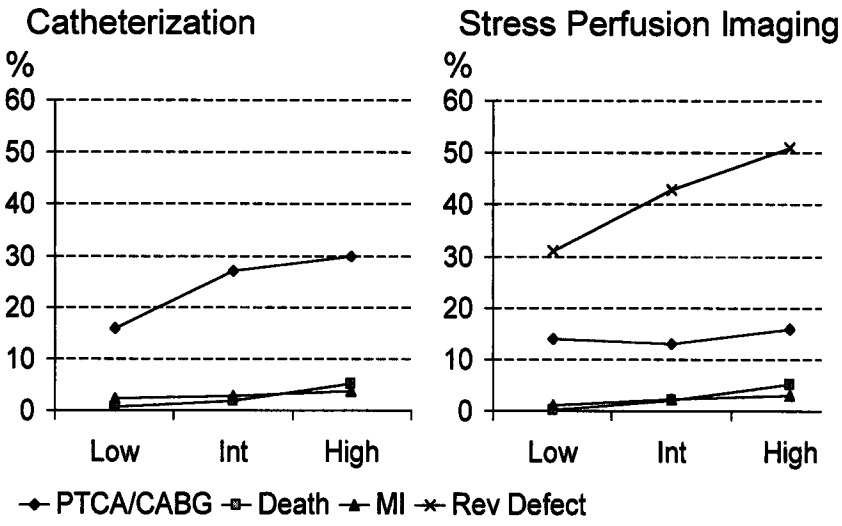


Fig 13. Subsequent event rates in the patient populations shown in Fig 12. The rates of MI and cardiac death were identical between the populations. What was different was an approximately 50% reduction in the revascularization rate in the group approached with myocardial perfusion imaging and selective catheterization. Death, cardiac death; REV defect, reversible defect. (Adapted and reprinted with permission from the American College of Cardiology [*Journal of the American College of Cardiology*, 1999, 33, 661-669].)

evidence that myocardial perfusion SPECT is effective in the prognostic stratification of patients. It would appear, however, that current data on risk stratification by myocardial perfusion SPECT underestimates the strength of this modality. In all the studies quoted above, patients referred for early revascularization after nuclear testing were excluded (censored) from consideration in the prognostic studies. Although there is a reason for this censorship, namely that the event rate may have been altered by the revascularization procedure, the exclusion results in the published data's inability to reflect the prognostic information data derived from scans performed in the highest-risk patient subset. A similar effect occurs to the extent that patients and physicians alter therapy and modify risk factors on the basis of the scan information, thereby likely reducing the event rate that might be observed for a given abnormal scan pattern in a natural history study.

Additionally, recent technical advances in the field of myocardial perfusion SPECT have typically not been included in the prognostic assessments. For example, the impact of quantitative analysis on prognosis has not been studied in any detail, but provides a vehicle for dissemination of the findings of semiquantitative analysis.[38] The potent information contained in the ejection fraction assessed from gated SPECT is likely to enhance the prognostic content of myocardial perfusion SPECT.[38a,39] A similar gain may occur through consideration of poststress wall motion abnormalities on gated SPECT.[40] In addition to the ejection fraction, other important information that can be derived from nuclear studies has not been included in the prognostic assessment. This information includes the transient ischemic dilation of the left ventricle[41,42] and the pulmonary uptake of radioactivity.[43,44] For practical purposes, preliminary data by Lewin et al[45] from our institution has shown a way of integrating the information of ejection fraction and perfusion defects from gated SPECT. When the ejection fraction poststress is less than 35%, the mortality rate is greater than 1%, regardless of the amount of ischemia SDS.[45] In general, we would recommend that these patients be considered for catheterization. In contrast, in patients with ejection fractions poststress of greater than 35%, there is a strong linear relationship between the amount of ischemia as measured by the SDS and cardiac events. When ejection fraction is relatively preserved, catheterization can be reserved for patients with moderately extensive ischemia. Of course, whenever severe ischemic symptoms are present, catheterization would be indicated for purposes of determining whether revascularization might be indicated for symptom relief.

POSTCATHETERIZATION PATIENTS

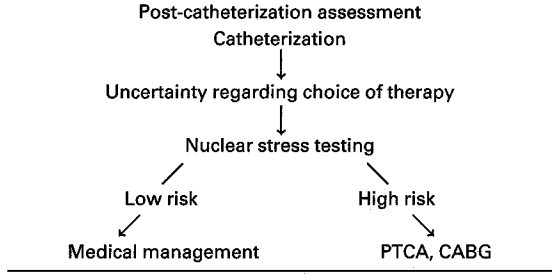
Although coronary angiography provides exquisite detail of coronary anatomy, the functional implications of coronary stenoses are not always clear from the angiographic data. High-grade stenoses in the absence of collaterals are appropriately considered lesions of clinical significance; frequently, however, lesions of lesser grade are observed, or the implications of higher-grade lesions may be unclear because of the presence of excellent collateral vessels. In these cases, the application of stress nuclear testing can help risk stratify patients on the basis of the extent of stress-induced ischemia.[46,47]

With regard to the ability of nuclear tests to risk stratify patients with known anatomy, several studies have documented that patients with no ischemia by nuclear testing have relatively low risk for cardiac events, despite the presence of known CAD.[48-50] These findings have led to the development of the algorithm shown in Table 2. When there is uncertainty regarding the appropriate choice of therapy after coronary angiography, nuclear testing can be effectively used to guide patient management decisions.

ASSESSMENT BEFORE VASCULAR SURGERY

Patients with peripheral vascular disease are at increased risk of having CAD. Peripheral vascular surgery, with its associated marked hemodynamic stresses, carries at least a moderate risk of perioperative events for patients with known CAD. Because these patients frequently cannot exercise, they are ideal candidates for the use of vasodilator stress in

Table 2. Nuclear Stress Testing After Catheterization



Abbreviations: PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

conjunction with nuclear scanning, and a large body of literature exists documenting the effectiveness of nuclear stress testing in this context. Risk assessment with nuclear imaging may aid both in estimating a patient's likelihood of a perioperative or postoperative event and in consideration of long-term prognosis. Recent guidelines have been developed suggesting that nuclear testing is appropriate for patients with an intermediate risk of a cardiac event at the time of the procedure.[51] A simplified version of the guidelines that pertain to prevascular surgery is shown in Table 3. As with virtually all of the clinical syndromes, stress nuclear studies are recommended for patients at intermediate risk for cardiac events.

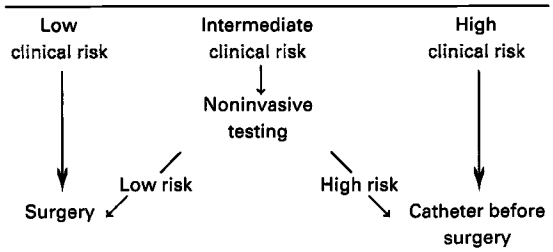
POST-PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY PATIENTS

Although nuclear cardiology testing before percutaneous transluminal coronary angioplasty (PTCA) could be useful to define the presence and extent of ischemia, it has been noted that only a minority of patients undergo stress testing before PTCA.[52] Nuclear testing is particularly valuable after PTCA because of the frequent occurrence of significant restenosis. Exercise thallium-201 SPECT data by Hecht et al[53] have shown that nuclear testing is accurate in defining the presence of restenosis, whether or not complete revascularization was achieved with PTCA and in asymptomatic as well as symptomatic patients.[54] Recent data have suggested that nuclear testing remains effective in detecting restenosis in patients undergoing angioplasty with coronary stenting.[55,56]

Less is known regarding the prognostic application of post-PTCA nuclear testing. A preliminary report by Lewin et al[57] from our institution has shown that event rates are strongly related to the summed stress score after PCTA, with a pattern very similar to that observed in patients with no known CAD; ie, patients with mildly abnormal scans appeared to have increased rates of nonfatal MI but low rates of cardiac death, whereas the rates of both of these events were in the intermediate to high range in patients with more abnormal scans. Accordingly, this preliminary report documented that there was an appropriate use of nuclear scan in guiding decisions for catheterization, with low early catheterization rates after nuclear scanning in patients with little evidence of ischemia.[57] A review of the use of nuclear testing after PTCA has recently been published.[58]

The general recommended approach of nuclear testing in the post-PTCA patient would therefore be as follows: in patients with single-vessel CAD and angina or interpretable ST segment depression pre-PTCA, post-PTCA assessment could be performed on a clinical or standard exercise testing basis. In other patients, when symptoms develop, nuclear testing can be helpful in defining the culprit vessel and assessing the extent of ischemic abnormality. This is also the recommendation of guidelines from the ACC/AHA on percutaneous interventions.[59] For patients with no symptoms, nuclear testing between 3 and 6 months after angioplasty is generally recommended. The exception to this rule would be patients with single-vessel disease and ischemic ST-segment depression pre-PTCA, in whom simple exercise testing could be used. Because virtually all restenoses occur within the first 6 months after intervention, the subsequent assessment of patients becomes similar to that of other groups of patients with chronic CAD, with a recommendation of repeat testing between 1 and 2 years after the 3- to 6-month test. Whenever moderate to severe ischemia is found by nuclear testing, consideration should be given to repeat catheterization.

Table 3. Guidelines for Perioperative Cardiovascular Evaluation



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POST-BYPASS SURGERY PATIENTS

Nuclear testing has become central in the assessment of the post-bypass patient. It is known that 75% of vein grafts can be expected to be occluded or severely stenosed by 10 years after surgery, particularly in patients undergoing saphenous vein graft surgery.[60,61] We have previously chosen a 5-year cut-off point to evaluate the post-bypass patient, and have shown that exercise thallium-201 SPECT is highly useful for the prediction of cardiac events in patients at that time point.[62] Recent studies have shown that exercise thallium-

201 SPECT is predictive of hard cardiac events even in the asymptomatic post-bypass patient.[63] Moreover, we have reported preliminary findings using technetium-99m sestamibi, showing that nuclear stress testing is effective in predicting subsequent events and determining a need for catheterization in the post-bypass population.[64]

In general, the recommendations for the post–bypass surgery patient are that when patients develop symptoms, SPECT imaging is useful in determining the presence and extent of CAD. In the asymptomatic patient, SPECT perfusion imaging should be considered in the 5 to 7 years postoperative time frame. Whenever moderate to severe ischemia is present, consideration of repeat catheterization arises.

ASSESSMENT OF MYOCARDIAL VIABILITY

In the setting of chronic CAD, nuclear cardiology studies are commonly used to assess viability in patients with abnormal ventricular function. The clinical setting in which this assessment most commonly arises is the evaluation of patients with poor ventricular function, when the likelihood of improvement after revascularization is being considered. This information can be useful in determining the appropriateness of medical management, revascularization, or cardiac transplantation.

Twenty-four hour redistribution thallium-201 scintigraphy and fluorine-18-FDG imaging are particularly effective in assessment of myocardial viability. Currently it is widely thought that resting myocardial perfusion scintigraphy with technetium-99m sestamibi or tetrofosmin (particularly if augmented by preinjection administration of nitroglycerin)[65,66] is as effective as rest/redistribution thallium-201 scintigraphy in assessing myocardial viability.

ASSESSMENT OF THERAPY

With the broadening of the application of medical therapy (as an alternative to revascularization) to various subgroups of patients with CAD, methods for evaluation of the efficacy of medical therapy become of increasing importance. In this regard, we consider it likely that nuclear cardiology techniques will find an additional area of growth in serial patient assessment. The discussion to this point in this article has focused on initial patient assessment. After a patient is defined as being an appropriate candidate for medical therapy, nuclear techniques can be effectively used to determine whether therapy has been successful or whether the patient's risk status may have worsened, thereby requiring a change in therapeutic regimen. A requirement for serial applications is that the nuclear techniques being used be highly reproducible, and that the degree of change in the assessed variables associated with measurement error be known. Our group has previously reported on 16 patients with stable CAD and reversible perfusion defects, evaluated with quantitative thallium-201 myocardial perfusion SPECT after exercise on two separate occasions. The concordance coefficient was 0.94, and the mean absolute deviation 5.1%.[67] Similar findings were reported with serial exercise thallium-201 SPECT by Mahmarian et al,[68] also using a quantitative analysis approach. These investigators showed that a $\geq$10% change in total perfusion defect size in an individual patient defined the 95% confidence interval for exceeding the variability of the method. Although the statistical analyses were different between these studies, the results are very similar. More recently, we have assessed the repeatability of exercise technetium-99m sestamibi SPECT. Using a previously defined quantitative analysis approach (Cedars-Emory quantitative analysis) and a newly developed technique (quantitative perfusion SPECT or QPS), we have shown high reproducibility of both methods.[69] We have also shown that the SSS, representing the semiquantitative 20-segment analysis of extent and severity of perfusion defects, is highly reproducible.[69] These data provide the validation for the clinical application of nuclear methods for sequential assessment of therapy.

For this application, Mahmarian et al[70] documented that transdermal nitroglycerin patch therapy reduces the extent of exercise-induced myocardial ischemia. Lewin et al,[71] have shown that a sustained improvement in myocardial perfusion can be achieved with isosorbide mononitrate. Most recently, Dakik et al[72] have shown that SPECT imaging can be used to show a reduction in perfusion defect size in patients undergoing intensive medical therapy versus coronary angioplasty after acute MI. This sequential assessment also is being applied in a large randomized trial comparing medical therapy with angioplasty (COURAGE), and in the evaluation of the response of myocardial perfusion to therapy with vascular endothelial growth factor.[73]

ACUTE CORONARY ARTERY DISEASE

Detection of Acute Ischemic Syndromes

Acute ischemic syndromes are best categorized as acute transmural (Q) MI and nontransmural (non-Q) MI as well as unstable angina pectoris. In general, all of these syndromes have the underlying pathophysiology of presence of severe obstruction or closure of a coronary artery secondary to acute thrombus formation or spasm in a segment of an artery. Because of this relationship to closure of a vessel, myocardial perfusion/function scintigraphy is an effective means of detecting and managing patients with acute ischemic syndromes.

Although the diagnosis of acute MI is frequently straightforward, in many patients it is not. For example, the ECG is diagnostic in only two thirds of patients with MI, at the time of their initial presentation to the emergency room. In nontransmural MI, and particularly in left circumflex artery MI, the ECG frequently is entirely normal.[74,75] Furthermore, the ECG is frequently nondiagnostic even when abnormal (eg, with left bundle branch block or pacemakers, etc). From the emergency physician's standpoint, the problem of missed MIs in the emergency room is of particular importance. It is has been estimated that up to 50,000 patients per year in the United States have MIs that are missed, representing approximately 4% of all patients with MIs who present to the emergency room. It has been shown that patients discharged from the emergency room with missed MIs have a substantially higher mortality rate.[76,77] Therefore, in the "rule-out MI" patient, an important clinical problem is how to distinguish those with true acute coronary syndromes, who may benefit from early intervention, from those who may require less intensive care, be discharged, or undergo immediate stress testing.

Technetium-99m sestamibi or tetrofosmin injected during chest pain provide an excellent opportunity to reduce this clinical problem because of their ability to assess ventricular function and myocardial perfusion with a single injection followed by imaging up to several hours later.[78-81]

After very promising results by Varetto et al[80] and Hilton et al,[78,79] Tatum et al[81] evaluated the use of technetium-99m sestamibi imaging in 438 patients presenting to the emergency department.[82] The investigators used technetium-99m sestamibi imaging in conjunction with a triage evaluation strategy. Nuclear testing was used only in patients with a moderate to low (but not very low) probability of an acute ischemic syndrome. Three hundred and thirty eight of 438 patients had normal study results, and 100 patients had abnormal study results. Subsequent deaths and MIs over the next year were found to occur only in the patients with abnormal technetium-99m sestamibi study results, whereas none of the 338 patients with normal technetium-99m sestamibi study results developed subsequent MI (these studies include assessment of perfusion as well as myocardial function using gated SPECT).

Several considerations are important for the most effective application of acute nuclear imaging. If a patient has had a prior MI, the nuclear studies are generally not useful. Also, combined assessment of perfusion and function should be routinely performed to minimize the false-negative rate. Technetium-99m sestamibi or technetium-99m tetrofosmin are preferable in this acute ischemic syndrome application, because unlike T1-201 they may be injected during chest pain in the emergency department and imaged 30 minutes to 4 hours later.

It is important to note that the accuracy of detecting an acute ischemic syndrome is related to the timing of injection with respect to the patient's chest pain. Ideally, the agent would be administered during chest pain. Patients with unstable angina could conceivably have intermittent coronary occlusion, with normalization of myocardial perfusion concomitant with the disappearance of chest pain. Because of this consideration, we have adopted a protocol suggested by Ziffer et al,[83] and use it for the assessment of those patients in whom chest pain has been relieved before injection. In this protocol, patients with ongoing chest pain and resolved chest pain are managed differently. The former are studied with technetium-99m sestamibi as noted above.

In patients whose chest pain has resolved, a resting thallium-201 injection would be performed instead of resting technetium-99m sestamibi or technetium-99m tetrofosmin. If the subsequent SPECT imaging is abnormal, the patient would be admitted and therapy for an acute ischemic syndrome begun, including consideration of early coronary angiography. Redistribution imaging may be useful for the assessment of myocardial viability. If the resting thallium-201 study is normal, the patient would not be discharged, because the possibility of resolved chest pain secondary to unstable angina would not yet have been evaluated. The

patient would instead be submitted to a stress technetium-99m sestamibi or tetrofosmin study. Based on the combined rest/stress assessment, patient management would range from discharge (with a normal scan) to admission (with a clearly abnormal scan). In this latter case, the presumptive diagnosis would be unstable angina, causing the resting chest pain that led to the emergency room presentation.

Ziffer et al[83] have recently published preliminary data on 2,737 patients undergoing this protocol. In 32% of the patients only resting imaging was performed, whereas in the remaining 68% of the patients rest and subsequent stress imaging were performed. Overall, 77% of all patients imaged were discharged without admission, and 23% were admitted. When the success of this protocol was evaluated, two aspects were of particular importance. The investigators compared the event for patients who were discharged from the hospital after imaging with the event rates that had previously been observed in patients discharged from the emergency room before the myocardial perfusion imaging protocol had been instituted. With the chest pain center and the myocardial perfusion imaging protocol, the annualized event rate in patients discharged from the emergency room was 0.17%. In the patients discharged in the period immediately before the opening of the chest pain center, the annualized cardiac event rate was 2.7%. Thus, use of myocardial perfusion scintigraphy in the chest pain center was associated with a significant reduction in the event rate (mortality and nonfatal MI) in patients discharged. In a subsequent preliminary communication, Ziffer et al[84] showed clear cost savings by applying myocardial perfusion scintigraphy to appropriately selected patients.

Initial Assessment of Prognosis

Cerqueira et al[85] and Miller et al[86] have documented that there is a strong relationship between the size of a myocardial perfusion defect (an indicator of infarct size) and subsequent mortality in the setting of acute MI. Assessment of prognosis by myocardial perfusion scintigraphy in acutely ischemic patients can be amplified by considering both left ventricular ejection fraction and perfusion defect size. These assessments can now be made with a single study using gated myocardial perfusion SPECT.

Selection of Therapy

An important and underappreciated application of myocardial perfusion scintigraphy in acute ischemic syndromes is the selection of the appropriate therapy for patients with a known ischemic syndrome. It has been suggested that considerations as to whether thrombolytic therapy or PTCA should be performed can be elucidated by resting myocardial perfusion scintigraphy in the following conditions: (1) patients presenting late (more than 12 hours) after chest pain,[87,88] as noted above; (2) patients with ST segment depression in whom injection can be made during chest pain (those with severe reduction in flow would be candidates for thrombolytic therapy or PTCA, whereas those without decrease in flow would not be good candidates); and (3) patients with left bundle branch block, in whom thrombolitic therapy or PTCA are generally recommended. These patients could most likely be better classified for therapy on the basis of resting myocardial perfusion scintigraphy, rather than through the use of clinical criteria alone. None of these applications have been well studied by randomized trials, but they remain interesting potential clinical applications.

Evaluation of Therapy

It has by now been well shown that myocardial perfusion scintigraphy is useful in the assessment of therapeutic efficacy for patients undergoing thrombolytic therapy or PTCA. Maddahi et al first showed this application using thallium-201 planar scintigraphy, in the early 1980s.[89,90] Subsequently, Gibbons et al[91] reported similar findings using technetium-99m sestamibi. On the basis of extensive work by that group of investigators, myocardial perfusion scintigraphy represents an efficient, less expensive end point for examining the efficacy of a variety of therapies in patients with acute MI before and after therapy (or even simply after therapy), compared with conventional mortality end points.

Assessment of Myocardial Viability

At times it becomes clinically important to assess the viability of abnormally contracting segments in the setting of acute MI. In this regard, it has become important to recognize the high frequency of myocardial stunning that occurs in the setting of an aborted acute MI. Since the earliest thrombolytic trials, it has been clear that severe and extensive wall motion abnormalities and severe

reduction of left ventricular function can be associated with the stunned myocardium when thrombolytic therapy or PTCA is applied early enough to abort the development of myocardial necrosis. Although the return of ventricular function may be delayed by up to several months, the degree of improvement in ventricular function can be dramatic. The finding of normal or nearly normal perfusion early after initial therapy (thrombolytic therapy or PTCA) can be accurately used to predict the return of ventricular function in a patient with an acute ischemic syndrome.

Discharge Planning

Practice guidelines in the United States have indicated that stress testing (with or without imaging) can be effective in risk stratification and guiding subsequent management of patients in whom the clinical indications of high risk are not present.[92] This suggestion is based on the results of several clinical trials, of which the TIMI II B study is probably the most widely quoted. In this study of 1,681 patients assigned to early catheterization and 1,658 patients assigned to watchful waiting strategies after acute MI with thrombolysis, there was no significant difference with respect to cardiac death, MI, or anginal status. Of importance, these excellent outcomes with watchful waiting were obtained without any standardized approach to the use of noninvasive testing.[92] Recently, the results of the VANQUISH trial (Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital) provided similar data for patients with non–Q-wave MI.[93] Common clinical thought had been that patients with non–Q-wave MIs would be potentially more in need of acute catheterization and consideration of revascularization, compared with patients with Q-wave MIs. Nonetheless, this supposition was not borne out by the VANQUISH study. Nine hundred twenty patients were randomly assigned to invasive (462 patients) management versus conservative (458 patients) management. The invasive management included early catheterization, performed a median of 2 days after MI. The conservative management included the use of radionuclide ventriculography, a predischarge symptom-limited exercise thallium-201 study or dipyridamole thallium-201 study, and then catheterization if recurrent angina developed with ECG changes (>2 mm ST segment depression on exercise testing), there were ≥2 reversible defects on the thallium-201 study or increased thallium-201 uptake was observed. The results of this multicenter trial are shown in Figure 14. The probability of event-free survival (Fig 14) was higher in patients undergoing conservative therapy than in patients undergoing the invasive therapy approach.

Despite these findings, there is discordance between the practice guidelines and the actual practice in the United States. Mark et al[94] reported that 72% of patients after acute MI underwent early catheterization in the United States, compared with only 25% of patients in Canada. Interestingly, there was no significant difference in 1-year mortality rates between the two countries.[94]

With respect to perfusion scintigraphy, it should be noted here that the post-MI application is one in which the use of pharmacological stress over low-level nuclear stress testing may be particularly advantageous. Although either type of stress would be recommended by the guidelines, our preference is to use pharmacological stress. The reasons are as follows: (1) pharmacological stress does not require that the patient be able to exercise; (2) it can be easily and safely used as early as 2 days after MI[95,96]; (3) it decreases rather than increases blood pressure, avoiding the potential problem of myocardial rupture; and (4) it produces a maximal hyperemic stimulus, thereby obviating the need for maximal stress testing after recovery. Brown et al[97] have shown that dipyridamole technetium-99m sestamibi SPECT is highly useful for the prediction of future cardiac events after MI. In a moderate-sized population of patients studied using a 17-

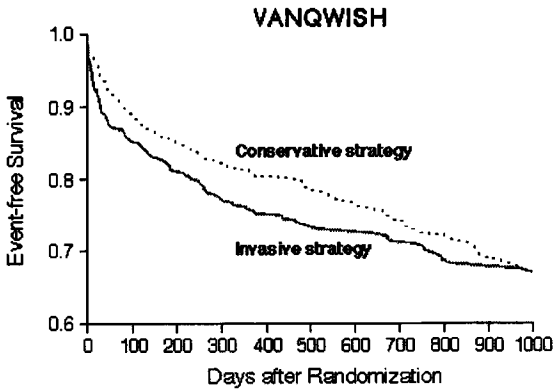


Fig 14. Kaplan-Meier analysis of the probability of event-free survival according to strategy group during 12 to 44 months of follow-up. The events included in this analysis were death and nonfatal MI (which together made up the primary end point). The Cox proportional-hazards ratio for the conservative as compared with the invasive strategy was 0.87 (95% confidence interval, 0.68 to 1.10). (Copyright ©1998 Massachusetts Medical Society. All rights reserved.)

Table 4. Post-MI, No Prior Catheterization

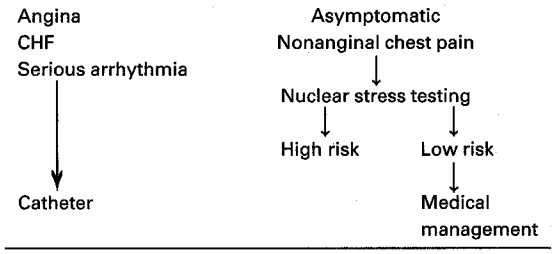
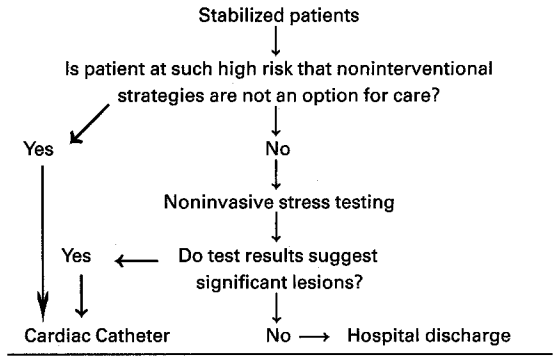


Table 5. Noninvasive Stress Testing in Unstable Angina



segment model, an average of 3.3 days after uncomplicated MI, patients with low-risk scans based on the SSS had a 3% probability of death or MI over a 2-year follow-up, compared with a 42% rate of death or MI in patients with high-risk summed scores. Mahmarian et al[98] have shown that there is incremental value in knowing the left ventricular ejection fraction as well as the extent of jeopardized myocardium, as determined by equilibrium blood pool scintigraphy and adenosine thallium-201 myocardial perfusion SPECT. These same investigators have shown the value of adding left ventricular ejection fraction to exercise myocardial perfusion SPECT.[99] The recent work of Dakik et al[72] suggests that the approach to medical therapy could safely be extended to patients considered to be at moderate to even high risk after acute MI, with serial nuclear studies providing the basis for selection of therapy as well as for subsequent assessment of its effectiveness and consideration for therapeutic change. Our approach to the use of noninvasive testing in the post-MI patient is shown in Table 4.

Patients with medically stabilized unstable angina are also candidates for noninvasive stress testing (Practice Guideline No. 10, US Department of Health and Human Services, Public Health Service).[100] Our approach to the application of nuclear stress testing in this setting is shown in Table 5, which represents a distillation of the above-referred practice guidelines.

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Pharmacological Stress Testing

Mark I. Travin and John P. Wexler

Pharmacological stress in conjunction with radionuclide myocardial perfusion imaging has become a widely used noninvasive method of assessing patients with known or suspected coronary artery disease. In the United States, over one third of perfusion imaging studies are performed with pharmacological stress. Pharmacological stress agents fall into two categories: coronary vasodilating agents such as dipyridamole and adenosine, and cardiac positive inotropic agents such as dobutamine and arbutamine. For both, in the presence of coronary artery disease (CAD), perfusion image abnormalities result from heterogeneity of coronary blood flow reserve. Vasodilating agents work directly on the coronary vessels to increase blood flow, whereas inotropic agents work indirectly by increasing myocardial work load, which then leads to an increase in coronary blood flow. Both classes of agents have high accuracies for diagnosing coronary artery disease, and they have excellent safety records with acceptably low occurrences of side effects. For dipyridamole planar thallium imaging, pooled analysis yields a sensitivity of 85% and a specificity of 87% for diagnosis of coronary disease, but there is a large variation in reported values depending on various factors, such as the extent of postcatheterization referral bias, the type of imaging (planar versus single photon emission computed tomography [SPECT]), the types of patients being studied (single versus multivessel disease, men versus women), and the imaging agent used (thallium versus one of the technetium-based agents). Diagnostic accuracies for adenosine are similar to those of dipyridamole, with reported overall sensitivities ranging from 83% to 97%, and specificities ranging from 38% to 94%. For dobutamine, pooled analyses yield a sensitivity of 82% and a specificity of 75%. There is some concern that dobutamine may interfere with uptake of technetium-99m sestamibi, lowering the sensitivity for detection of disease, and thus the vasdodilating agents are generally preferred. Pharmacological stress testing has high clinical use for risk stratifying patients with known or suspected CAD, in patients after myocardial infarction, and in patients needing noncardiac surgery. Vasodilating agents are particularly advantageous in assessing post–myocardial infarction patients, allowing testing as soon as 2 days after the event. Like patients undergoing exercise stress testing, patients with normal perfusion images by pharmacological stress have a <1% annual incidence of cardiac events. The likelihood of an event increases with the extent and severity of perfusion abnormalities. However, it is important to consider clinical variables when using perfusion imaging for risk stratification, particularly in the presurgery patients. As with exercise testing, adjunct markers such as ST segment depression during testing, lung uptake of radiotracer (if thallium is used), and ventricular cavity dilatation add additional prognostic information to that available from the perfusion images alone. The aim of current research is to find better agents that are easier to use and that have fewer side effects. MRE-0470 is an experimental vasodilating agent that is more receptor selective than adenosine and promises a lower incidence of hypotension. Arbutamine more closely simulates exercise than dobutamine, and it can be administered by a closed-loop computerized delivery device. Work is also underway to look at novel uses of pharmacological stress agents, such as acquiring gated SPECT images during dobutamine infusion to enhance detection of myocardial viability. With increasing use of noninvasive testing in elderly patients and in patients with comorbidities that preclude adequate exercise, pharmacological stress testing has become an indispensable tool for radionuclide myocardial perfusion imaging studies. A good understanding of pharmacological stress testing is essential for performing high-quality nuclear cardiology studies and for properly interpreting and acting on the results.

STRESS RADIONUCLIDE myocardial perfusion imaging is widely accepted to have high diagnostic and prognostic use in the assessment of patients with known or suspected coronary artery disease.[1-3] With wider use of this noninvasive imaging technique, more patients who are referred for stress perfusion imaging cannot exercise to an adequate myocardial work load. Many of these patients are elderly and debilitated, with significant comorbidities such as peripheral vascular disease, disabling arthritis, previous stroke, orthopedic problems (eg, low back pain), chronic pulmonary disease, and extremity amputation. Some patients are receiving heart-rate-limiting medications such as β-blockers, whereas others are simply afraid or poorly motivated to exercise on a treadmill. The diagnostic accuracy of perfusion imaging is reduced when patients cannot exercise to an adequate myocardial workload.[4,5] For this reason, many patients require pharmacological stress to obtain a

From the Department of Nuclear Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

Address reprint requests to Mark I. Travin, MD, Department of Nuclear Medicine, Montefiore Medical Center, 111 E 210th Street, Bronx, NY 10467-2490.

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satisfactory myocardial perfusion imaging study. In a 1997 American Society of Nuclear Cardiology survey, 34% of perfusion imaging studies were performed using pharmacological stress.[6] In 1998, in our facility at Montefiore Medical Center, which serves an elderly population with frequent comorbidities, over 60% of patients referred for perfusion imaging required pharmacological stress.

Pharmacological stress protocols can be classified into two subgroups: those that use vasodilating agents that directly assess differences in coronary blood flow reserve (ie, dipyridamole or adenosine), and those that use agents that pharmacologically increase myocardial work and oxygen demand, assessing differences in coronary blood flow reserve in response to the increased demand (ie, dobutamine and arbutamine).

AUTOREGULATION AND CORONARY FLOW RESERVE

Myocardial perfusion imaging assesses abnormalities of both resting coronary blood flow and coronary blood flow reserve in response to a stress. Because quantitative measurements of absolute blood flow are not feasible with single-photon-emitting agents, perfusion image abnormalities are the results of relative differences of baseline coronary blood flow and/or coronary flow reserve in various myocardial territories.

Normally, the major determinant of coronary blood flow is myocardial oxygen consumption.[7,8] In the setting of constant myocardial oxygen consumption, autonomic and chemical mediators finely autoregulate the coronary circulation so that changes in vascular caliber maintain constant coronary blood flow over a wide range of perfusion pressures.[8,9] In the presence of an atherosclerotic coronary artery stenosis, across which there is a drop in perfusion pressure, autoregulatory mechanisms compensate and decrease distal arteriolar resistance. Normal resting distal blood flow is thus maintained until the stenosis becomes critically narrowed to approximately 85% to 90% of the original diameter, at which point normal resting distal coronary blood flow cannot be maintained.[10,11]

Physical exercise increases myocardial work load, which in turn increases myocardial oxygen consumption. Autoregulatory mechanisms increase coronary flow to meet the oxygen demand. In the normal artery, blood flow can increase three to four times the normal rate.[12] In the setting of an epicardial coronary artery stenosis, however, the microcirculation distal to the stenosis has already used up a portion of its flow reserve and thus, depending on the severity of the stenosis, has decreased flow reserve relative to the distal microcirculation of an artery without a stenosis. An agent that artificially increases myocardial work, such as dobutamine, will produce a similar effect. In both of these instances, when the blood flow increase through the stenotic artery is unable to match the increased myocardial oxygen demand, ischemia will result.

Similarly, administration of a vasodilator such as dipyridamole or adenosine, although not causing an increase in myocardial work and oxygen consumption, will nevertheless result in a smaller increase in coronary blood flow to a territory perfused by a stenotic artery than to a territory perfused by a normal coronary artery. Because there is no increase in oxygen demand, ischemia will usually not occur. Nevertheless, administration of a radionuclide tracer, such as thallium-201 ^{201}Tl or technetium-99m sestamibi, that is delivered to and taken up by myocardial cells in proportion to coronary blood flow, will result in images showing this differences in coronary flow reserve. Differences in regional myocardial blood flow result in regional differences in tracer concentration, and hence, in perfusion defects. Induction of actual myocardial ischemia by hemodynamic or metabolic criteria is not required to produce a reversible perfusion defect.[13] However, these defects will reflect the physiological impairment of flow reserve caused by the atherosclerotic stenosis and may not necessarily relate to the apparent anatomic narrowing seen on a coronary angiogram.

CORONARY STEAL

In most cases, vasodilating agents increase blood flow throughout the heart, with perfusion defects being the result of a heterogeneity of blood flow reserve. In some instances, however, blood flow may actually be shunted away from and decreased to some myocardial territories, a phenomenon known as *coronary steal.*[14-16] For example, in a territory dependent on blood supplied by collateral vessels, a vasodilator may shunt more blood down the collateral feeding artery system (particularly if there is also a stenosis in the collateral feeding artery), decreasing the blood flow to the collateral-

dependent territory. In another instance, vasodilators can sometimes shunt blood away from the myocardial subendocardium to the subepicardium.[17] In the presence of coronary steal, a vasodilator can induce true myocardial ischemia with typical symptoms and electrocardiographic abnormalities. The presence of such steal often indicates severe multivessel disease.

VASODILATING AGENTS FOR PHARMACOLOGICAL STRESS

The first report of vasodilator stress was in 1977 by Strauss and Pitt,[18] who examined the effects of dimethyladenosine on blood flow and regional myocardial ^{201}Tl uptake in dogs with experimental coronary artery stenoses. They found that dimethyladenosine increased blood flow in areas perfused by normal arteries more than in areas perfused by arteries with a stenosis, resulting in a relatively greater amount of thallium uptake in the normal compared with abnormal areas.

In 1978 Gould et al[19-21] published a series of studies describing the use of dipyridamole for myocardial perfusion imaging with Tl-201. Intravenous infusion of dipyridamole was found to result in high-quality perfusion images equal to or better than those produced with treadmill stress, and the diagnostic accuracies were found to be equivalent. Dipyridamole infusion was found to be extremely safe, with minimal side effects that could be readily reversed by intravenous administration of aminophylline. Intravenous dipyridamole was approved for use in myocardial perfusion imaging in 1991, and by 1992 it was used in 20% of the more than 2.5 million perfusion studies performed in the United States. Shortly thereafter, adenosine, through which dipyridamole induces its coronary vasodilator effect, was approved, and it is now also widely used.

MECHANISMS AND PHARMACOLOGY

Adenosine and dipyridamole share a common mechanism of action that leads to vasodilatation, as depicted in Figure 1. Endogenous adenosine is normally synthesized within vascular smooth muscle cells and can leave the cell. In the extracellular space, adenosine either re-enters the cell, or it binds to two types of receptors in the cell membrane, A1 and A2. Binding to and activation of A1 receptors in the heart results in heart rate slowing and atrioventricular block, whereas binding to A2 receptors causes vascular vasodilation. Exogenous dipyridamole blocks cellular reuptake of adenosine, and thus increases the amount of endogenous adenosine available for cell membrane receptor binding, causing vascular vasodilatation. Methylxanthines, such as theophylline or caffeine, block adenosine binding to A1 and A2 receptors, antagonizing the effects of adenosine or dipyridamole.

Both agents are capable of increasing myocardial blood flow 3 to 5 times the resting level in regions supplied by normal coronary arteries. Intravenous dipyridamole produces its maximal coronary vasodilatory effect after 5 minutes, lasting for

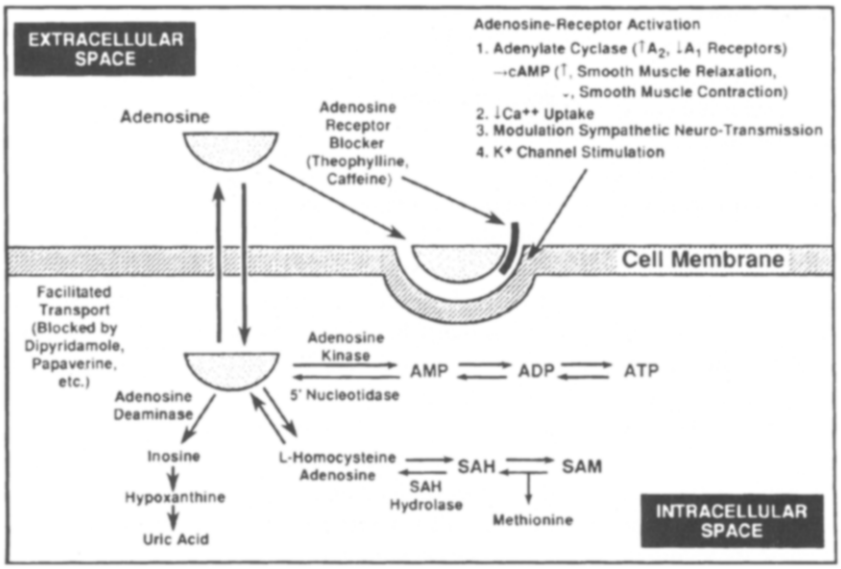

Fig 1. Mechanisms of vasodilating stress agents. Adenosine is synthesized intracellularly and leaves the cells to act on surface membrane receptors. Dipyridamole blocks adenosine re-entry into the cell, increasing extracellular adenosine that can bind to the receptor. Methylxanthines, such as theophylline and caffeine, competitively block the receptor sites. AMP, adenosine monophosphate; SAH, S-adenosyl-L-homocysteine. (Reprinted with permission.[81])

at least 10 to 30 minutes after infusion.[22] Adenosine has a direct, immediate, and very short-lived effect. With intravenous adenosine infusion, maximal coronary vasodilation occurs in 2 minutes, and because adenosine has a serum half-life of 2 to 10 seconds, its effect is reversed immediately by terminating the infusion.[23-26]

The initial myocardial distribution of intravenously administered ^{201}Tl is proportional to the increased coronary blood flow resulting from administration of dipyridamole or adenosine.[27] Several investigators have shown that in the presence of an experimental coronary stenosis in canine models of ischemia or in humans, dipyridamole- or adenosine-induced vasodilatation results in both diminished ^{201}Tl uptake and also delayed redistribution similar to that observed with exercise scintigraphy.[14,15,28]

Although myocardial uptake of thallium increases linearly with myocardial blood flow at normal or modestly increased levels of myocardial flow, thallium uptake fails to increase at higher flow levels, such as those associated with maximal blood flow induced by adenosine or dipyridamole. Thus, there has been some concern that defects may sometimes not be detected. This could be even more of a problem with the radiotracer Technetium-99m (^{99m}Tc) sestamibi, which plateaus at a lower blood flow. However, a study by Santos-Ocampo et al[29] reported that in the clinical setting, the results from pharmacological (dipyridamole or adenosine) ^{99m}Tc sestamibi perfusion imaging is comparable with that obtained from exercise.

PROTOCOLS

Dipyridamole

Dipyridamole is customarily given as an intravenous infusion of 0.142 mg/kg per minute over 4 minutes. At about 7 minutes, maximal vasodilatory effect is achieved, at which time radiotracer is injected intravenously. Most individuals experience a 10 bpm increase in heart rate and a 10 mm Hg decrease in systolic blood pressure.

Many laboratories combine dipyridamole with some form of exercise.[30-32] Beginning 2 minutes prior to tracer injection, 4 minutes of isometric handgrip exercise is commonly performed to increase mean aortic root pressure, which theoretically should increase coronary flow and improve tracer uptake. Other laboratories use an aerobic exercise protocol of some type, usually a treadmill. Studies show that adding exercise to dipyridamole stress reduces the incidence of vasodilator side effects; results in a better heart-to-liver ratio, improving image quality; and, in a report by Stein et al,[33] results in improved detection of ischemia.

Severe side effects from dipyridamole stress testing are extremely rare. A study by Ranhosky et al[34] of 3,911 patients reported 4 cases of myocardial infarction, 2 of which were fatal, and 6 cases of acute bronchospasm. Chest pain occurred in 19.7% of patients, headache in 12.2%, and dizziness in 11.8%. Ischemic ST changes were seen in 7.5%. There have been rare reports of neurological events (eg, transient ischemic attacks [TIAs]).[35] Lette et al[36] reported that life-threatening side effects had a frequency of about 1/10,000, similar to that reported for exercise testing in a similar patient population.

The side effects of dipyridamole can be reversed with intravenous aminophylline in almost all patients. Generally, a bolus dose of 50 to 75 mg is given, followed by, if necessary, a second bolus at 20 minutes or an intravenous infusion of 250 to 500 mg over 20 minutes. Typically, 10% to 30% of patients treated with dipyridamole require aminophylline. The aminophylline is usually sufficient, but other therapeutic measures, such as nitroglycerine for angina, may sometimes be needed. If possible, it is important to try to delay reversing any dipyridamole effects until at least 1 minute after radiotracer injection.

Bronchospastic or severe obstructive lung disease are contraindications to dipyridamole stress testing, and dobutamine or a similar agent should be used instead. Caffeine blocks the effect of dipyridamole. Because the biological half-life of caffeine may be as long as 8.5 hours, caffeine intake should be withheld for 24 hours before testing.[37]

Adenosine

Adenosine is infused intravenously at a dosage of 140 μg/kg/min over 6 minutes. Radiotracer is injected at the end of the third minute. Side effects with adenosine are more frequent than with dipyridamole, but because of the ultrashort (2-second) half-life, they can be reversed immediately by terminating the infusion. Verani et al[38] observed side effects in 83% of patients, including chest, throat, or jaw pain, headache, flushing, and ischemic electrocardiographic changes. Some form of atrioventricular block occurs in about 10% of

patients, with third-degree block occurring in <1%. Depending on the severity of the block and on hemodynamic stability, treatment includes down-titration or discontinuation of the infusion. Aminophylline may be used but is rarely necessary. Adenosine stress testing is contraindicated in patients with sick sinus syndrome, as well as in patients with bronchospastic lung disease.

DIAGNOSTIC ACCURACY OF VASODILATOR STRESS PERFUSION IMAGING

Numerous studies have reported that both dipyridamole and adenosine radionuclide myocardial perfusion imaging have high accuracies for diagnosing the presence or absence of coronary artery disease, comparable with exercise stress. In a 1989 review by Leppo[39] of published studies of 215 patients undergoing dipyridamole and exercise stress, the cumulative sensitivity of dipyridamole planar Tl-201 imaging for detection of coronary disease was 79% and the specificity was 95%, compared with 79% and 92%, respectively, for exercise stress. In a later pooled analysis by Beller[27] of studies involving 897 patients, the sensitivity of dipyridamole planar thallium-201 imaging was 85.4% and the specificity was 86.8% (Table 1). Varma et al[52] compared myocardial ^{201}Tl imaging after exercise and intravenous dipyridamole infusion in 189 planar segment pairs of 21 patients. There was an 87.5% agreement between stress modalities when each segment was classified as normal or abnormal, but there was 92% concordance when the segments were grouped according to coronary supply regions. A slightly higher proportion of redistributing defects was found after dipyridamole infusion than after exercise (17% versus 10%, $P < .05$). For the 15 patients who underwent catheterization, there was a sensitivity of 61% for both dipyridamole and exercise for detection of a stenosis greater than 50%, and both had a specificity of 100%.

Table 1. Sensitivity and Specificity of Dipyridamole Stress Tl-201 Scintigraphy for Detection of Coronary Artery Disease

Investigator	Patients (n) With CAD	Patients (n) Without CAD		Sensitivity (%)	Specificity (%)
Albro[21]	51	11		67	91
Leppo[40]	40	20		93	80
Schmoliner[41]	60	–		95	–
Francisco[42]	51	35		90	96
Timmis[43]	20	–		85	–
Narita[44]	35	15		69	100
Machecourt[45]	58	10		90	90
Okada[46]	23	7		91	100
Sochor[47]	149	45		92	81
Ruddy[48]	53	27		85	93
Taillefer[49]	19	6		79	86
Lam[50]	101	31		85	71
Laarman[51]	18	12		89	67
Total	678	219	Mean	85.4	86.8

Modified and reprinted with permission.[27]

Although similarly high diagnostic accuracies have been shown for single photon emission computed tomography (SPECT), there has been some decline in reported specificity because of poststress referral bias for cardiac catheterization.[53,54] Kong et al[55] evaluated 43 women and 71 men who underwent dipyridamole thallium-201 SPECT imaging within 3 months of cardiac catheterization. Although the overall sensitivity was 87% in women and 94% in men, specificities were 58% and 63%, respectively.[55] The sensitivity for detecting disease in patients with multivessel disease was high in both women (100%) and men (94%), but for women the sensitivity in patients with one-vessel CAD was 60%, compared with 94% for men ($P = .001$).

Mendelson et al[56] compared the diagnostic accuracies of planar versus SPECT dipyridamole Tl-201 imaging in 79 patients. The overall detection of CAD was 89% for SPECT compared with 67% for planar imaging ($P < .001$). For individual territories, the sensitivity of SPECT for detection of disease in the anterior wall was 69%, compared with 44% for planar imaging ($P < .01$), and for the posterior territory these sensitivities were 80% and 54%, respectively ($P < .01$). Specificities could not be assessed for overall detection of CAD because of the high prevalence of disease in the study population, but for the left anterior descending (LAD) territory they were 96% for planar and 100% for SPECT, whereas for the posterior wall these were 95% for planar and 70% for SPECT.

Nishimura et al[57] examined the diagnostic value of adenosine ^{201}Tl SPECT imaging for detection of CAD in 101 consecutive patients. The sensitivity for identifying the 70 patients with coronary disease using quantitative analysis was 87% in the total group, and 76%, 86%, and 90% for patients with single-, double-, and triple-vessel disease, respectively. In all cases, sensitivity was higher for patients with previous myocardial infarction. For individual stenoses, the sensitivities ranged from

65% to 68%. Despite the potential for catheterization referral bias, the specificity for the 31 patients without disease was 90%, although for the 12 patients whose catheterization followed perfusion imaging, this was lower, at 83%. Table 2 summarizes the diagnostic accuracy of adenosine ^{201}Tl SPECT imaging in several other studies.

In a multicenter prospective crossover trial study comparing adenosine and exercise ^{201}Tl SPECT 30 days apart in the same patients, Nishimura et al[64] found that agreement on the presence of normal or abnormal images was 82.8% visually, and 86% by computer quantitation. Agreement on localization of the defect to a particular vascular territory ranged from 82.7% to 91.4%. Although there was a good correlation of defect size between the two stress modalities, defect size was significantly greater with adenosine stress ($P = .0073$).

Similarly, Gupta et al[65] found good correlation between exercise and adenosine stress perfusion imaging results. As shown in Fig 2, concordance in the left anterior descending coronary artery territory was 91.8%, in the left circumflex territory it was 94.8%, and for the right coronary artery this was 90.3%.

Among the few studies comparing dipyridamole and adenosine, Taillefer et al[66] had 54 patients undergo planar ^{201}Tl studies with the two pharmacological stress modalities 2 to 7 days apart. The sensitivity for detecting CAD was similar, 90.7% for adenosine and 87.0% for dipyridamole. Overall, there was an 87% concordance (normal or ischemia) between dipyridamole and adenosine images for 486 segments ($\kappa = .74$), but ischemia was detected more often with adenosine than with dipyridamole. Interestingly, although side effects, particularly flushing, dyspnea, chest discomfort, and gastrointestinal discomfort, were more frequent with adenosine (overall, 83% versus 64.8%), most patients preferred adenosine over dipyridamole because of the shorter duration of the effects.

Table 2. Diagnostic Value of ^{201}Tl Tomography

Investigator	Patients (n)	Sensitivity (%)	Specificity (%)
Allman[58]	76	85	38
Coyne[59]	100	83	75
Gupta[46]	144	83	82
Iskandrian[60]	339	90	90
Marwick[61]	97	86	71
O'Keefe[62]	42	97	67
Verani[63]	89	83	94

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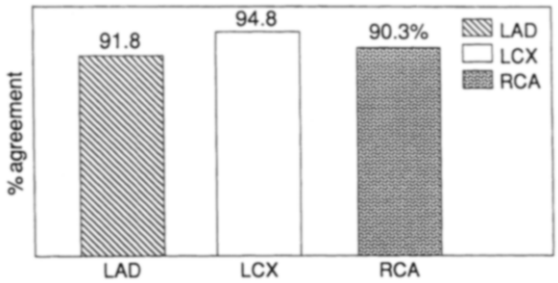

Fig 2. Concordance between adenosine SPECT and exercise treadmill SPECT in individual coronary artery territories in 134 patients. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery. (Reprinted with permission from the American College of Cardiology, Journal of the American College of Cardiology, 1992, 19, 248-257.)

Santos-Ocampo et al,[29] compared exercise, dipyridamole, and adenosine ^{99m}Tc sestamibi SPECT images in 10 normal patients and 10 patients with known coronary disease. The myocardial uptake of sestamibi was comparable among the three stress modalities, and when present, defect sizes and intensities were equivalent.

Currently, about 70% of perfusion imaging studies in the United States use a ^{99m}Tc based agent, but only a few reports are available on the diagnostic accuracy of vasodilator pharmacological stress with these agents. Tartagni et al[62] used a dipyridamole stress protocol to assess 30 patients with 1-day stress/rest ^{99m}Tc sestamibi and stress/delay ^{201}Tl imaging protocols. Sensitivity and specificity for coronary disease were 100% and 75%, respectively, for both radiotracers. Interestingly, using either tracer, a lower detection of left anterior descending coronary artery stenosis compared with the right coronary artery (68% versus 89% for thallium, and 75% versus 89% for sestamibi) was observed.

Matzer et al[68] reported on the dual-isotope (rest ^{201}Tl, stress ^{99m}Tc sestamibi) approach when used in conjunction with either adenosine (82 patients) or dipyridamole (50 patients) stress. In patients with no previous myocardial infarction, the sensitivity of perfusion imaging was 97% and the specificity was 81% for identification of a $\geq$70% stenosis. For patients with a low pretest likelihood of disease, the normalcy rate was 96%. There were no significant differences between the results with dipyridamole and those with adenosine stress.

Miller et al[69] examined the diagnostic accuracy of same-day rest dipyridamole stress Tc-99m ses-

tamibi SPECT compared with coronary angiography in a predominantly male (98.8%) Veterans Affairs population. Image sensitivity for the presence of CAD (≥50%) was 91%, and specificity was strikingly low at 28%, attributed to posttest referral bias in this population with high pretest probability of disease. With regard to individual vessels, sensitivity for detection of disease ≥70% in the territory of the LAD coronary artery (46.7%) and left circumflex (46.2%) were lower than for the right coronary artery (70.6%).

Technetium-99m tetrofosmin, a newer agent for assessment of myocardial perfusion, has the advantage of more rapid hepatic clearance than Tc-99m sestamibi, promising better images sooner after completion of stress.[70] Studies have shown a high diagnostic accuracy for CAD, comparable to that of Tl-201, and many facilities are now using this radiotracer.[71,72] However, in a recent report by Taillefer et al[73] using dipyridamole stress, tetrofosmin detected fewer ischemic segments and yielded a higher ischemic-to-normal ratio than ^{99m}Tc sestamibi imaging performed in the same patients, suggesting a poorer visualization of ischemia with tetrofosmin when using dipyridamole.

GENDER CONSIDERATIONS

Concerns have been raised that the diagnostic accuracy of stress perfusion imaging is lower in women than in men.[74] Hansen et al[75] suggested that smaller hearts in women reduce the sensitivity of perfusion imaging.

Nevertheless, Amanullah et al[76] found excellent diagnostic accuracies in 130 women who underwent adenosine ^{99m}Tc sestamibi SPECT perfusion imaging and cardiac catheterization. The sensitivity, specificity, and predictive accuracy of the imaging study for detecting disease ≥70% were 95%, 66%, and 85%, respectively. For an additional 71 women with a low pretest likelihood of CAD, the normalcy rate was 93%.

LEFT BUNDLE BRANCH BLOCK

Numerous studies have reported improved diagnostic accuracy with vasodilator pharmacological stress compared with exercise in patients with a left bundle branch block. It is thought that the increased heart rate and myocardial work load associated with exercise decreases septal blood flow, which would not occur with vasodilator stress. Burns et al[77] saw that for 16 patients with left bundle branch block, the specificity in terms of identifying the absence of a left anterior descending coronary artery stenosis was 20% to 30% for exercise compared with 80% to 90% for dipyridamole stress. Similarly, O'Keefe et al[62] reported that in patients with a left bundle branch block, the overall predictive accuracy of perfusion imaging was 93% in the adenosine thallium group compared with 68% for the exercise thallium group ($P = .01$).

ADJUNCT MARKERS

Chest pain is fairly common during vasodilator pharmacological stress, occurring in approximately 10% to 20% of dipyridamole patients, and in up to 57% of adenosine patients.[34,36,38] Pearlman and Boucher[78] reported that chest pain during dipyridamole testing was not related to the severity of CAD and had little diagnostic value. Similarly, there is no evidence for any association between adenosine-induced chest discomfort and CAD.[60]

The presence of pharmacological stress-induced ST-segment depression does seem to be of clinical importance. Villanueva et al[79] studied 204 consecutive patients undergoing dipyridamole stress Tl-201 imaging. Fifteen percent of patients developed ST depression, and these patients were more likely to have redistributing perfusion defects (64% versus 38%, $P < .02$). By logistic regression, the most powerful correlate of ST depression was the number of reversible thallium defects. In a dipyridamole stress echocardiographic study, Cortigiani et al[80] found that three-vessel and/or left main coronary artery disease was found in 41% of patients with and 21% of patients without ST depression, and by logistic regression ST ischemia in four or more leads had an odds ratio of 3.5 for predicting a cardiac event. In a review by Iskandrian et al,[81] the positive predictive value of ST depression for coronary disease is high at 90%; however, the negative predictive value is low because 70% of patients with coronary disease show no ST-segment depression.

A study by Chambers and Brown[82] suggested that dipyridamole-induced ST segment depression is related to the presence of collateral vessels. Similarly, Nishimura et al[83] found that the presence of ST depression during adenosine stress was most strongly associated with collateral vessels, suggesting that these electrocardiographic findings are related to coronary steal. The presence of ST

depression during adenosine stress has been shown to correlate with a worsened prognosis.[84]

PROGNOSTIC USE OF VASODILATOR STRESS PERFUSION IMAGING

As has been shown for exercise stress myocardial perfusion imaging, vasodilator pharmacological stress perfusion imaging is a powerful tool for predicting patient outcome.[1,2] Younis et al[85] followed up 177 asymptomatic patients who underwent intravenous dipyridamole planar thallium imaging. The occurrence of death or nonfatal myocardial infarction during a 14 ± 10 month follow-up was significantly greater when the scan was abnormal (18% versus 0%, $P < .01$). Of 18 clinical, scintigraphic, and angiographic variables, a combined fixed and reversible thallium defect was the only predictor of death or infarction.

Hendel et al[86] correlated the imaging results of 516 consecutive patients referred for dipyridamole planar thallium studies with cardiac events—death and myocardial infarction—over a mean follow-up period of 21 months. Of patients with an abnormal scan, 13.6% had a cardiac event, compared with 2% of those with normal images. By logistic regression analysis, an abnormal scan was an independent and significant predictor of myocardial infarction or death, having a relative risk of 3.1, higher than clinical variables of congestive heart failure, diabetes mellitus, gender, prior myocardial infarction, or peripheral vascular disease. Figure 3 shows the survival curves in patients with normal versus abnormal dipyridamole thallium scans.

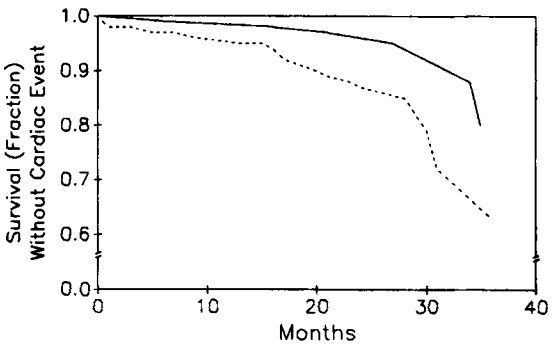

Fig 3. Event-free survival curves in patients with normal versus abnormal dipyridamole thallium-201 SPECT images. *Solid line,* 172 patients with normal scan results; *dashed line,* 332 patients with abnormal scan results. Cardiac death or myocardial infarction occurred more frequently in patients with an abnormal scan result; $P < .005$). (Reprinted with permission from the American College of Cardiology, Journal of the American College of Cardiology, 1990, 15, 109-116.)

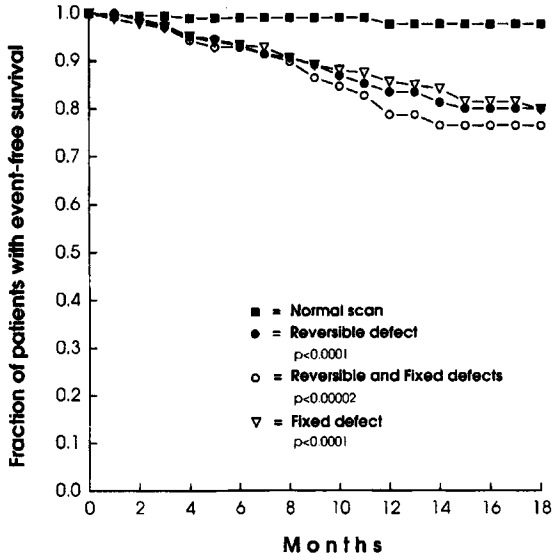

Fig 4. Survival curves of patients with normal versus abnormal dipyridamole Tc-99m sestamibi SPECT images. Patients with reversible and/or fixed defects had worsened prognosis (all $P < .0001$). (Reprinted from the American Journal of Cardiology, 73, Stratmann et al, Prognostic value of dipyridamole technetium-99m sestamibi myocardial tomography in patients with stable chest pain who are unable to exercise, 647-652, 1994, with permission from Excerpta Medica Inc.)

Heller et al[87] evaluated the prognostic value of dipyridamole stress perfusion SPECT imaging using the radiotracer Tc-99m sestamibi. For 512 patients followed up for 12.8 ± 6.8 months, those with an abnormal perfusion scan had significantly more cardiac events than those with normal perfusion (7.4% versus 1.3%, $P < .01$). Cox proportional hazards regression analysis showed that a reversible perfusion defect was the strongest predictor of a cardiac event, with a relative risk of 4.41. Large defects were found to be particularly associated with more cardiac events, whereas patients with small defects were at minimal risk.

In another study evaluating the prognostic value of dipyridamole stress Tc-99m sestamibi imaging, Stratmann et al[88] followed up 534 patients with stable angina for 13 ± 5 months after testing. Cardiac events occurred in 2% of patients with normal Tc-99m sestamibi scans, compared with 15% with abnormal scans, 17% with reversible perfusion defects, and 16% with fixed defects (all, $P < .01$). Patients with an abnormal scan had a relative risk of 8.4. Figure 4 shows survival curves

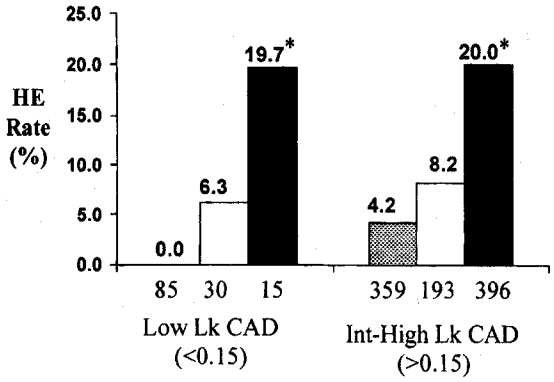

Fig 5. Hard event rates in relation to results of adenosine dual isotope SPECT image scans and pretest likelihood of coronary artery disease. *Stippled bars,* normal scan results; *clear bars,* mildly abnormal scan results; *solid bars,* moderately to severely abnormal scan results; HE, hard events; Lk, likelihood. *$P < .05$. (Reprinted from the American Journal of Cardiology, 80, Hachamovitch 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, 426-433, 1997, with permission from Excerpta Medica Inc.)

for patients with normal versus abnormal dipyridamole Tc-99m sestamibi perfusion scans.

Iskandrian et al[89] correlated the results of adenosine SPECT thallium imaging with high-risk coronary anatomy in 339 patients. Three variables were independently predictive of left main or three-vessel CAD: Thallium defects in multiple vascular territories, ST segment depression during adenosine infusion, and thallium lung uptake.

Hachamovitch[90] reported on the incremental prognostic value of adenosine dual isotope SPECT imaging in 1,159 patients followed up for 27.5 ± 9.1 months. After adjusting for clinical and historical variables, nuclear testing increased the ability to predict cardiac death sevenfold, and any hard event fivefold. As shown in Figure 5, for both patients with low and patients with intermediate-high pretest likelihoods of coronary disease, the results of adenosine sestamibi perfusion imaging effectively risk stratified patients into high (event rate, 19.7% to 20%), intermediate (event rate, 6.3% to 8.2%), and low (event rate, 0% to 4.2%) risk categories. From the same group, Amanullah et al[91] showed that adenosine SPECT perfusion imaging added significant incremental prognostic information to clinical and physiological variables in women. Women with normal cardiac scans had a low cardiac death rate of 0.9% per year of follow-up, compared with 4.1% for patients with moderately abnormal scans and 7.5% for those with severely abnormal scans.

VASODILATOR STRESS PERFUSION IMAGING AFTER AN ACUTE ISCHEMIC EVENT

Pharmacological stress imaging also has been shown to be useful in risk stratifying patients after ischemic event. Younis et al[92] evaluated the prognostic value of dipyridamole planar thallium scintigraphy in 77 patients after an episode of unstable angina or an acute myocardial infarction. No patient with a normal image had a subsequent myocardial infarction or cardiac death, compared with an 18.5% event rate for patients with a thallium perfusion defect ($P = .05$), and a 19% event rate for those with a reversible defect. By logistic regression analysis, a reversible thallium defect ($P < .001$) and the extent of coronary disease ($P < .009$) were the only significant predictors of a cardiac event. Figure 6 shows survival curves after an acute event in patients with normal versus abnormal scans.

Leppo et al[93] performed dipyridamole planar thallium scintigraphy on 51 patients 10 to 16 days postinfarction. Ninety-two percent of patients who died or reinfarcted had one or more redistributing thallium defects, compared with 56% of patients who had no events ($P < .01$). In patients who also underwent treadmill exercise thallium imaging, the pharmacological nuclear stress test was better able

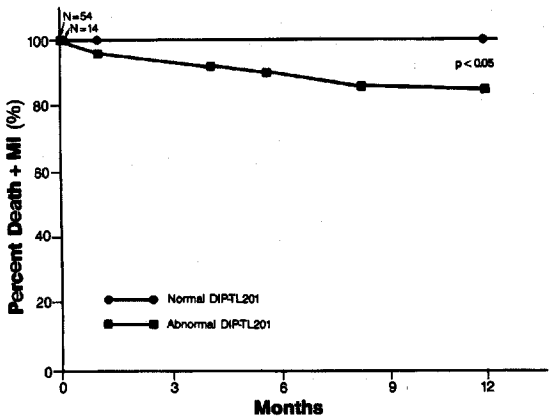

Fig 6. Event-free survival rates for patients with normal versus abnormal dipyridamole SPECT thallium scan results after a recent acute coronary ischemic syndrome. (Reprinted from the American Journal of Cardiology, 64, Younis et al, Prognostic value of intravenous dipyridamole thallium scintigraphy after an acute myocardial ischemic event, 161-166, 1989, with permission from Excerpta Medica Inc.)

to detect ischemia. By multivariate analysis, the presence of redistribution seen on dipyridamole thallium imaging was the only significant predictor of a cardiac event.

Vasodilator pharmacological stress, because there is minimal to no increase in the myocardial work load, allows earlier risk stratification of the postinfarct patient. Mahmarian et al[94] performed adenosine SPECT thallium imaging on 120 clinically stable patients 5 ± 3 days after infarction. Most side effects were benign, and the few episodes of ischemia resolved without adverse sequelae within 1 to 2 minutes of terminating the infusion. SPECT imaging identified 99% of infarct-related arteries and 82% of severely stenosed (≥70%) noninfarct arteries, and it accurately predicted multivessel disease in 69% of patients. The size of perfusion defects helped predict subsequent events—the positive predictive accuracy for developing a cardiac event was 70% when the perfusion defect size was >30%.

In an initial small study, Brown et al[95] performed dipyridamole thallium imaging 2 to 3 days after infarction. None of the 50 patients in the study had an adverse reaction to the test. However, of the 20 patients with infarct zone redistribution, 10 patients had an in-hospital event, and 5 additional patients had an event in the postdischarge period, yielding an event rate of 75% over 1 year. On the other hand, only 1 of 30 patients without infarct zone redistribution had an event. Based in part on these provocative findings, a follow-up multicenter study further examining the safety and use of early postinfarction dipyridamole nuclear stress testing was undertaken. Heller et al[96] reported on 284 patients who underwent dipyridamole stress perfusion imaging 3.3 ± 0.7 days after infarction, some as early as 48 hours after. There were no adverse clinical events either during or immediately after the infusion. Although 3 patients had unstable angina ≥4.2 hours after infusion, no patient had recurrent infarction and there were no deaths, confirming the safety of early postinfarction dipyridamole perfusion imaging.

RISK STRATIFICATION IN THE ELDERLY

A large percentage of patients undergoing vasodilator pharmacological stress testing are elderly, and such patients are at higher risk than younger patients for adverse events. Shaw et al[97] reported on the predictive value of dipyridamole Tl-201 imaging in 348 patients greater than 70 years old. For patients with normal scan results, the rate of cardiac death or nonfatal myocardial infarction was 5%, compared with 35% for patients with an abnormal scan, and the rate increased with the extent of thallium image abnormalities. By logistic regression analysis, an abnormal thallium image was the single best predictor of a cardiac event, with a relative risk of 7.2.

RISK STRATIFICATION BEFORE VASCULAR SURGERY

Pharmacological stress imaging is widely used for risk stratification of patients undergoing noncardiac surgery. Patients undergoing vascular surgery are at a particularly high risk for a perioperative cardiac event because they frequently have extensive underlying coronary disease that is undetected because of exertional limitations. One of the first reports of the use of preoperative dipyridamole perfusion imaging in patients before peripheral vascular surgery is by Boucher et al.[98] Of 16 patients who had ischemia detected by Tl-201 imaging, 8 (50%) patients had perioperative ischemic event (myocardial infarction, death, or unstable angina), whereas none of the 32 patients without evidence of thallium ischemia had an event. Six additional patients who had thallium redistribution underwent coronary angiography before surgery; all had severe multivessel disease, and 4 of the patients required bypass surgery.

Similarly, Leppo et al[99] saw that of 15 patients with a postoperative myocardial infarction, 14 patients had thallium redistribution on a preoperative dipyridamole thallium study. The event rate in patients with thallium redistribution was 33% (14 of 42), compared with 2% (1 of 47) for patients without redistribution.

Although the above studies showed that thallium redistribution was an adverse prognostic indicator, fixed thallium defects appeared benign. A study by Hendel et al,[100] however, showed that this was not the case in long-term follow-up. As in the studies cited, a reversible defect predicted a high perioperative cardiac event rate, in this case 14.4%, compared with 1% for patients with normal scans, and by multivariate analysis this was the best predictor, elevating the risk 4.3-fold. However, patients with a fixed defect had a 24% rate of a late event (over 5 years), and Cox analysis showed that a fixed thallium defect was the strongest factor in predict-

ing a late event and increased the relative risk almost fivefold.

It is important that the results of any testing modality be interpreted in a clinical context. Work by Eagle et al has suggested that there are certain preoperative clinical scenarios in which dipyridamole perfusion imaging does not add significant clinical use. In one report, Eagle et al[101] saw that for 50 patients without evidence of congestive heart failure, angina, prior myocardial infarction, or diabetes, there were no adverse events during vascular surgery, suggesting that preoperative dipyridamole thallium imaging would not have been necessary. In a follow-up study, these investigators evaluated the predictive value of clinical and dipyridamole thallium image findings in 254 consecutive patients undergoing vascular surgery.[102] Logistic regression identified five clinical predictors (Q waves, history of ventricular ectopic activity, diabetes, advanced age, angina) and two dipyridamole-thallium predictors of postoperative events. It was only in the group with one or two of these clinical predictors that the results of thallium imaging effectively risk-stratified patients. Because of very high or low cardiac risk, thallium imaging appeared unnecessary in patients with either no clinical risk factors or three or more risk factors.

There are two noteworthy studies that have reported no clinical value for preoperative dipyridamole stress perfusion imaging. Mangano et al[103] tested 60 consecutive patients (59 men and 1 woman from San Francisco Veterans Affairs Medical Center) scheduled for elective vascular surgery, and they uniquely blinded all treating physicians to the results of the scintigraphic studies. No association was found between redistributing defects and adverse cardiac outcomes or perioperative ischemic events. Similarly, in 457 consecutive patients undergoing elective abdominal aortic surgery, Baron et al[104] found that dipyridamole thallim-SPECT did not accurately predict adverse cardiac outcomes.

These two studies differed in important ways from studies showing value from preoperative dipyridamole testing. In both, consecutive patients scheduled for surgery were tested, rather than only those who were especially referred for surgery before testing. Therefore, these studies included a larger percentage of lower-risk patients, which would diminish the predictive value of the test. In the study by Mangano et al,[103] there were only three events. The study by Baron et al[104] did not analyze for cardiac deaths.

In 1996, Eagle et al[105] summarized 23 publications describing the use of dipyridamole thallium stress testing in the preoperative evaluation of patients before vascular and nonvascular surgery (Table 3). Although the negative predictive value of the absence of thallium redistribution was consistently greater than 95%, the positive predictive value varied widely from 4% to 20% (although for the majority it was over 10%). It is likely that this variation was in part the result of differences in patient populations. In addition, in later studies, patients with more abnormal images were more likely to have had intervention before surgery, lessening the predictive value. Finally, improved surgical techniques, including more aggressive use of cardiac medications, especially in sicker patients, would result in a decrease in the apparent value of preoperative screening.[124] However, it is probably true that the cost effectiveness of preoperative dipyridamole perfusion imaging is likely to be improved if its use is restricted to patients who cannot exercise and whose risk status cannot be reasonably estimated on the basis of clinical factors alone (as recommended by Mangano and Goldman[125] in a recent study). They add that the absence of randomized trials makes any recommendations subject to debate.

ADJUNCT MARKERS OF HIGHER RISK DURING VASODILATOR STRESS

For treadmill exercise myocardial perfusion imaging, findings such as thallium lung uptake or transient left ventricular cavity dilatation have been shown to indicate a higher likelihood of extensive CAD and a higher risk of an adverse prognosis.[126,127] These adjunct markers of higher risk have also been found to be important in the setting of pharmacological stress testing. Iskandrian et al[128] reported on 59 patients who underwent adenosine stress SPECT thallium imaging. The lung-to-heart ratio in the initial images was significantly higher in patients with CAD than in normal patients, increasing with the extent of disease. There was a significant correlation between the lung-to-heart ratio and the severity and extent of perfusion abnormality. Left ventricular dilatation was seen more frequently in patients with coronary disease than in those without, and it correlated with the extent of thallium perfusion abnormality. This dilatation was found to be mostly an increase in cavity dimension (a 30% increase) and to a lesser extent an increase in cardiac size (a 6% increase).

Table 3. Dipyridamole-Thallium Imaging for Preoperative Assessment of Cardiac Risk

Investigator	n	Patients With Ischemia by Tl-Rd (%)	Events (MI/Death)	Perioperative Events: % Rd Scans (Positive Predictive Value)	Perioperative Events: % Normal Scan (Negative Predictive Value)	Comments
Vascular surgery						
Boucher 1985[98]	48	16 (33)	3 (6)	19 (3/16)	100 (32/32)	First study to define risk of Tl redistribution
Culter 1987[106]	116	54 (47)	11 (10)	20 (11/54)	100 (60/60)	Only aortic surgery
Fletcher 1988[107]	67	15 (22)	3 (4)	20 (3/15)	100 (56/56)	
Sachs 1988[108]	46	14 (31)	2 (4)	14 (2/14)	100 (24/24)	
Eagle 1989[102]	200	82 (41)	15 (8)	16 (13/82)	98 (61/62)	Defined clinical risk
McEnroe 1990[109]	95	34 (36)	7 (7)	9 (3/34)	96 (44/46)	Fixed defects predict events
Younis 1990[110]	111	40 (36)	8 (7)	15 (6/40)	100 (51/51)	Includes long-term follow-up
Mangano 1991[103]	60	22 (37)	3 (5)	5 (1/22)	95 (19/20)	Managing physicians blinded to scan results
Strawn 1991[111]	68	n/a	4 (6)	n/a	100 (21/21)	
Watters 1991[112]	26	15 (58)	3 (12)	20 (3/15)	100 (11/11)	Includes echo (TEE) studies
Hendel 1992[100]	327	167 (51)	28 (9)	14 (23/167)	99 (97/98)	Includes long-term follow-up
Lette 1992[113]	355	161 (45)	30 (8)	17 (28/161)	99 (160/162)	Used quantitative scan index
Madsen 1992[114]	65	45 (69)	5 (8)	11 (5/45)	100 (20/20)	
Brown 1993[115]	231	77 (33)	12 (5)	13 (10/77)	99 (120/121)	Prognostic utility enhanced by combined scan and clinical factors
Kresowik 1993[116]	170	67 (39)	5 (3)	4 (3/67)	98 (64/65)	
Baron 1994[104]	457	160 (35)	22 (5)	4 (7/160)	96 (195/203) NFMI only	Did not analyze for cardiac deaths; no independent value of scan
Bry 1994[117]	237	110 (46)	17 (7)	11 (12/110)	100 (97/97)	Cost-effectiveness data included
Nonvascular surgery*						
Camp 1990[118]	40	9 (23)	6 (15)	67 (6/9)	100 (23/23)	Diabetes mellitus, renal transplant
Iqbal 1991[119]	31	11 (41)	3 (11)	27 (3/11)	100 (20/20)	Exercise 86%, DM, pancreas transplant
Coley 1992[120]	100	36 (36)	4 (4)	8 (3/36)	98 (63/64)	Define clinical risk factors in patients with known or suspected CAD
Shaw 1992[121]	60	28 (47)	6 (10)	21 (6/28)	100 (19/19)	Used adenosine
Takase 1993[122]	53	15 (28)	6 (11)	27 (4/15)	100 (32/32)	Patients with documented or suspected CAD include rest echocardiogram
Younis 1994[123]	161	50 (31)	15 (9)	18 (9/50)	98 (87/89)	Intermediate- to high-risk CAD

Note: All studies except those by Coley[120] and Shaw[121] acquired patient information prospectively. Only in reports by Mangano[103] and Baron[104] were scan results blinded from attending physicians. Patients with fixed defects were omitted from calculation of positive and negative predictive values.

Abbreviations: Rd, redistribution; n, number of patients who underwent surgery; MI, myocardial infarction; TEE, transesophageal echocardiography; NFMI, nonfatal myocardial infarction; DM, diabetes mellitus; CAD, coronary artery disease.

*Studies using pharmacological and/or exercise thallium testing.

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From this, the investigators speculated that cavity dilatation is more likely the result of subendocardial ischemia and resultant apparent myocardial thinning than a true increase in myocardial dimension.

Nishimura et al[129] also found that thallium lung uptake associated with adenosine perfusion imaging correlated with the extent of CAD–a lung-to-heart ratio of >0.45 in planar images was found in 6 patients (21%) with single-vessel disease and 17

patients (35%) of those with multivessel disease. Patients with elevated lung thallium activity had more hypoperfused myocardial segments, more segments with redistribution, and larger initial perfusion defects than those with normal lung activity.

Several studies have supported the relationship of transient left ventricular cavity dilatation on dipyridamole thallium imaging to multivessel CAD.[130-132] The adverse prognostic implications of ventricular cavity dilatation were described by McClellan et al.[133] In 512 consecutive patients who underwent dipyridamole Tc-99m sestamibi SPECT perfusion imaging, transient cavity dilatation occurred in 14% and was associated with an event rate (over 12.8 ± 6.8 months) of 11.4%; fixed dilatation was also present in 14% of patients and predicted an event rate of 13.5%, compared with a 1.9% event rate for patients without dilatation ($P < .01$). Cavity dilatation added incremental prognostic value to the presence and extent of perfusion defects, and it was a significant and independent predictor by Cox proportional hazards regression analysis.

NEWER VASODILATOR STRESS AGENTS

Work is underway to develop vasodilator pharmacological stress agents that do not have the side effects of dipyridamole or adenosine. In 1995, Miyagawa et al[134] reported on the use of intravenous adenosine triphosphate (ATP) for SPECT thallium imaging. Although 56% of patients had some adverse effects, these were transient and mild. Atrioventricular block occurred in 2% of patients. Diagnostic accuracies were high, by visual analysis a sensitivity of 88% and specificity of 80%, and by quantitative analysis a sensitivity of 91% and a specificity of 86%.

Other investigators are studying agents that work by more selectively stimulating A2A receptors, hoping to avoid the unwanted side effects that result from stimulation of A1, A2b, and A3 receptors.[135] MRE-0470 (WRC-0470) is a potent, highly selective adenosine A2A receptor agonist. In a canine model, this agent produced a nearly fivefold increase in coronary flow in a nonstenotic artery without producing significant hypotension. Maximal coronary flow was achieved at approximately 2 minutes and remained stable. Phase I Food and Drug Administration clinical trials of this agent are anticipated by the end of 1998. Another A2A receptor agonist (CGS-21680) is also currently under study.

STRESS IMAGING WITH POSITIVE INOTROPIC PHARMACOLOGICAL AGENTS

Pharmacological stress testing using positive inotropic agents is usually reserved for patients who are unable to exercise adequately and who have contraindications to dipyridamole or adenosine infusion, such as those with bronchospastic pulmonary disease, those receiving xanthine derivatives, or those who have consumed caffeine. The most commonly used agent for this purpose is dobutamine, although there has been some recent work with arbutamine.[136-139] These agents work by stimulating beta receptors in the heart, augmenting both contractility and heart rate, increasing myocardial oxygen demand. The coronary circulation responds to the increased demand by increasing blood flow twofold to threefold, comparable with that occurring during physical exercise, but less than with dipyridamole or adenosine. However, stress testing with these agents is not equivalent to physical exercise because other useful information, such as duration of exercise, exercise capacity, and reproduction of symptoms, is not obtained. In addition, the peak heart rate is usually lower than that achieved with exercise. Thus, pharmacological stress testing with these agents should be considered as a last resort in patients who cannot exercise or who cannot undergo vasodilator pharmacological stress.

PROTOCOL

Dobutamine is infused starting at a low dose of 5 μg/kg/min and increased every 3 minutes, usually in stages of 10 μg/kg/min, 20 μg/kg/min, 30 μg/kg/min, and 40 μg/kg/min. A radiopharmaceutical is injected at peak infusion, 2 to 3 minutes before termination. Many laboratories supplement dobutamine infusion with 0.5 to 1.0 mg of atropine intravenously to achieve the desired heart rate.

SIDE EFFECTS AND SAFETY

In most cases, dobutamine increases heart rate, systolic blood pressure (although a decrease in blood pressure can sometimes be observed as a result of dobutamine's peripheral vasodilatory effect), and rate pressure product. In a study by Hays et al,[138] 75% of patients experienced one or more side effects during dobutamine infusion, including typical (26%) and atypical (5%) chest pain, palpitation (29%), flushing (14%), headache (14%), and dyspnea (14%). Ventricular and supraventricular arrhythmias may be seen. Nevertheless, serious

side effects are rare. In a study of 1,076 consecutive patients undergoing dobutamine-atropine stress myocardial perfusion imaging, Elhendy et al[140] reported no infarction and no death. Hypotension occurred in 3.4% of patients, supraventricular tachyarrhythmias in 4.4%, and ventricular tachycardia in 3.8%; all arrhythmias terminated spontaneously or after metoprolol administration.

With regard to ST segment changes, in a consecutive series of 1,012 patients, Dakik et al[141] found that 26% of patients had depression ≥1 mm and 16% had depression ≥2 mm. Patients with ST segment depression did not differ from those without ST segment changes with respect to the prevalence of prior myocardial infarction, abnormal perfusion scans, reversible perfusion defects, or the mean perfusion defect size. However, patients with ≥1 mm ST segment elevation had a higher incidence of prior myocardial infarction, abnormal perfusion scans, and reversible perfusion defects, and a larger perfusion defect size.

DIAGNOSTIC ACCURACY OF DOBUTAMINE STRESS PERFUSION IMAGING

The diagnostic accuracy of dobutamine perfusion imaging was first reported by Mason et al[142] in 1984. For the 24 patients studied with planar imaging, the sensitivity was 94% and the specificity was 87%, better than values obtained for exercise stress (60% and 63%, respectively). Similarly, Pennel et al,[139] using SPECT to study 50 patients with exercise limitations, found a higher sensitivity (97%) and specificity (80%) for dobutamine stress than exercise (78% and 44%, respectively; $P < .01$). Hays et al[138] reported that the sensitivity of dobutamine tomography was 86% overall, 84% in patients with single-vessel disease, 82% in those with double-vessel disease, and 100% in those with triple-vessel disease; the specificity was 90% for patients and 86% for individual vessels. In a total of 14 studies containing 942 patients from 1992 to 1997, the overall sensitivity of dobutamine scintigraphy was 82% (range, 70% to 100%) and the specificity was 75% (range, 64% to 100%).

With regard to Tc-99m sestamibi, several studies have shown that dobutamine stress has a lower sensitivity for identification of single-vessel disease. Senior et al[143] reported a sensitivity of 77% for predicting multivessel disease but a lower sensitivity for detection of single-vessel disease. Marwick et al[61] reported an 89% sensitivity for patients with multivessel disease but a 71% sensitivity for single-vessel disease. Although the decreased sensitivity in these latter studies may be related to differences in patient selection, a recent study by Wu et al[144] found that in a canine model of flow-limiting, single-vessel stenosis, at dobutamine infusion doses >10 μg/kg/min, Tc-99m sestamibi uptake underestimated microsphere flow, leading to underestimation of ischemia. Similarly, Calnon et al,[145] also using a canine model, found that myocardial sestamibi uptake significantly underestimated the dobutamine-induced flow heterogeneity. It was theorized that dobutamine induces a calcium influx that blunts the negative mitochondrial membrane driving potential, thereby diminishing uptake of the cationic molecule sestamibi.

These findings suggest that dobutamine sestamibi studies should be interpreted with some caution, because myocardial ischemia might be underestimated. However, one must be cautious in applying a canine model to people, as well as in applying laboratory data to a clinical scenario. A summary by Geleijnse et al[146] of six studies containing 269 patients showed that the accuracy of dobutamine Tc-99m sestamibi imaging was acceptable, with an overall sensitivity of 84%, a specificity of 71%, sensitivity for single-vessel disease of 79%, and a sensitivity for multivessel disease of 88%.

PROGNOSTIC USE OF DOBUTAMINE STRESS PERFUSION IMAGING

To date there are few studies reporting on the prognostic use of dobutamine stress perfusion imaging. The first was by Senior et al[147] who tested and followed up 61 patients for 19 ± 11 months. Univariate Cox regression analysis showed that patients with cardiac events (death, myocardial infarction, unstable angina, congestive heart failure) were more likely to have reversible defects (95% versus 59%, $P = .02$) and defects in multiple vascular territories (80% versus 34%, $P = .002$) than patients without events. By multivariate analysis of clinical, exercise testing, and SPECT variables, the independent predictors of cardiac events were a history of myocardial infarction ($P < .001$), number of reversible segments ($P = .001$), and the presence of defects in multiple vascular territories ($P = .01$).

Geleijnse et al[148] studied the prognostic value of dobutamine-atropine Tc-99m sestamibi SPECT imaging in 392 consecutive patients with chest pain.

Multivariate models showed that an abnormal sestamibi scan result was the most important predictor of a future cardiac event (odds ratio [OR] of 2.1), followed by a reversible perfusion defect (OR, 3.2), a history of heart failure (OR, 2.6), and older age (OR, 2.1). Event-free survival curves are shown in Figure 7. The event rate increases with the extent of reversible defects. In another study, this same group saw that for 80 women with chest pain who were unable to exercise and who had normal dobutamine sestamibi SPECT imaging study results, the hard event rate was 0%, and the soft event rate (two patients referred for revascularization) was 1.3%.[146]

ARBUTAMINE

Arbutamine is a recently approved pharmacological stress agent that is delivered by a closed-loop computerized delivery system that constantly monitors the heart rate response to the arbutamine infusion. The system automatically changes the delivery rate, increasing or decreasing the infusion rate as appropriate, allowing a predictable time to achieve the desired heart rate. In addition, whereas dobutamine has strong β-1 but weak β-2 and α-1 properties, arbutamine is a mixed β-1 and β-2 agonist with a mild affinity for α-1 receptors. Arbutamine has a similar degree of inotropic and chronotropic activity as dobutamine, but less peripheral vasodilating activity.[149] Arbutamine was designed specifically to simulate exercise.

In a study of 210 patients with symptoms and angiographic evidence of coronary disease, Dennis et al[136] saw that although the hemodynamic response to arbutamine was similar to that for exercise, the sensitivity for detecting ischemia by either angina or ST segment change was 84% for arbutamine compared with 75% for exercise testing ($P = .014$). Kiat et al[137] studied a cohort of 184 patients using arbutamine SPECT thallium imaging, and also found a hemodynamic response very similar to that for exercise. For the 122 patients who underwent cardiac catheterization, the sensitivity for detecting CAD (≥50%) was 87% (95% for detecting ≥70% stenoses), and the normalcy rate in 62 patients with a low pretest likelihood of disease was 87%. The diagnostic accuracy of arbutamine perfusion imaging was similar to that of exercise. The majority of side effects associated with arbutamine—tremor (23%), flushing (10%), headache (10%), paresthesia (8%), dizziness (8%), hot flashes (4%)—were mild and resolved at the end of infusion. Arrhythmias were common (up to 75%), but most were premature atrial and ventricular contractions, and no episodes of sustained ventricular tachycardia or ventricular fibrillation were observed. Angina was noted in 57% of patients and was severe or prolonged in 5%; ST segment depression occurred in 1.3% of the catheterized group and was effectively treated with metoprolol. The frequency of hypotension was 7% to 8%, necessitating discontinuation of arbutamine infusion in 5% of patients. In an accompanying editorial, Marwick[150] wrote that arbutamine appears to be an effective "exercise simulating" agent for patients who are unable to exercise, but that it still has many of the troublesome side effects associated with dobutamine, including hypotension, and it has a longer half-life. In addition, studies are needed to assess the accuracy obtained when using this agent in women, as well as to compare arbutamine with other pharmacological stressors, especially dobutamine. Whether arbutamine will fulfill the requirements of the "optimal" stress agent remains to be seen.

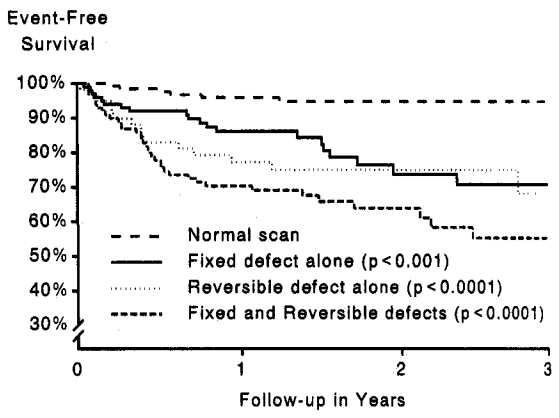

Fig 7. Event-free survival curves in relation to results of dobutamine thallium-201 SPECT imaging. (Reprinted with permission from the American College of Cardiology, Journal of the American College of Cardiology, 1996, 28, 447-454.)

NOVEL USES OF PHARMACOLOGICAL STRESS

In recent years, radionuclide perfusion imaging has become an important method of assessing the presence and extent of viable but dysfunctional myocardium in patients with CAD and left ventricular dysfunction.[151] Standard techniques used for assessment of viability include rest-redistribution

Tl-201, stress-redistribution, reinjection Tl-201, and rest (with or without stress) Tc-99m sestamibi. Recently, Iskandrian and Acio[157] reported on a new technique that combines dobutamine infusion with gated SPECT[152-156] to assess myocardial viability. In their protocol, after the acquisition of rest/delayed thallium images and stress Tc-99m sestamibi perfusion images with gating, dobutamine is infused at a low dose (5 μg/kg/min), and gated SPECT sestamibi images are acquired during the infusion. Gated SPECT images at rest and with dobutamine infusion are compared with attention to improvement in wall motion and thickening on a segmental basis (contractile reserve positive) or lack of improvement (contractile reserve negative), and changes in ejection fraction and volume. Segments with baseline dysfunction but positive contractile reserve are considered to be viable. Levine et al[158] applied this technique to 12 patients with left ventricular dysfunction who then underwent revascularization. Vascular territories with baseline abnormal wall motion that improved with low-dose dobutamine infusion had a significant improvement after revascularization, whereas segments that did not respond to low-dose dobutamine showed no significant improvement. Duncan et al[159] saw that low-dose dobutamine gated SPECT had a similar sensitivity but improved specificity compared with rest/redistribution thallium in predicting myocardial function improvement with revascularization.

SHOULD ALL PERFUSION IMAGING STUDIES BE PERFORMED WITH PHARMACOLOGICAL STRESS?

Although pharmacological stress perfusion imaging has high diagnostic and prognostic use and allows evaluation of the large cohort of patients who are unable to exercise to an adequate myocardial work load, its routine use in all patients would deprive the clinician of valuable exercise data. The Duke Treadmill score, which incorporates exercise capacity, exercise-induced ischemic ST depression, and exercise-induced angina into a composite index, has been shown to be highly predictive of cardiac events, and a normogram using this score enabled an annual mortality rate of patients to be estimated.[160] Hachamovitch et al,[161] reported that although perfusion image variables increased prognostic predictive power fivefold, this was after a twofold increase in power from exercise variables.

In the postinfarction patient, a review by DeBusk[162] highlighted the extreme prognostic importance of peak work load on a low-level exercise test. A study by Weld et al[163] reported a 16-fold increase in cardiac death for patients unable to achieve a four MET work load. Other benefits of performing treadmill exercise in these patients include optimization of discharge medical therapy, setting safe exercise levels for the patient, reassuring the patient and their spouse, and helping to guide rehabilitation therapy.[164]

Pharmacological stress has become an indispensable tool for the performance of stress radionuclide myocardial perfusion imaging. Both currently available vasodilator stress agents, dipyridamole and adenosine, and the positive inotropic agent dobutamine allow accurate diagnosis of CAD comparable with values obtained using exercise stress, while broadening the population of patients who can be evaluated. Pharmacological stress perfusion imaging also allows effective risk stratification of patients in terms of the potential for future cardiac events. There also appear to be potential applications for assessment of myocardial viability. Work is underway to develop agents that are easier to use and that have fewer side effects.

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Stress Myocardial Perfusion Imaging Versus Echocardiography for the Diagnosis and Risk Stratification of Patients with Known or Suspected Coronary Artery Disease

Mario S. Verani

Stress perfusion imaging and stress echocardiography (ECHO) are both very useful for assessment of diagnosis and risk stratification of patients with coronary artery disease (CAD). Both techniques have been well validated during exercise and inotropic stress, but coronary vasodilation stress is better used in combination with perfusion imaging. The overall sensitivity for detection of CAD is slightly higher by single photon emission computed tomography (SPECT) than by two-dimensional (2D) ECHO during all stress modalities, whereas the specificity is slightly higher by ECHO, although the differences in general are not statistically significant. SPECT, however, appears to be superior to ECHO in the diagnosis of isolated circumflex stenosis, as well as for the correct identification of multivessel CAD. A substantially greater amount of information is available regarding risk stratification with SPECT than with 2D ECHO. Although the data suggest that both techniques are very useful for risk stratification of patients with stable CAD, after myocardial infarction, and for preoperative risk stratification, the risk for cardiac events is lower in the presence of a normal stress SPECT study than of a normal stress ECHO.

STRESS MYOCARDIAL perfusion imaging and stress echocardiography (ECHO) are invaluable techniques for the assessment of suspected or documented coronary artery disease (CAD). Both can be used in combination with a variety of exercise modalities as well as with several pharmacological stress agents. Each technique has its own advantages (Tables 1 and 2) and disadvantages (Tables 3 and 4).

The development of these two stress imaging modalities in the last 2 decades has been astonishing. Myocardial perfusion imaging has been in clinical use since the mid 1970s, whereas exercise two-dimensional (2D) ECHO, which was initially reported in 1979 by Feigenbaum's group,[1] has been increasingly used only during the past decade. Although there is no reliable information on the overall use of these two techniques in the United States, some data are available from Medicare-insured patients (American patients of at least 65 years of age). The most current data from the Medicare population (1996) show that a total of 1.2 million patients per year underwent stress perfusion imaging, compared with 303,000 patients who received stress ECHO (unpublished data). Radiopharmaceutical companies estimate that 4.2 million myocardial perfusion studies were performed in the United States in 1998 (personal communication, Richard Williamson, DuPont Radiopharmaceuticals, March 1999). This represents a 15% increase on a yearly basis. Corresponding national figures for stress ECHO are not available.

The worldwide rate of use of perfusion imaging is much lower than that in the United States, which is a reflection of the availability of resources as well as of the number of physicians trained and licensed to use these techniques. In the United States, radiologists, nuclear medicine specialists, and cardiologists with the required training in nuclear procedures all perform and interpret myocardial perfusion images. In many other countries, only specialists in nuclear medicine may perform these functions.

Although the availability of ECHO is much greater than that of nuclear cardiac imaging, stress ECHO has had limited clinical application in most European countries and is only beginning to be used outside of Europe and the United States.

RATIONALE FOR USING PERFUSION IMAGING OR ECHO IN CAD

The ischemic cascade predicts that an absolute or relative decrease in myocardial perfusion is the earliest pathophysiological event during myocardial ischemia, followed in order of appearance by alterations in diastolic function, abnormalities in regional and global systolic function, ischemic electrocardiographic ST-segment changes and, lastly, angina pectoris.[2] Thus, monitoring alterations in myocardial perfusion may be the most

From the Section of Cardiology, Baylor College of Medicine, and The Methodist Hospital, Houston, TX.

Address reprint requests to Mario S. Verani, MD, FACC, FACP, Director, Nuclear Cardiology, The Methodist Hospital, 6550 Fannin, SM 677, Houston, TX 77030.

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Table 1. Advantages of Stress Perfusion Imaging

Good images can be obtained in most patients by using technetium-99m
Amenable to computer quantification
Ability to combine perfusion and functional evaluation
Relatively easy to interpret
Less observer dependency
Can be performed during treadmill exercise
Time-proven
Solid diagnostic and prognostic data base

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sensitive means of demonstrating myocardial ischemia. In animal models of acute myocardial ischemia, regional systolic dysfunction occurs when the myocardial blood flow is reduced to less than 50% of the baseline values. Hence, it is theoretically possible that a 60% regional reduction in myocardial blood flow may cause no abnormalities of regional function, yet perfusion imaging might show this imbalance in myocardial perfusion. In practice, alterations in myocardial blood flow during stress are rapidly followed by alterations in regional ventricular contraction. Consequently, the most pertinent issue is the ability of different techniques to show heterogeneous myocardial perfusion versus regional ventricular contraction. In this regard, the necessity to completely visualize the left ventricular myocardial walls is of pivotal importance. Although single photon emission computed tomography (SPECT) and 2D ECHO are both tomographic techniques, SPECT allows a more complete analysis of all myocardial walls. Computer postprocessing routinely divides the heart in slices every 5 or 6 mm, from top to bottom, front to back, and side to side, allowing complete visualization of all ventricular segments. ECHO, on the other hand, provides more limited sections of each of the imaging planes. Moreover, incomplete visualization of the endocardial border by ECHO is a common problem and compromises the recognition of changes in wall motion during stress. In addition, ECHO dropout, particularly prominent in the lateral wall of the left ventricle,

Table 2. Advantages of Stress ECHO

Totally noninvasive
Detects true ischemia
Comprehensive
Wide availability
Relatively low cost
Controlled by cardiologists

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Table 3. Disadvantages of Stress Perfusion Imaging

Assesses relative flow
Presence of photon attenuation and other artifacts
Low specificity
Lack of standardization
Tracer roll-off at high flows
Cost, availability, and regulatory issues

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coupled with foreshortening of the apex, are common hindrances. Advances in imaging techniques, such as harmonic imaging, and the recent availability of contrast ECHO agents have both improved the delineation of the left ventricular edges but have not yet solved the problem entirely.

Several recent reviews have addressed the diagnostic accuracy of SPECT and 2D ECHO.[3-7] A recent meta-analysis by O'Keefe et al[3] of 12 studies on exercise SPECT, including a total of 2,626 patients, showed an overall sensitivity of 90% for SPECT and 81% for exercise ECHO ($P < .0001$), with a specificity of 72% and 89%, respectively ($P = .06$) (Fig 1).

Fewer studies have provided data on the ability of these two imaging techniques to correctly localize ischemia to the diseased coronary artery. A summary of these reports (Fig 2) shows a slightly higher, statistically nonsignificant, sensitivity for SPECT than for 2D ECHO. For circumflex stenosis, however, the data indicate a significantly higher sensitivity with SPECT. Such a difference may be ascribed to the well-recognized difficulties in completely visualizing the lateral wall of the left ventricle by ECHO.

Although these figures are a measure of the diagnostic accuracy of each of the techniques, an appropriate comparison between them requires studying the same patients with both techniques, ideally at the same time. This is necessary because sensitivity and specificity values are very dependent on the characteristics of the population being studied. The sensitivity may appear higher in

Table 4. Disadvantages of Stress ECHO

Suboptimal images are common
Poor visualization of some regions
Computer quantification is difficult
Technical skill is pivotal
Loose criteria for normal response to stress
Difficult to perform during exercise
Subjective interpretation
Difficult to identify ischemia superimposed on infarct

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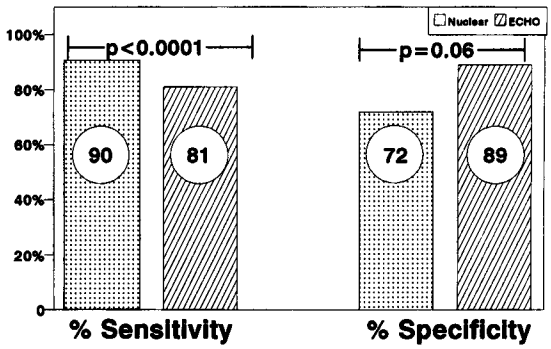

Fig 1. Sensitivity and specificity of exercise SPECT and exercise ECHO. (Reprinted from the American Journal of Cardiology, 75, O'Keefe et al, Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity, 25D-34D, 1995, with permission from Excerpta Medica Inc.)

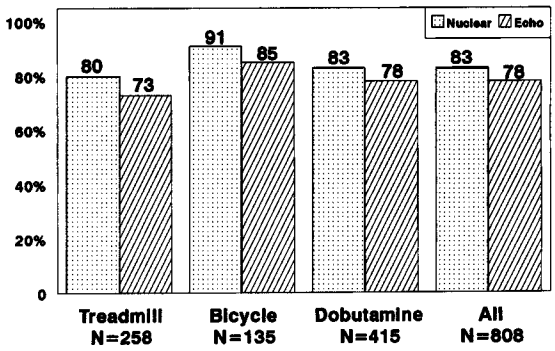

Fig 3. Sensitivity of SPECT and ECG during stress in the same patients. Although the sensitivity is slightly higher for every stressor used with SPECT, the differences are not statistically significant. (Reprinted from the American Journal of Cardiology, 75, O'Keefe et al, Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity, 25D-34D, 1995, with permission from Excerpta Medica Inc.)

populations with higher prevalence of CAD, more severe coronary stenosis (≥70% versus 50% to 70%), more extensive CAD (multivessel versus single-vessel), and with a higher frequency of prior myocardial infarction. Even the use of meta-analytical statistical techniques may not correct the essential problem of varying population characteristics or totally conceal the investigators' biases toward nuclear cardiology or ECHO.[8] The few studies directly comparing the two techniques in the same patients will be discussed below.

STRESS SPECT AND STRESS ECHO IN THE SAME PATIENTS

As reported by O'Keefe et al,[3] 11 studies including 808 patients have directly compared stress SPECT with stress ECHO. The results of these studies are summarized in Figure 3. Although the sensitivity was slightly higher by SPECT for each of the stress modalities studied, the differences did not reach statistical significance. Conversely, the specificity was slightly but insignificantly higher by ECHO.

The studies also indicate a higher overall sensitivity by SPECT with regard to detection of single-vessel CAD (76% versus 67%, $P < .05$) (Fig 4).

CORRECT IDENTIFICATION OF MULTIVESSEL DISEASE

One of the goals of noninvasive cardiac imaging is the detection of high-risk CAD, in addition to the

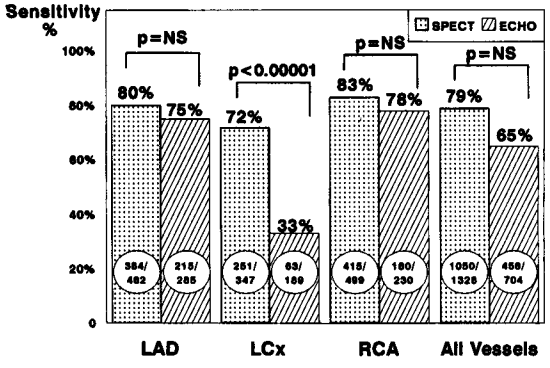

Fig 2. Sensitivity of exercise SPECT and exercise ECG for individual coronary artery stenosis. (Reprinted from the American Journal of Cardiology, 75, O'Keefe et al, Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity, 25D-34D, 1995, with permission from Excerpta Medica Inc.)

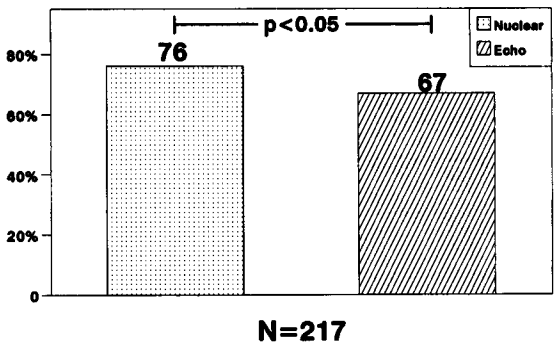

Fig 4. Diagnosis of single-vessel disease (same patient sensitivity). (Reprinted from the American Journal of Cardiology, 75, O'Keefe et al, Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity, 25D-34D, 1995, with permission from Excerpta Medica Inc.)

simple identification of any degree of CAD. In this regard, to the extent that a multivessel distribution of perfusion or wall motion abnormalities during stress denotes multivessel CAD, and hence may be a marker of a worse prognosis, it is of interest to determine the ability of the two imaging techniques in identifying multivessel CAD. Although such a comparison has not been performed in the same patients, O'Keefe et al[3] compiled the literature that had data on the identification of multivessel disease by the individual techniques (Fig 5). In these studies, SPECT correctly identified the presence of multivessel disease in 72% of the patients, whereas ECHO did so in 50% of the patients. This difference was statistically significant ($P < .001$).

PRETEST AND POSTTEST REFERRAL BIAS

It is generally appreciated that most newly reported tests perform better when they are first described rather than subsequently, when they are widely applied into clinical practice. This was first noticed with exercise radionuclide angiography[9] and has affected both stress perfusion imaging and stress ECHO.

A pretest referral bias may occur when patients with a high likelihood of disease are referred for testing. Such is the case with older patients, those unable to exercise, those with diabetes mellitus, and those with a history of prior myocardial infarction or prior coronary revascularization. All of these factors would tend to increase the perceived positive predictive value of the test. Another

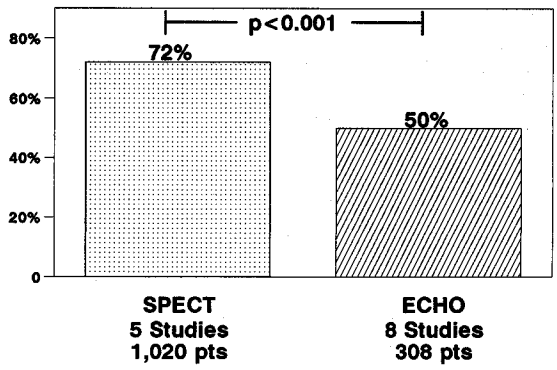

Fig 5. Multivessel disease identification by SPECT and stress ECG. (Reprinted from the American Journal of Cardiology, 75, O'Keefe et al, Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity, 25D-34D, 1995, with permission from Excerpta Medica Inc.)

type of pretest bias may be the referral for noninvasive imaging of patients who already had coronary angiography that showed borderline lesions (typically lesions between 40% and 70%). In this situation, a negative noninvasive imaging study may be interpreted as a demonstration that the observed stenosis is not functionally significant. Alternatively, if the stenosis happens to be >50%, the noninvasive test may be interpreted as a false-negative result, that is, the sensitivity will be lowered, even if the stenosis is not functionally significant.

A posttest referral bias occurs when the noninvasive test that is first performed drives the performance of the subsequent test, which will be considered the gold standard. Because stress perfusion imaging is often performed before coronary angiography, there is a strong tendency to refer to angiography patients with an abnormal SPECT result. In most institutions, the overwhelming majority of patients with a normal SPECT study result do not undergo coronary angiography,[10-13] thus decreasing the pool of truly normal individuals for proper comparison between SPECT and coronary angiography. This type of bias tends to increase the positive prediction value while decreasing the negative predictive value of the test. Because stress perfusion imaging has been used clinically for a longer time than stress ECHO, this bias is more apparent in reports on perfusion imaging.

Although stress ECHO reports have been less affected by a posttest referral bias, recent trends indicate a decreasing specificity of the test. For example, a large recent study of 3,679 consecutive patients who underwent exercise ECHO showed an observed sensitivity and specificity of 78% and 44% in men, and 79% and 37% in women, respectively.[14] Mathematical techniques have been used to attempt to correct for this type of referral bias, taking into consideration the large number of patients with a normal noninvasive imaging study who do not undergo coronary angiography, as well as those with abnormal study results who also do not receive coronary angiography. In the recent Mayo Clinic study,[14] the net effect of this correction was to merely reverse sensitivity and specificity. For example, the new values of sensitivity and specificity after correction were 42% and 83% in men and 32% and 85% in women, respectively.

PHARMACOLOGICAL STRESS TESTING

The advent of pharmacological stress testing represented a major contribution to the assessment of patients by either perfusion imaging or ECHO. At the present time in the United States, approximately one third of all stress perfusion imaging studies are performed using pharmacological stress. Although these data are not available for ECHO, it is likely that more than half of the stress ECHO procedures use pharmacological rather than exercise stress. Vasodilator and inotropic stresses have been used with both imaging techniques, but the mechanisms of abnormal tests results are fundamentally different between perfusion imaging and 2D ECHO. With perfusion imaging, the aim of the stress agent is to produce a differential myocardial perfusion across the left ventricle, with a higher myocardial blood flow and tracer uptake occurring in the normally perfused myocardial segments and a relatively lower perfusion and tracer uptake in regions perfused by vessels with functionally significant coronary stenosis.[2] An absolute decrease in perfusion relative to the baseline values does not usually occur in the territories perfused by the stenotic vessels, that is, a relatively low perfusion cannot be equated to myocardial ischemia as denoted by anaerobic metabolism, adenosine triphosphate (ATP) breakdown, or lactate production. Hence, perfusion imaging may be abnormal in the presence of a differential perfusion, even if ischemia is not actually present. Stress ECHO, on the other hand, depends on the production of actual myocardial ischemia, of which the deterioration in wall motion will be a particular manifestation.

On the basis of these considerations, pharmacological vasodilation, which usually does not produce ischemia, would be ideally suited to be used in combination with perfusion imaging.[15,16] These physiological concepts do indeed translate into a higher sensitivity of pharmacological vasodilation when it is coupled with perfusion imaging,[2] rather than with echocardiography. A recent compilation of pharmacological vasodilation ECHO showed an overall sensitivity of only 63%.[4] Concomitant administration of atropine with either dipyridamole or adenosine ECHO may increase the sensitivity of the test. In a recent study,[17] the sensitivity of dipyridamole ECHO increased from 68% to 82% with the addition of atropine.

Inotropic stresses would appear to be an ideal combination with ECHO because they produce an increase in myocardial oxygen demand that may outstrip the vasodilatory capacity of the artery with a significant coronary stenosis, thereby producing myocardial ischemia and deterioration of wall motion. In practice, the reported sensitivity with dobutamine ECHO has been acceptable, although somewhat lower than that of exercise ECHO. The reported sensitivity with dobutamine perfusion imaging, however, has been similar or even higher than that of dobutamine ECHO.[4]

PHARMACOLOGICAL PERFUSION IMAGING

The reported sensitivities for dipyridamole and adenosine perfusion imaging are, in general, as high as those results reported with exercise perfusion imaging. In a compilation of 14 studies comprising 965 patients, the overall sensitivity of dipyridamole perfusion imaging was 87% with a specificity of 75%.[7] In more recent studies exclusively using SPECT imaging in combination with dipyridamole, the sensitivity was 90% and the specificity 78%.[4,18-21] Adenosine perfusion imaging also has been remarkably sensitive. A recent compilation of 8 studies including 925 patients showed an average sensitivity of 89% and specificity of 83%.[3,16,22-28] Although there are fewer patients reported with dobutamine perfusion imaging, the overall sensitivity of this technique is 91%, with a specificity of 86%.[3,7] Despite the antagonism between dobutamine and sestamibi, which has been shown in animal experiments,[29] the average reported sensitivity of dobutamine sestamibi SPECT is high at 86%.[30-41] A direct comparison between pharmacological vasodilation echocardiography and perfusion scintigraphy shows an overall sensitivity of 66% and 90%, with specificity of 91% and 79%, respectively.[5] The recent addition of atropine increases the sensitivity of vasodilator stress ECHO,[17] although these results require confirmation in larger numbers of patients from other institutions.

O'Keefe et al,[3] summarized 14 studies on dobutamine ECHO, in a total of 1,049 patients, with an average sensitivity of 81% and specificity of 83%. When the five studies that included patients studied by both dobutamine SPECT and dobutamine ECHO simultaneously were separately analyzed, the overall sensitivity was 78% with ECHO and 83% with SPECT, with corresponding specificities of 85% and 75%.

A few studies also have compared perfusion imaging with ECHO using multiple stressors. In

the most recent of these, Santoro et al[42] reported a comparison among exercise treadmill testing, dipyridamole ECHO, dobutamine ECHO, dipyridamole sestamibi SPECT, and dobutamine sestamibi SPECT imaging in the same patients. The sensitivity was 58% for exercise ECHO testing, 55% for dipyridamole ECHO, 61% for dobutamine ECHO, 97% for dipyridamole sestamibi SPECT, and 91% for dobutamine sestamibi SPECT. The corresponding specificities were 67%, 96%, 96%, 89%, and 91%, respectively. Perfusion imaging with either dipyridamole or dobutamine also had a higher sensitivity for detection of all stenotic arteries: 75% by dipyridamole sestamibi SPECT and 73% by dobutamine sestamibi SPECT, versus 32% by dipyridamole ECHO and 39% by dobutamine ECHO. The nuclear techniques were more sensitive for the correct prediction of multivessel disease: 48% for dipyridamole sestamibi SPECT and 67% for dobutamine sestamibi SPECT, versus 14% for dipyridamole ECHO and 29% for dobutamine ECHO.

Oguzhan et al[43] recently reported a comparison among ECG stress testing, dobutamine ECHO, and exercise sestamibi SPECT in 70 patients. Dobutamine ECHO and exercise sestamibi SPECT had a higher sensitivity than exercise ECG testing (90%, 96%, and 57%, respectively). In this study, dobutamine ECHO had a higher specificity than both exercise ECG testing and exercise sestamibi SPECT (90%, 71%, and 62%, respectively).

Takeuchi et al[44] reported a comparison between dobutamine ECHO and stress (exercise or dipyridamole) thallium-201 SPECT. The sensitivity and specificity of dobutamine ECHO were 72% and 91% versus 78% and 70%, respectively, for SPECT. These differences were not statistically significant.

Ho et al[45] compared dobutamine ECHO with exercise thallium SPECT. The overall sensitivity and specificity of dobutamine ECHO were 92% and 77%, whereas those of thallium SPECT were 76% and 77%, respectively. These differences were not statistically significant. The sensitivity was similar for the two techniques in patients who exercised maximally, but higher by dobutamine ECHO than by SPECT performed during a submaximal exercise.

Kisacik et al[46] recently compared dobutamine ECHO and Tc-99m sestamibi SPECT. In this study, dobutamine ECHO had a sensitivity of 94% with a specificity of 86%, compared with 94% and 64%, respectively, for dobutamine SPECT.

Khattar et al[47] recently showed that the combination of sestamibi SPECT and dobutamine ECHO has incremental value for detection of multivessel disease. Whether such a combination of tests would be cost-effective remains to be determined.

Huang et al[48] compared simultaneous dobutamine ECHO and dobutamine thallium SPECT in 93 patients who also underwent coronary angiography. Dobutamine ECHO had a sensitivity of 93% and thallium SPECT had a sensitivity of 90%, with corresponding specificities of 77% and 81%, respectively.

Thus, the totality of studies indicate little difference in diagnostic accuracy between dobutamine ECHO and dobutamine SPECT. Higher sensitivity, however, can be obtained with maximal exercise SPECT, pharmacological vasodilator SPECT, or maximal exercise ECG than with dobutamine ECHO.

RISK STRATIFICATION BY STRESS SPECT AND STRESS ECHO

Extensive published data show a powerful role of myocardial perfusion imaging with respect to risk stratification. The number and extent of perfusion abnormalities, the involvement of multiple vascular territories, the presence and extent of reversible hypoperfusion, an increase in thallium-201 lung uptake, and transient left ventricular cavity dilatation during stress all have been shown to be markers of cardiac events. The extent of perfusion abnormalities, left ventricular dilatation, and increased thallium lung uptake are especially good predictors of cardiac death or congestive heart failure, whereas the presence and extent of myocardial ischemia are good predictors of ischemic cardiac events (myocardial infarction or unstable angina) or death.[49] It has been shown that the risk of death or myocardial infarction after a normal stress myocardial perfusion study is less than 1% per year, based on more than 7,500 patients reported.[12,50] A normal stress SPECT result indicates an exceedingly low risk even in patients with angiographic CAD.[49] It has been shown that myocardial perfusion imaging adds incremental information to the clinical and exercise variables.[12,50]

The effectiveness of perfusion imaging for risk stratification applies to both men and women; in fact, it has been suggested that noninvasive stratification is more effective in women than in men.[11] A recent report from The Economics of Noninvasive

Diagnosis (END) Multicenter Study Group[51] has compared the economics of two strategies in the management of patients with CAD: A direct referral to coronary angiography versus an initial referral to SPECT, with subsequent referral to coronary angiography on the basis of the noninvasive test results. A large number of patients (n = 11,372) with stable angina were studied. As expected, coronary revascularization rates were higher for patients directly taken to catheterization, as compared with those initially undergoinging stress perfusion imaging (50% versus 30%, $P < .0001$). Cardiac death or myocardial infarction rates, however, were similar for patients initially assessed by perfusion imaging or coronary angiography, whereas the cost of care was higher for patients taken directly to cardiac catheterization.

Stress myocardial perfusion imaging also has been shown to be a powerful technique for risk stratification of patients with a recent myocardial infarction[52-59] or unstable angina.[60,61] Stress perfusion imaging, particularly using pharmacological vasodilation, has been widely used in the preoperative risk stratification of patients undergoing noncardiac surgeries,[62] as well as after coronary artery bypass graft surgery.[63-66]

With regard to stress ECHO, there is a paucity of studies reporting on the risk stratifying ability of this technique. In five recent studies in patients with known or suspected CAD, in a total of 1,493 patients, cardiac events occurred at a rate of 9.4% per year in patients with a negative stress ECG. These studies were performed during exercise,[67-69] dobutamine,[70-72] or dipyridamole.[73] Cardiac death or nonfatal myocardial infarction occurred at the rate of 2.5%[6] per year. Although not very high, this rate is approximately two- to three-fold higher than that of a normal stress perfusion study. The prognostic value of stress ECHO in patients with myocardial infarction has been recently reviewed.[74] Two small studies performed in the late 1980s showed that a positive stress ECHO was a good predictor of cardiac events (50% to 94%), whereas a negative stress ECHO was associated with a 13% to 17% cardiac event rate in the first year.[74] Three studies using dipyridamole ECHO showed event rates between 33% and 50% for patients with a positive dipyridamole ECHO and 12% to 18% in those with a negative dipyridamole ECHO in the first year.[74]

More recently, Geleijnse et al[75] assessed dobutamine-atropine stress using both ECHO and sestamibi SPECT as imaging modalities in a series of 220 consecutive patients with chest pain. Dobutamine ECHO was positive for ischemia in 76 patients and sestamibi SPECT in 91 patients. In this study, the addition of sestamibi SPECT, when confined to nonischemic ECHO studies in which a target heart rate was not achieved, had a significant incremental value for risk stratification. The addition of ECHO to nondiagnostic SPECT studies had no significant incremental value.

Marcovitz et al[76] observed that the risk of cardiac events was highest in patients with an abnormal wall motion at rest who also had an ischemic response during dobutamine stress ECHO. Krivokapich et al[77] recently reported on 558 consecutive patients who underwent dobutamine stress ECHO at their institution. The event rates for myocardial infarction and death were 10% and 8%, respectively, when dobutamine ECHO was positive, and 3% and 3% per year, respectively, if the test was negative.

Other investigators recently have reported the value of dobutamine stress ECHO for risk stratification after myocardial infarction.[78-80] Although the test appeared useful for risk stratifying these patients, the safety of high-dose dobutamine imaging very early after myocardial infarction requires confirmation in larger number of subjects.[81]

Similarly to SPECT, dobutamine ECHO has also been found useful in the risk stratification of patients before noncardiac surgery.[82-84]

Only recently has the long-term prognostic value of exercise ECHO been compared with exercise thallium-201 SPECT in patients with stable CAD.[85] Two hundred forty-eight patients who simultaneously underwent treadmill exercise thallium SPECT and ECHO were followed up for a mean of 3.7 years. With the use of stepwise logistic regression analysis, the best predictive models were exercise ECHO combined with exercise ECG or exercise thallium SPECT combined with exercise ECG. Both models had a comparable value for the prediction of cardiac events. With exercise ECHO, exercise wall motion score and presence of ischemia were the strongest predictors of events. For the model containing the variable thallium SPECT, the strongest predictor was the presence of an ischemic perfusion defect. For the prediction of ischemic events and/or cardiac death, only the ECHO and thallium parameters were significant predictors, but not the clinical or exercise treadmill

variables. This study concluded that in patients evaluated for CAD, exercise ECHO and thallium-201 SPECT combined with ECG variables provided comparable prognostic information.

McCully et al[86] recently have reported on the outcomes of 1,325 patients with a normal exercise ECHO who were followed up for a mean of 23 months. During follow-up, 3 patients died of cardiac causes and 10 patients had a nonfatal myocardial infarction. Twenty additional patients underwent coronary revascularization. The investigators found an overall event rate per person per year of 0.9%. Interestingly, patients with a good workload (>7 metabolic equivalents [METs] for men and >5 METs for women) had a significantly better prognosis than those with a low workload.

INCREMENTAL PROGNOSTIC VALUE OF PERFUSION AND FUNCTION VARIABLES

As recently shown in different subsets of patients with CAD, the combinationof myocardial perfusion variables with the left ventricular ejection fraction may enhance our ability to risk stratify patients.[54,55,87] The recently introduced technique of gated SPECT, which combines perfusion and function information, therefore has the potential to further improve the prognostic stratification of patients with CAD.

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The Potential for Myocardial Imaging With Hypoxia Markers

Albert J. Sinusas

Direct "hot spot" imaging of myocardial tissue hypoxia is potentially of great clinical importance because available noninvasive approaches for the detection of myocardial ischemia have generally been based on the detection of flow heterogeneity or identification of regional alterations of myocardial metabolism. These existing approaches provide only an indirect assessment of regional myocardial ischemia, and may be affected by either sympathetic activation or substrate availability. The assessment of tissue oxygenation with hypoxic compounds may be the best indicator of the balance of flow and oxygen consumption. These compounds may provide a means of identifying dysfunctional chronically ischemic but viable "hibernating" myocardium and find a critical place in the assessment of angiogenesis. Nitroimidazole compounds hold promise for positive imaging of hypoxia in the heart. However, refinement of these compounds is needed to improve target specificity. The potential of technetium-99m (Tc99m) complexes derived from removal of the nitroimidazole moiety from a nitroimidazole-containing ligand is interesting and warrants further investigation. Experimental studies support the possibility of identifying myocardial hypoxia with the positron-emitting compound F18-fluoromisonidazole noninvasively. The potential of a Tc99m labeled nitroimidazole for positive imaging of myocardial ischemia is tremendous because single-photon imaging is more widely available. The true clinical potential of these nitroimidazole compounds can only be defined with future experimental and clinical studies. Ideally, these studies should include comparisons of tracer uptake with independent measures of regional ischemia or measures of oxygen tension, potentially using magnetic resonance imaging.

IMAGING OF myocardial hypoxia holds great potential for evaluation and management of patients with cardiovascular disease. Hypoxia imaging may offer a new approach for assessment of myocardial ischemia, and could provide a novel noninvasive method of evaluating angiogenesis. Angiogenesis represents the formation of new capillary blood vessels from existing microvessels by cellular outgrowth.[1] Hypoxia resulting from deficient vascular supply has been assumed to drive angiogenesis.[2] Imaging with markers of hypoxia may provide new insights regarding the pathophysiology of myocardial hibernation, the development of cardiomyopathies, natural collateral development, and response to angiogenic therapies.

Noninvasive approaches for the detection of myocardial ischemia generally have involved either the detection of flow heterogeneity or identification of regional alterations of myocardial metabolism. Myocardial perfusion scintigraphy relies on the identification of flow heterogeneity, which is not necessarily equivalent to development of true myocardial ischemia. Although analysis of myocardial metabolism may provide a more direct index of regional ischemia, this approach may be influenced by substrate availability. Both of these approaches have limitations and provide only an indirect assessment of regional myocardial ischemia.

Alternatively, myocardial ischemia could be detected by direct measurement of reduced tissue oxygen tension. Normally there is a tight coupling of oxygen use and delivery. The myocardium uses oxygen to meet its metabolic demands. Reduction of intracellular oxygen is associated with an immediate reduction in regional myocardial function. Sustained reduction in myocardial oxygen is associated with permanent cellular injury.

A family of radiopharmaceuticals that incorporates nitroimidazole moieties has been developed to detect regional tissue oxygen tension (Po_2). Nitroimidazoles were first developed as selective radiosensitizers of hypoxic cells and used as adjuvants to radiotherapy in the treatment of tumors.[3] In tumor cell models, labeled fluoromisonidazole is retained in proportion to the degree of tissue hypoxia in viable cells, but is not retained in necrotic cells. In 1981, it was suggested that this class of compounds could be used for the direct visualization of tissue hypoxia.[4] Studies have subsequently shown localization and increased retention of fluoromisonidazole in ischemic canine myocardium.[5-8] Recently, a class of technetium-99m (Tc99m) labeled nitroimidazoles has been developed for imaging of hypoxic tissue.

Measurement of tissue oxygen may provide an

From the Animal Research Laboratories, Section of Cardiovascular Medicine; the Department of Medicine, and the Department of Diagnostic Radiology; Yale University School of Medicine, New Haven, CT.

Address reprint requests to Albert J. Sinusas, MD, Yale University School of Medicine, PO Box 208042, TE-2, New Haven, CT 06520-8042.

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approach for positive imaging of myocardial hypoxia. The assessment of tissue oxygenation with nitroimidazoles may be the best indicator of the balance of flow and oxygen consumption, and may be the most sensitive and specific predictor of the physiological significance of a coronary stenosis. Scintigraphic detection of myocardial hypoxia may predict the development of cardiomyopathies as well as coronary collaterals, and permit the future evaluation of angiogenic therapies.

CHEMISTRY

Nitroimidazole-containing compounds were initially labeled with fluorine-18 or iodine-123, although now Tc99m labeled nitroimidazoles are available for potential imaging of hypoxic tissue. Four classes of Tc99m labeled compounds have been evaluated for this purpose: (1) Tc99m labeled boronic acid dioxime (BATO) incorporating nitroimidazoles, (2) Tc99m propylene amine oxime (PnAO) and amido PnAO nitroimidazoles, (3) Schiff-base nitroimidazoles, and (4) butylene amine oxine (BrAO) ligands without an attached nitroimidazole.[9] Of the Tc99m labeled compounds, the PnAO analogs have been most widely studied. The nitroimidazole group on the imidazole ring is responsible for the bioactivation of the molecule in the cytosol. Many modifications of this class of compounds have been made to increase the myocardial retention and optimize target-to-background activity. Increasing the lipophilicity increases the percent uptake into myocytes under both hypoxic and normoxic conditions.[10] Unfortunately, increasing the lipophilicity also increases hepatocellular uptake and retention, which complicates in vivo imaging of the heart.

A potential alternative Tc99m labeled agent for detection of ischemic or hypoxic myocardium is 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione (Tc99m-HL91). Interestingly, this Tc99m complex was derived from removal of the 2-nitroimidazole moiety from a nitroimidazole-containing ligand. The chemical structure of ^{99m}Tc-nitroimidazole, HL-91, and ^{18}F-fluoromisionidazole are shown in Figure 1.

MECHANISM OF MYOCARDIAL RETENTION OF NITROIMIDAZOLES

The presumed mechanism of myocardial retention of nitroimidazole-containing compounds is summarized in Figure 2. Most of the data currently available regarding the mechanism of retention of this class of compounds is derived from work with misonidazole.[7] The nitroimidazoles are believed to passively diffuse across the cell membrane. Once in the cytoplasm of the myocardial cell, there is a nitro-reduction, with formation of the R-NO_2 radical anion. This step occurs independent of the oxygen tension. In the presence of normoxic conditions, the radical anion interacts with oxygen,

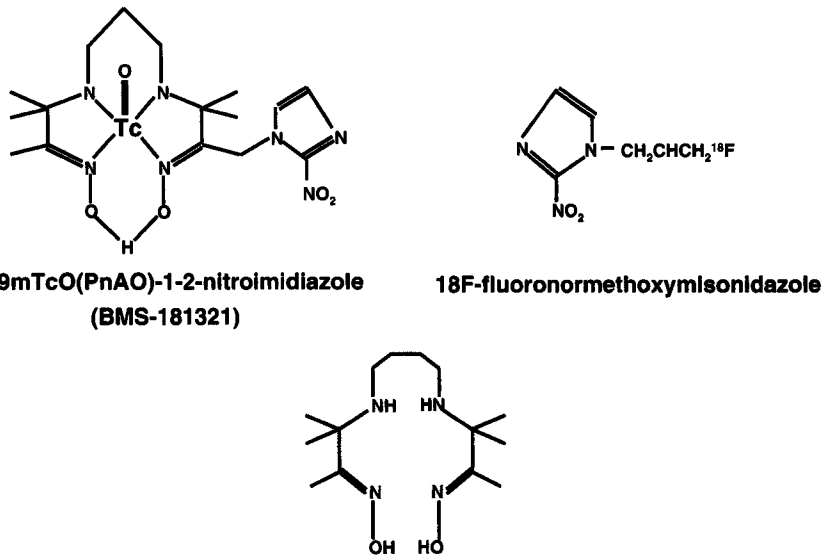

Fig 1. Chemical structure of ^{99m}Tc-nitroimidazole, ^{18}F-misonidazole, and HL-91.

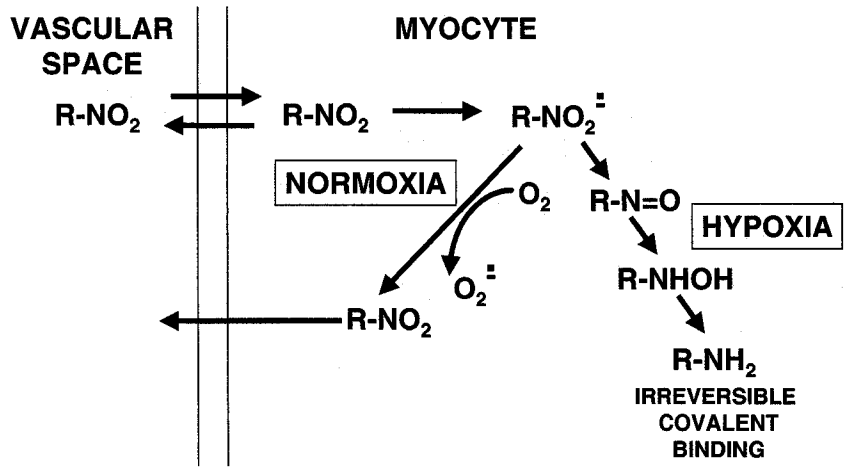

Fig 2. Mechanism of retention of nitroimidazoles in the heart. $R\text{-}NO_2$, reduced nitrate. (Adapted and reprinted with permission.[7])

yielding superoxide and noncharged misonidazole. Formation of the free radical anion is reversed in presence of oxygen because oxygen has a higher electron affinity. The noncharged misonidazole then diffuses back out of the cell. In contrast, under hypoxic conditions, the misonidazole radical anion is reduced further, yielding nitroso compounds and hydroxylamines. The reduced metabolites of nitroimidazole have a lower permeability and are retained within the cell. The amines may bind to intracellular macromolecules and remain trapped within the cell. Alternatively, the change in charge of the compound may result in cellular trapping without intracellular binding.

MISONIDAZOLE

Experimental studies have shown the potential of the positron-emitting radiotracer F18-misonidazole for the detection of hypoxic myocardium. Studies have shown increased retention of fluoromisonidazole in hypoxic isolated myocytes[11] and intact ischemic canine myocardium.[5-8] The wide application of this approach has been limited in part by the availability of positron-emission tomographic (PET) technology. In addition, fluoromisonidazole has shown fairly slow clearance from the blood,[8] which may complicate clinical imaging.

Shelton et al,[6] showed a 200% increase in myocardial retention of F18-misonidazole under hypoxic or ischemic conditions.[6] Ischemic hearts showed increased extraction of the tracer. Normal myocardial tissue retained about 18% of delivered tracer. These investigators showed increased accumulation and retention of misonidazole under hypoxic conditions independent of a reduction in flow. The retention of misonidazole in isolated perfused rabbit hearts did not reverse with reoxygenation, suggesting that a degree of irreversible binding occurred. Martin et al[11] confirmed that F18-fluoromisonidazole is retained in myocardial cells in proportion to the level of tissue hypoxia. Pilot canine studies showed increased accumulation of misonidazole in the presence of coronary occlusion.

Martin et al[5] also evaluated the retention of [3H]fluoromisonidazole in a canine model of coronary occlusion. Increased retention of [3H]fluoromisonidazole was seen in myocardial regions with moderate reductions in flow. Retention of [3H]fluoromisonidazole was not increased in infarcted regions. These investigators observed a 1.8- to 2.4-fold increase in myocardial retention in ischemic regions relative to control nonischemic regions.

Subsequently, Shelton et al[7] performed PET F18-fluoromisonidazole imaging in dogs after 3, 6, and 24 hours of coronary occlusion. The myocardial retention of F18-fluoromisonidazole decreased with progressively longer periods of coronary occlusion. Necrotic myocardium should show less intracellular binding because the capacity for enzymatic nitroreduction is diminished. In addition, there may be reduced trapping of F18-fluoromisonidazole secondary to loss of sarcolemmal integrity. Martin et al confirmed these findings in acute canine models of complete and partial coronary occlusion.[8]

Thus, several experimental studies have shown the potential of F18-fluoromisonidazole for direct detection of viable ischemic myocardium.

TECHNETIUM-99m LABELED NITROIMIDAZOLES

The development of Tc99m labeled nitroimidazole compounds may provide an alternative approach for positive imaging of regional myocardial hypoxia.

One of these Tc99m labeled nitroimidazole compounds, (oxo[[3,3,9,9-tetramethyl-1-(2-nitro-1H-imidazol-1-yl)-4,8-diazaundecane-2, 10-dione dioxoimato] (3-)-N,N′,N′′,N′′′]technetium) nitroimidazole (BMS181321), has shown promise for direct assessment of myocardial ischemia using in vitro and in vivo preparations.[12-20] This compound represents one of a class of technetium (V) oxo PnAO complexes.

Several investigators, using an isolated-buffer-perfused rat heart preparation, showed a 2- to 4-fold increase in myocardial retention of BMS181321 under hypoxic conditions.[13,16,18] Using an isolated mitochondrial preparation, Rumsey et al[12] showed a higher association of BMS181321 with isolated mitochondria under hypoxic conditions. Rumsey et al[12] also showed that the myocardial washout of BMS181321 was biexponential. Applying the multiple indicator-dilution method and blood perfused heart preparation, Dahlberg et al[21] showed that BMS181321 has a high initial extraction under both ischemic and normoxic conditions, followed by rapid clearance. In this in vitro model, the net extraction of BMS181321 was increased during low-flow ischemic conditions.

Ng et al[16] also have evaluated the effect of hypoxia on BMS181321 kinetics independent of flow using an isolated-buffer-perfused rat heart preparation. The retention of BMS181321 was shown to be inversely proportional to the perfusate oxygen level, after both a bolus injection and constant infusion of the tracer. There is a sigmoidal relationship between myocardial retention of BMS181321 and the perfusate oxygen level (Fig 3). In this in vitro model, the perfusate oxygen level must be below 60% before significant trapping of BMS181321 occurs. At perfusate oxygen levels below 50%, there is little change in relative retention. Under these experimental conditions, BMS181321 showed triexponential myocardial clearance rather than biexponential.

Two independent groups of investigators evaluated the retention of BMS181321 using in vivo rabbit models of coronary occlusion with and without reperfusion.[20,22] Both groups showed selective retention of BMS181321 in the viable peri-infarct regions using macroautoradiographic techniques. BMS181321 was not significantly retained in regions with necrosis. Fukuchi et al[22] also showed that timing of BMS181321 injection relative to the ischemic insult and reperfusion was also a critical factor affecting BMS181321 retention. Figure 4 shows the typical increase in myocardial BMS181321 observed in the ischemic peri-infarct region using macroautoradiography.

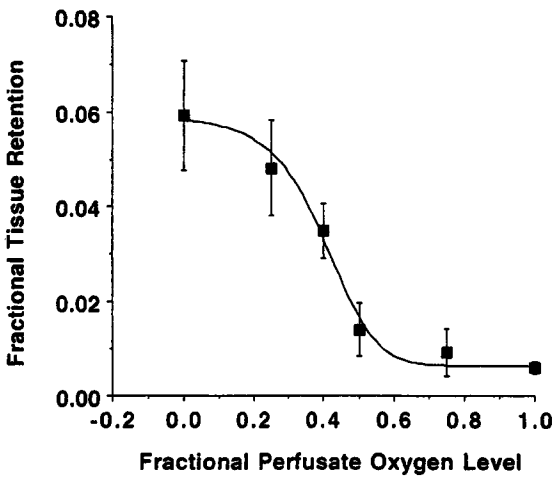

Fig 3. Plot of relation between fractional perfusate oxygen level and tissue retention fraction for normoxic and hypoxic conditions in isolated rat heart. Each data value represents an average and standard deviation of five hearts. Curve fitting was performed using a modified Hill equation. (Reprinted with permission from NG C et al, Kinetic analysis of technetium-99m-labeled nitroimidazole (BMS181321), as a tracer for myocardial hypoxia, Circulation, 92, 1261-1268.)

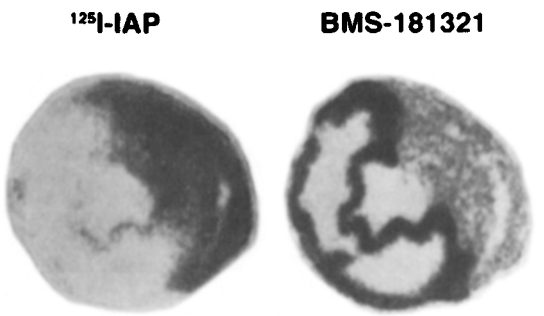

Fig 4. Dual-tracer autoradiograms obtained with ^{125}I-iodoantipyrine (^{125}I-IAP) and BMS-181321 (BMS) after sustained coronary occlusion without reperfusion. BMS was injected during ischemia. ^{125}I-IAP uptake, an index of flow, was almost absent in the ischemic risk area. Increased myocardial BMS uptake is seen localized at the margins of the risk area. (Fukuchi K, et al. Ischemic and reperfused myocardium detected with technetium-99m-nitroimidazole. *Journal of Nuclear Medicine*. 1996;37:761-766.)

Shi et al,[15] using a canine model of partial coronary occlusion and pacing-induced demand ischemia, showed preferential retention of BMS181321 in ischemic but viable myocardium. In this in vivo preparation, myocardial BMS181321 retention was inversely related to myocardial blood flow (Fig 5). A 61% increase in myocardial activity was seen in ischemic regions by ex vivo single photon emission computed tomography (SPECT) imaging within 1 hour of tracer injection. This increase in myocardial BMS181321 activity was confirmed by postmortem gamma well counting of myocardial tissue. Serial planar images were obtained after the intravenous injection of BMS181321. BMS181321 cleared very rapidly from the blood; however, it accumulated rapidly in the liver, resulting in a poor target-to-background ratio during the initial 60 minutes after an intravenous injection. Thus, the relatively low cardiac specificity of BMS181321 may limit the feasibility of imaging with this radiotracer clinically.

Stone et al[17] evaluated the kinetics of BMS181321 using an intact working extracorporeally perfused open-chest swine model of ischemia and reperfusion. Both in vivo dynamic planar imaging and ex vivo imaging were performed. In this model, BMS181321 showed biexponential clearance from myocardial tissue. The early phase was similar in normal and ischemic regions. The investigators suggest that the early phase may represent clearance of free tracer from both the extracellular and intracellular spaces. The ischemic regions showed

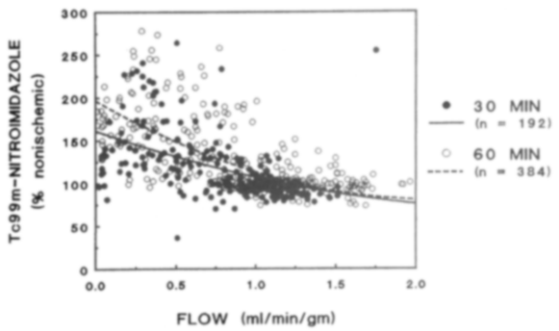

Fig 5. Correlation of relative myocardial ^{99m}Tc-nitroimidazole activity (percent nonischemic) and absolute regional myocardial blood flow (mL/min/g). Dogs were killed either 30 minutes (*solid circles*) or 60 minutes (*open circles*) after injection of ^{99m}Tc-nitroimidazole during partial coronary occlusion and pacing-induced demand ischemia. There was increased myocardial ^{99m}Tc-nitroimidazole activity in the low-flow regions. (Shi CQ, et al. Technetium-99m-nitroimidazole (BMS181321): A positive imaging agent for detecting myocardial ischemia. *Journal of Nuclear Medicine.* 1995;36:1078-1086.

decreased slow washout of BMS181321.[17] This may reflect delayed clearance of intracellular tracer, which has been reduced beyond the initial reduction and is unable to diffuse out of the myocytes. There was a 70% increase in retention in ischemic/reperfused regions, similar to the increase observed by Shi et al[15] in a canine model of low-flow-demand ischemia. However, the percent of the injected dose that was retained in the ischemic region was very small (0.008% ± 0.001% injected dose) in spite of delivery directly into the coronary artery.

Rumsey et al,[13] evaluated the feasibility of BMS181321 SPECT imaging for the detection of myocardial ischemia in two canine models. In one group of dogs, BMS181321 was injected under control conditions and the distal left anterior descending coronary artery was subsequently occluded for 1 to 10 minutes. BMS181321 was not preferentially retained in the ischemic region after only 1 minute of coronary occlusion. Longer periods of coronary occlusion, however, resulted in increased retention of BMS181321, which was detectable by in vivo SPECT imaging. In a second model of sustained low-flow ischemia, BMS181321 was preferentially retained in the ischemic region (Fig 6). Focal uptake in the ischemic region was apparent on SPECT imaging in all dogs. Autoradiographic analysis showed a 3.5- ± 0.4-fold increase in relative BMS181321 activity in the central ischemic region. As in previous in vivo experimental studies, significant hepatic uptake was noted.

In a preliminary study, BMS194796, a more hydrophilic nitroimidazole derivative of BMS181321, has shown improved myocardial retention relative to BMS181321 after profound transient ischemia.[23] These investigators observed a 2-fold increase in BMS194796 retention in low-flow ischemic regions after 2 minutes of total coronary occlusion by using an open-chest canine model. This more hydrophilic nitroimidazole also showed less retention in the liver. These data suggest potential for BMS194796 for noninvasive detection of transient ischemia.

Thus, several experimental studies show the potential of Tc99m labeled nitroimidazoles for the detection of regional myocardial ischemia. Further modification of these compounds may be necessary to improve retention in hypoxic tissue and optimize target-to-background activity ratios. However, this

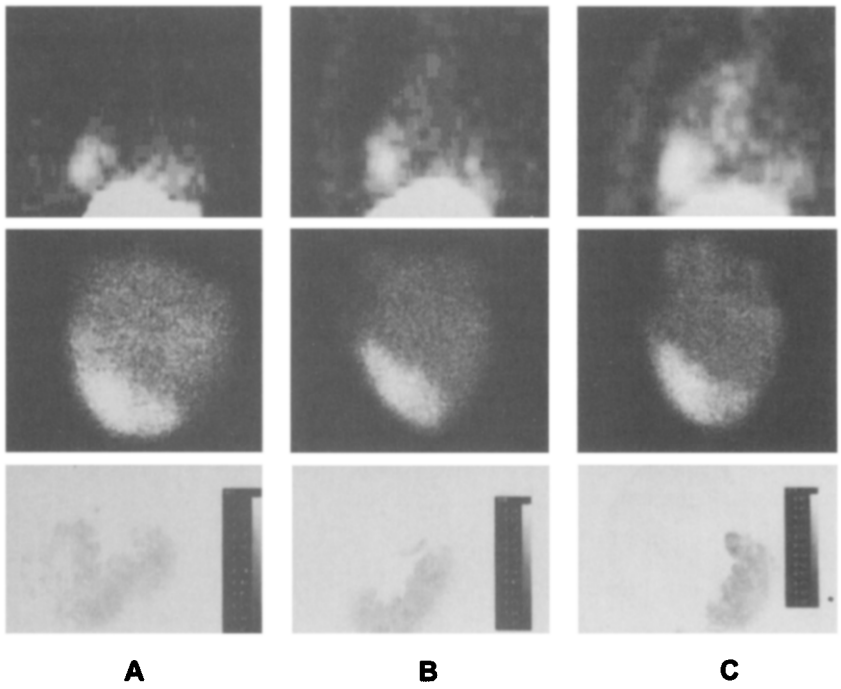

Fig 6. Myocardial BMS181321 uptake in three canine hearts (image sets A, B, and C) subjected to sustained left anterior descending coronary artery ischemia. Ischemia was maintained for 8 to 10 minutes before injection of BMS181321. SPECT images (*top row*) were acquired 160, 182, and 141 minutes postinjection, respectively. Planar images were acquired of the excised hearts (*middle row*). Lower panel of images represents autoradiographs of short-axis myocardial slices through the central ischemic region. Selective retention of BMS181321 was observed in hearts subjected to sustained regional ischemia. (Rumsey WL, et al. SPECT imaging of ischemic myocardium using a technetium-99m-nitroimidazole ligand. *Journal of Nuclear Medicine.* 1995;36: 1445-1450.)

class of Tc99m labeled nitroimidazoles has never been evaluated clinically for detection of myocardial ischemia.

ALTERNATIVE HYPOXIC AGENTS

Tc99m-HL91 is a potential alternative agent for detection of myocardial hypoxia. Preliminary in vitro and in vivo studies showed improved retention in hypoxic myocardium of Tc99m-HL91 over the parent compound.[24] Okada et al,[25] observed significantly more early retention of Tc99m-HL91 under conditions of low-flow ischemia than during normal-flow-hypoxia conditions, using an isolated perfused rat heart preparation (Fig 7). However, Tc99m-HL91 myocardial uptake was only 2.3% of the injected dose in control hearts perfused with the compound.

Dorantes et al[26] recently showed a small (20%) increase in myocardial Tc99m-HL91 in ischemic and bordering regions in a canine model of low-flow ischemia with superimposed stunning. Okada et al,[27] using an intact canine model of low-flow ischemia, showed increased myocardial retention of Tc99m-HL91 in the central ischemic region with both in vivo and ex vivo imaging. These investigators subsequently showed less myocardial retention of Tc99m-HL91 in the presence of necrosis.[28]

POTENTIAL CLINICAL APPLICATIONS

Detection of Ischemia

Imaging with nitroimidazole compounds offers a potential approach for identification of stress-

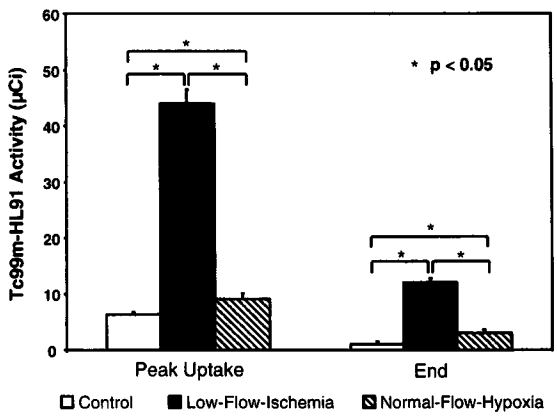

Fig 7. Peak myocardial ^{99m}Tc-HL91 uptake and activity at end of 60-minute clearance phase for three groups of Krebs-Henseleit perfused rat hearts; control group (n = 6), low-flow ischemia group (n = 7), and normal-flow hypoxia group (n = 8). ^{99m}Tc-HL91 was infused over a 10-minute period, and washed out with nonradioactive perfusate over 60 minutes. Myocardial ^{99m}Tc-HL91 activity was assessed using a NaI probe. The peak low-flow-ischemia/control activity ratio was 7:1. The peak normal-flow-hypoxia/control activity ratio was 1.4:1. (Adapted and reprinted with permission from Okada RD et al, 99mTc-HL91. Effects of low flow and hypoxia on a new ischemia-avid myocardial imaging agent, Circulation, 95, 1892-1899.)

induced myocardial ischemia for detection of coronary artery disease. Preliminary studies suggest that nitroimidazoles may not reliably distinguish viable from nonviable myocardium when administered during acute infarction or after reperfusion. Under these conditions, cells are rapidly undergoing a transition from reversible to irreversible ischemic injury. Perhaps more appropriate use of nitroimidazoles would be for (1) detection of persistent ischemia in the remote period after myocardial infarction, or (2) in the presence of chronic ischemia in patients with multivessel coronary artery disease, a condition termed myocardial hibernation. These applications would permit identification of patients with ischemic dysfunction who may benefit from coronary revascularization.

Definition of the Potential Role of Hypoxia in Development of Cardiomyopathy

Some cardiomyopathic processes have been attributed to ischemia or hypoxia. In the cardiomyopathic Syrian hamster, the development of cardiomyopathy has been associated with abnormalities of the microvascular circulation[29] and metabolic processes.[30] Similar pathophysiology has been observed in cardiomyopathies in human beings.[31,32] Watanabe et al[19] showed a significant increase in the BMS-181321 uptake in the cardiomyopathic Syrian hamster at 25 weeks in comparison with controls. These results are shown in Fig 8. The 25-week time point corresponds to the fibrotic and healing stage of this natural cardiomyopathic model, which precedes the development of hypertrophy and dilatation. These data support a potential role of hypoxia in the development of cardiomyopathy. These findings also suggest the potential of hypoxia imaging for the identification of precardiomyopathic conditions, which precede the development of clinical failure.

Evaluation of Angiogenesis

Hypoxia and factors associated with low oxygen saturation, such as cellular pH and lactate concentration, can induce release of angiogenic peptides.[33] Hypoxia will also induce expression of some angiogenic factors, including vascular endothelial growth factor (VEGF),[2,34] platelet-derived growth factor (PDGF), and transforming growth factor-B1 (TGF-B1).[35] The mechanisms by which cells sense hypoxia remains undefined. Similar to erythropoietin, hypoxia-induced VEGF gene expression depends on heme-containing protein.[36] Hypoxia induces each of the angiogenic factors differently. Induction of VEGF and PDGF in response to hypoxia is caused by transcriptional activation. In contrast, release of active TGF-B1 by hypoxia is caused by post-transcriptional modification of the molecule.[37] However, hypoxia is not the sole force driving release of angiogenic activity.

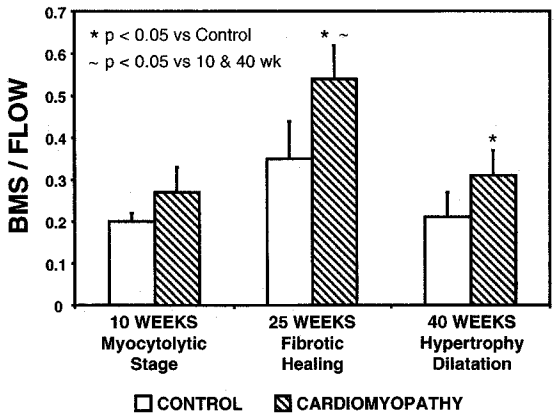

Fig 8. Myocardial BMS-181321 uptake (BMS) normalized to quantitative ^{125}I-iodoantipyrine concentration (flow) in cardiomyopathic and control hamsters. BMS and ^{125}I-iodoantipyrine were injected into cardiomyopathic Syrian hamsters and control hamsters at age 10, 25, and 40 weeks (n = 6 in each group). Cardiomyopathic hamsters were in the myocytolytic stage at age 10 weeks, in the fibrotic and healing stage at age 25 weeks, and in the hypertrophy and dilatation stage at age 40 weeks. The myocardial uptake of BMS and ^{125}I-iodoantipyrine was measured by dual tracer autoradiography. BMS uptake was normalized to ^{125}I-iodoantipyrine uptake, an index of flow. The cardiomyopathic hamsters showed a significant increase in normalized myocardial BMS uptake relative to controls at age 25 and 40 weeks. (Reprinted from Watanabe Y, et al: Contribution of hypoxia to the development of cardiomyopathy in hamsters. Cardiovasc Res 35:217-222, 1997. Created from Table 3 with permission of Elsevier Science.)

The administration of these angiogenic peptides may provide an alternative therapy for patients with myocardial ischemia, who cannot be revascularized by conventional means. Initial experimental[38,39] and clinical[40] trials have used intracoronary administration of VEGF or direct intramuscular transfection of genes encoding angiogenic factors such as VEGF. These strategies were designed to promote angiogenesis by increasing circulating growth factors. Thus, identification of persistent myocardial ischemia by imaging markers of hypoxia could be a useful means of objectively evaluating these angiogenic therapies.

POTENTIAL LIMITATIONS OF HYPOXIC IMAGING

In vitro studies with BMS181321 have shown that profound reductions in the perfused oxygen

level may be associated with only minimal increases in tracer retention.[16] Accordingly, the oxygen tension in the myocardium must be reduced below a significant threshold before the BMS181321 compound is retained. Preliminary studies by Ng et al[41] also suggest that the newer compound, HL91, is also retained in the myocardium only if the oxygen level is substantially reduced.

Regarding the class of technetium (V) oxo PnAO complexes, increasing the lipophilicity increases the percent uptake into myocytes under both hypoxic and normoxic conditions.[10] Unfortunately, increasing the lipophilicity also increases hepatocellular uptake and retention, which complicates in vivo imaging of the heart. None of the nitroimidazole compounds that have undergone in vitro and in vivo testing have shown sufficient cardiac specificity and adequate target-to-background uptake.

A potential weakness of this approach may relate to the relatively high tissue oxygen levels often observed in transiently ischemic myocardium. These agents may be insensitive markers for myocardial stunning because under these conditions myocardial oxygen tension seems to be normal.[26] These compounds may be better suited for chronically ischemic tissues.

There are several approaches for the assessment of myocardial oxygen tension: Myoglobin and NADH fluorescence, phosphorescence quenching, near-infrared spectroscopy, electrochemical oxygen probes, nuclear magnetic resonance, myoglobin spectroscopy, and electron paramagnetic resonance (EPR). In vivo studies using a polarographic technique show that the myocardium under normal conditions has a partial pressure of oxygen of approximately 50 mm Hg.[42] Dorantes et al[9] showed that in vivo myocardial oxygen tension using an implanted electrochemical probe was 26 ± 3 mm Hg under control conditions, and decreased to only 17 ± 6 mm Hg during total coronary occlusion. These studies also show that myocardial oxygen tension recovers quickly after an ischemic insult. EPR oximetry is an alternative approach for measurement of oxygen tension in vivo.[43] Using this EPR oximetry approach, investigators have shown that increases in flow produce a sigmoidal increase in oxygen tension. Several investigators have recently shown the feasibility of detecting changes in the ratio of oxygen supply and demand noninvasively using magnetic imaging techniques.[44-46] The deoxygenation of hemoglobin to deoxyhemoglobin causes a local magnetic field inhomogeneity resulting in signal loss in a T_2*-weighted image because hemoglobin is diamagnetic, whereas deoxyhemoglobin is paramagnetic. These other approaches for assessment of myocardial oxygen tension need to be related to uptake and retention of potential radiotracers for detection of hypoxia.

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Current Status of Radionuclide Tracer Imaging of Thrombi and Atheroma

Manuel D. Cerqueira

The imaging of thrombi and atherosclerotic plaques has great potential for decision making in the management of patients with all types of disease within the circulatory system. This importance is owing to the developments showing that areas of moderate stenosis with underlying atheroma are physiologically reactive and capable of causing reversible clinical symptoms that can progress to irreversible end-organ damage if not effectively treated. Identifying and quantifying areas of smaller vulnerable plaque and areas of acute thrombosis will assist in identification of patients at risk and help determine when and how to treat these patients. Initial efforts in this area used nonspecific constituents of thrombi and atheroma that were radiolabeled using long-lived isotopes, which had high background activity that required imaging over 48 to 72 hours. Newer approaches have focused on the use of small antibody fragments or small peptides, so-called *molecular recognition units,* that specifically target antigens present only in areas of thrombosis or active atherogenesis. These compounds are labeled Technetium-99 m (^{99m}Tc) and provide excellent images. Efforts to image thrombi have been directed at the IIB/IIIA receptor, which is present in low concentration on the cell membrane of circulating quiescent platelets, but on stimulation and active thrombosis, more than 80,000 potential binding sites per platelet appear. One such peptide has been clinically approved for imaging of deep vein thrombophlebitis. Parallel efforts are being made for imaging areas of active atherogenesis by targeting smooth muscle cells and other constituents unique for vulnerable plaques. Efforts in developing these modalities are important to expand the applications to new areas in nuclear cardiology.

OVER THE past decade, we have developed two very important concepts in cardiology that have influenced how we think about ischemic events in the circulatory system and identified new directions for imaging in cardiovascular nuclear medicine. The first concept is that less severe atherosclerotic plaques are more physiologically reactive and more vulnerable to rupture. Plaque rupture exposes the subendothelial surface to blood elements that can cause acute thrombosis and acute ischemic events. For a long time we had accepted the fact that atheroma develop incrementally over time.[1] With our new understanding we have accepted the fact that acute ischemic syndromes initially cause symptoms owing to acute thrombosis and that this is a reversible stage if blood flow is reestablished in a short time period. If flow is not reestablished, there is eventual permanent end-organ damage. These findings are true in the coronary circulation and equally as important in other arterial and vascular beds in the body. Thus, the ability to image the presence and extent of vulnerable plaque and thrombi may allow assessment of risk for having acute events and to determine long-term prognosis. Imaging of thrombi has been attempted for many years and is a promising diagnostic technique with many recent innovations made possible by the use of antibody components and small peptides directed toward epitopes or specific constituents of thrombi. Atheroma imaging has been a slowly evolving field, but the recently recognized importance of vulnerable plaques and atherosclerotic burden makes it a very important area of research with broad implications for clinical management of coronary artery disease (CAD).[2]

In this article, the clinical syndromes associated with thrombosis, basic principles that have guided development of thrombus-imaging agents, specific agents for thrombus imaging, and the ongoing work on imaging of atheroma will be addressed.

THE POTENTIAL CLINICAL ROLE FOR DETECTION OF THROMBOSIS

Acute vascular syndromes are caused by formation of arterial or venous thrombi that are capable of producing the clinical syndromes listed in Tables 1 and 2.[3] The syndromes in Table 1 cause symptoms that, if detected and intervened upon early, are potentially reversible. The first four syndromes are related to the coronary circulation and the heart chambers. The others involve the noncardiac arterial system and the venous system. These symptoms serve as an early warning to begin treatment

From the Division of Cardiology, Department of Medicine, and the Division of Nuclear Medicine, Department of Radiology, Georgetown University Hospital, Washington, DC.

Address reprint requests to Manuel D. Cerqueira, MD, Associate Chief of Cardiology, Georgetown University Hospital (PHC-5), 3800 Reservoir Road NW, Washington, DC 20007.

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Table 1. Early and Potentially Reversible Clinical Stage of Acute Vascular Syndromes

Unstable angina
Coronary circulation
PTCA or stent restenosis
Graft restenosis
Formation of thrombi in the ventricles or atria
Native or prosthetic valve thrombi
Transient ischemic attacks
Prosthetic vascular graft stenosis
Venous thrombophlebitis

with thrombolytic agents and/or anticoagulants, which may prevent progression and thereby reduce morbidity and mortality and improve long-term outcome. If the early symptoms are not detected or are inadequately treated, they may progress to catastrophic and irreversible organ damage as listed in Table 2.

Available methods for detection of thrombi include physical examination, ultrasound, and contrast angiography. In patients with early evidence of thrombosis, clinical criteria using physical examination and symptoms may suggest that thrombi are present, but these techniques are seldom definitive. Contrast angiography remains the gold standard for definitive diagnosis but it is not immediately available, it is associated with procedural risks, and in comparison to alternative techniques it is relatively expensive. Vascular and cardiac ultrasound techniques are safe and available but are not clinically applicable for detecting thrombi in the coronary arteries or in other small vessels. Even in larger vessels, sensitivity may be low, as the thrombi may have embolized leaving only luminal irregularities. Perhaps more importantly, ultrasound is incapable of differentiating between active acute thrombosis, which increases the risk of the events listed in Table 2 and old, stable thrombi or atheroma that may be present in the heart or vasculature. The latter pose less risk for embolization.

Table 2. Late and Irreversible Stage of Acute Vascular Syndromes

Acute myocardial infarction
Coronary restenosis/occlusion
PTCA or stent occlusion
Graft occlusion
Systemic embolization of chamber thrombi
Prosthetic heart valve stenosis/closure
Cerebral vascular accident
Prosthetic arterial graft occlusion
Pulmonary embolism

For all types of thrombi, indiscriminate, preventive anticoagulation is not a feasible alternative therapy in many patients because of bleeding risks. Thus, safe, accurate, and less expensive tests for the early diagnosing of arterial and venous thrombosis are needed for best practice patient management. The terms *clot* and *thrombi* have different meaning and there is confusion regarding appropriate usage. In this article the terms *thrombus* or *thrombi* will be used to specifically refer to clotting that occurs within the intravascular space: arterial, venous, and in the atrial and ventricular chambers. *Clot* usually refers to thrombosis that is outside the intravascular space. Thus, clotting in the cardiac chambers is still within the intravascular space and thrombus is the appropriate term. However, by convention, left ventricular or atrial clots are acceptable terms.

Target Options for Thrombus Imaging

There are multiple thrombus-specific epitopes or binding sites capable of binding a radiotracer to a thrombus to permit imaging.[4-6] Any constituent of thrombi present in sufficiently high concentrations can serve as a target for potential imaging agents. Table 3 lists the general classes of components and the specific agents that have been tested. Iodine-123, Iodine-125, and Iodine-131 (^{123}I, ^{125}I, and ^{131}I), indium-111 (^{111}In), and technetium-99m (^{99m}Tc) have all been used to radiolabel the epitopes. The ideal agent will use ^{99m}Tc because of its

Table 3. Possible Targeting Agents for Thrombus Detection and Imaging

Red blood cells
Macroaggregated albumin
Clotting factors
Factor XIII
Plasmin
Plasminogen
Tissue plasminogen activator (t-PA)
Fibrinogen/fibrin
^{125}I and ^{123}I Fibrinogen
Monoclonal antibodies to fibrin
Platelets
^{111}In Platelets
IIB/IIIA receptors
Antibodies
Synthetic peptides
Annexin-V
Thrombospondin
GMP-140
Others
Streptokinase
Heparin

excellent imaging characteristics, intermediate keV energy, widespread availability, short half-life, and low cost.

Early agents for imaging or detection were not specific for epitopes present only in active thrombosis and the resultant background activity was high. They cleared slowly from the blood and required a long time to be sufficiently concentrated in the area of thrombosis to be distinct from the background and allow detection. Under these conditions, long-lived isotopes such as ^{125}I and ^{111}In, were appropriate radiolabeling methods to allow activity counting or imaging. It was only when the highly specific thrombus targeting agents with rapid blood pool clearance became available that using ^{99m}Tc was clinically practical.

Desirable Features of Thrombus Imaging Agents

Although many epitopes or specific binding sites in thrombi have been investigated, only a few have the desirable features that increase the success of imaging. These desirable characteristics are listed in Table 4 and the features are described below.

Variation in Type of Antigenic Sites in Arterial and Venous Thrombi

Arterial and venous thrombi differ in the relative proportion of fibrin and platelets and it may be possible to optimize detection and even differentiate between the two types of thrombi by using the appropriate targeting agents.[7,8] Arterial thrombi, formed when some blood flow is maintained and additional platelets are preferentially recruited, have a 4:1 ratio of platelets to fibrin. This has been called a white thrombus. Venous thrombi consist mainly of a fibrin polymer mesh with large numbers of trapped red blood cells and relatively few platelets because there is minimal blood flow to recruit additional platelets. The large number of red blood cells give it a characteristic color and it is referred to as a red thrombus.[7] This predominance of fibrin, red blood cells, and fewer platelets in venous thrombi reflects the normal make-up of blood. Only a small number of platelets aggregate on the surface of these venous thrombi as stasis, due to a higher extent of occlusion, lower pressures and an absence of collateral channels usually prevents recruitment of additional platelets from passing blood. Thus, the selection of which thrombus imaging agent will work best in a particular clinical setting may be determined by the type of thrombus that is clinically suspected. This basic difference in composition between thrombi may allow differentiation between arterial and venous thrombi. Agents directed at fibrin will probably work best for venous thrombi and platelet-specific agents will probably work better for arterial thrombi. The clinical syndromes listed in Tables 1 and 2 are sufficiently different, that symptoms at presentation alone may allow differentiation and imaging will provide little, if any, additional value for discriminating between them.

Table 4. Factors Important for Thrombus Imaging

Variation in predominate type of antigenic site in thrombi
Arterial thrombi: predominately platelets
Venous thrombi: predominately fibrin and red blood cells
Delivery rate of radiolabeled agent to thrombus binding sites
Specificity of binding sites for active thrombosis
Number of binding sites
Affinity of radiolabeled compound for binding sites
Detachment rate
Clearance of background activity
Size of agents: antibody versus fragments versus peptides

Delivery Rate of Radiolabeled Agents to Thrombus Binding Sites

The degree to which blood flow is maintained to the area of thrombosis is critically important for which targeting agents will work best and whether imaging will be possible. Maintained flow is important for the composition of the thrombus and whether the radiotracer is able to access the binding sites. A sudden and total occlusion will cause immediate clinical symptoms and create a thrombus that has the composition of blood, as there will not be recruitment of additional blood constituents. This will also limit the ability of the radiolabeled thrombus imaging agents to reach and interact with potential binding sites. This limited number of epitope-specific binding in combination with limited access is the worst scenario for thrombus imaging. In such situations, access of the imaging agent may be limited to the surfaces at the extreme ends of the thrombus with no access to the bulk of the thrombus in the middle that has the majority of binding sites. The existence or formation of collateral vessels and phasic flow owing to spasm may give greater access of the radiotracer. Fortunately, with such rapid and total occlusion, the clinical symptoms may be sufficient to make the diagnosis

or suggest the need for angiographic or ultrasound studies. Thrombus imaging in such a situation may not provide any additional or incremental clinical value and will increase the cost of diagnosis.

A more common clinical situation, in which diagnosis is frequently difficult, involves the early stages of acute vascular syndromes as listed in Table 1, which allow more opportunities for reversal. These reversible syndromes consist of transient ischemic attacks or unstable angina in the arterial circulation and thrombophlebitis in the venous system. Usually the occlusion is incomplete and this allows recruitment and accumulation of a greater number of platelets, which provide a high number of binding sites. The continuation of some flow also allows access of the radiolabeled imaging agent to the target. It is important to clinically consider and perform imaging at this stage of reversibility before there is progression to the stages listed in Table 2. This is also the time of greatest clinical need for diagnosis and the highest diagnostic accuracy for thrombus imaging.

Number, Specificity, Affinity, and Detachment Rates of Binding Sites

The ideal thrombus imaging agent should bind specifically and with a high avidity and affinity to an epitope present in very high concentration in the thrombus. It should clear from the blood rapidly to allow visualization of the thrombus from the surrounding vascular space. Once it binds, the agent should remain strongly attached to the thrombus and stay in the area of thrombosis.

The greater the number of unique binding sites, the more opportunity for interaction between these sites and the radiolabeled targeting compound. When this happens there is a greater likelihood of visualizing thrombi. Platelets are unique in that they are heavily concentrated at the area of thrombosis and have a large concentration of many different types of membrane receptors.[3] Whether these binding sites are exposed on the external membrane surface or remain within the membrane is determined, in part, by the state of platelet activation. The IIB/IIIA receptor, for example, is expressed in small numbers on the external surface of circulating quiescent platelets, but increases to more than 80,000 binding sites per platelet during stimulation. Thus, agents, which target the IIB/IIIA receptor, have minimal binding to quiescent circulating platelets in blood, but high binding to stimulated platelets in the areas of thrombus formation.

Examples of nonspecific thrombus targeting agents include radiolabeled fibrinogen and quiescent platelets.[9-11] Over time both accumulate in high concentration at the site of thrombus formation, but unfortunately they continue to remain in high concentration within the intravascular space. Fibrinogen selectively accumulates over time at the site of thrombus formation by being converted to fibrin, but the majority remains within the intravascular space and this requires extremely high uptake in the thrombus to distinguish thrombi from the background blood pool. Antibodies directed to fibrin are more thrombus specific as they do not attach to circulating fibrinogen, which lacks the exposed binding site, but attach specifically to fibrin, which is present at very high concentrations only in the thrombus.[8,12]

^{111}In labelled platelets have similar problems as they remain within the intravascular space and undergo time-dependent accumulation in thrombi. Optimal visualization is best at 48 to 72 hours after injection. In a similar manner, antibodies and small molecular weight peptides directed to stimulated platelet targets are thrombus specific.

It is very important for the radiolabel to bind tightly to the targeting agent and for the targeting agent to remain in the area where it is bound. If the radiolabel is loosely attached or enzymatically split from the carrier into small protein fragments, it may leave the area of thrombosis and get trapped in the liver or kidneys by nonspecific mechanisms. Under such circumstances, sensitivity for thrombus detection is decreased owing to lower uptake by the thrombus and the high background activity.

Consideration needs to be given in the future to injecting not just a single thrombus-specific radiolabeled imaging agent, but rather a cocktail consisting of two or more agents radiolabeled with the same radioisotope and directed at platelet constituents, fibrin, or both. This cocktail approach increases the number of available binding sites and the chance of detecting the intravascular thrombotic process.

Clearance of Background Activity

Fibrinogen and platelets remain trapped within the blood pool. This results in very high blood pool background activity, which prevents early thrombus detection and requires very high target-to-

background ratios. Even if there is very active ongoing intravascular thrombosis taking up the targeting agent, it may not be possible to image the thrombus for 48 to 72 hours when the time-dependent uptake in the thrombus finally exceeds the high background levels. This time requirement also mandates the use of long-lived radioisotopes such as ^{111}In. This radioisotope has a high energy level and multiple peaks, which is not optimal for imaging.

Monoclonal antibody fragments and the newer small synthetic peptides all have very rapid renal clearance with serum half-lives of less than 2 hours. A favorable target-to-background ratio is reached early with these characteristics, allowing a diagnosis to be made in hours rather than days. Because imaging is completed a short time after injection, these compounds can be labeled with ^{99m}Tc, which optimizes imaging and decreases cost. A negative feature of a rapid blood clearance is that it decreases the exposure time between the target sites and the epitope and may ultimately result in a lower absolute concentration of radioactivity in the area of thrombosis, despite a favorable target-to-background ratio.

Size of Targeting Agents: Cells Versus Whole Antibody Versus Fragments Versus Peptides

The trend in research is toward the use of small antibody fragments and synthetic peptides that are radiolabeled using ^{99m}Tc. These compounds specifically bind tightly to components present only at the site of thrombosis and provide the advantages of rapid blood clearance, better penetration into areas of partial or complete occlusion, and ease of production. Whole antibodies are not being developed as the large size results in a prolonged dwell time in the blood resulting in high background activity and poor visualization of even thrombus avid agents taken up in high concentrations.

Antibody fragments provide a compromise between the slow clearance of whole antibodies and the very rapid clearance of the peptides. Their major limitation is that they require splitting of the whole antibody and are more complicated to produce.

Thrombus Imaging

Any of the constituents of thrombi have the potential to be used for imaging. Although there have been attempts made to use heparin, streptokinase, and other compounds, their alternatives are not being actively pursued at present owing to the availability of platelet-specific antibody fragments and peptide compounds.

The Historical Use of General Blood Constituents

^{99m}Tc labeled red blood cells are capable of identifying left ventricular clots. These clots appear as photopenic defects owing to displacement of the labeled blood pool. Like contrast venography, ^{99m}Tc macroaggregated albumin radionuclide venograms are performed by injecting the radioisotope bilaterally into veins in the feet and measuring the flow into the venous circulation. This technique can be used to identify thrombophlebitis of the lower extremities.[13] Despite these abilities, these techniques are seldom used. They have limited clinical value because ultrasound of the lower extremities and the heart is more accurate in these situations. ^{99m}Tc macroaggregated albumin continues to be used widely for ventilation-perfusion scanning, but to perform radionuclide ventriculography it must be injected into veins in both feet, which increases patient discomfort and the time and cost of performing the study. Bilateral cannulation of the dorsal veins of the feet is technically challenging.

Imaging with Various Clotting Factors

Plasmin, plasminogen, tissue plasminogen activator, and clotting factor XIII have been investigated as potential agents for imaging thrombi.[14-17] Clotting factor XIII is an endogenous human protein that cross-links polymerized fibrin molecules once clot formation has started and this helps to stabilize the thrombi. Because it cross-links fibrin and not fibrinogen, antibodies targeting Factor XIII are specific for areas of active thrombosis. Studies performed in a dog model of carotid thrombosis using ^{131}I radiolabeling of factor XIII showed thrombus-to-blood ratios (3:1) that were comparable to those achieved using an antibody fragment against fibrin (4:1).[8,16] Recombinant technology allows production of large quantities of factor XIII and radiolabeling with ^{99m}Tc should be possible without influencing the cross-linking properties. To date, there has been no further evaluation using this compound as it is a very large molecule that does not have a rapid blood clearance and most of the effort at developing new agents is focused on the use of peptides.

Among the various plasmin-related compounds,

the most success has been achieved using recombinant tissue plasminogen activator. The molecule is enzymatically inactivated, so that it binds to fibrin without resulting in fibrinolysis as this would cause radiolabel release and entrapment within the liver.[18] Butler's original studies with rabbits showed a rapid blood clearance with a serum half time of 4.6 minutes and good visualization of thrombi using planar imaging. Ord[17] not only inactivated the tissue plasminogen activator (t-PA), but also conjugated it to the radiolabel so that the whole complex is trapped in the area of thrombosis to slow its clearance from the blood. Radiolabeling was performed using ^{123}I and thrombi were visualized in rabbit and dog models using planar or SPECT gamma camera imaging. Thrombi-to-blood ratios were as high as 43:1 when the compound was given at the same time that formation of the thrombi was started in the experimental mode. When the compound was injected 30 minutes after the formation of thrombi, the target-to-background ratio decreased to 2.8:1. Administering radiolabeled t-PA before or during thrombus formation is often not possible in the acute vascular syndromes listed in Table 2. This is especially true for acute myocardial infarction, in which patients usually present at least 1 to 2 hours after the onset of symptoms and a totally occlusive thrombus is generally present. Because there are few clinical situations in which the radiotracer can be administered before or at the time of thrombus formation, the clinical value of such a compound will be limited. Recent development efforts using clotting factors have been limited as other compounds under investigation that target fibrin and components of platelets offer better imaging characteristics.

Imaging With Fibrinogen and Fibrin

Because of the poor specificity and long delay to imaging of radiolabeled fibrinogen, development efforts have focused on antibodies directed to various components of fibrin, which is found only at the site of active thrombosis and not in the blood pool. These efforts have tried to meet and optimize the principles outlined in Table 4. Major advances have been made possible by developments in immunology that have allowed the identification and mass production of monoclonal antibodies that are highly specific for various components of fibrin. These whole antibodies have been further split into smaller fragments that allow improved penetration to the area of thrombosis and rapid blood clearance, essential features to visualize thrombi.

Antibody Imaging

^{125}I fibrinogen had been used without imaging to detect focal areas with high radioactive counts presumably owing to deep venous thrombophlibitis (DVT). Early animal studies showed that polyclonal whole antibodies directed to fibrin and labeled with ^{131}I or ^{111}In were capable of detecting and imaging venous thrombi of various ages.[19] However, these large molecules had a serum half-life that was greater than 24 hours and optimal imaging was best achieved at 24 to 48 hours; clearly, much too long after injection to be of clinical value. Subsequent work has focused on developing monoclonal antibodies directed at epitopes found only on fibrin, which makes uptake highly specific. Efforts have also focused on fragmenting the whole antibody into smaller components.[20-25] These small molecules are rapidly cleared from the blood and accurate diagnostic images can be obtained 1 to 6 hours after injection. The better penetration and higher specificity permit earlier imaging, which makes possible the use of a ^{99m}Tc label. A molecule with similar properties has been described by Kanke et al.[26]

Two antifibrin antibodies have been identified and developed for clinical use, 59D8 and T2G1s. Both antibodies bind to a sequence of 7 amino acids on the beta chain of human fibrin. They have identical properties and are presumed to be the same molecule. The binding site is exposed only on cross-linked fibrin molecules undergoing thrombin digestion. This epitope is present only at the site of active thrombosis and it is not accessible on fibrinogen. The antibody has the highest uptake and retention on recently formed thrombi. The use of heparin or other types of anticoagulation will not markedly alter the ability to obtain diagnostic images. It also has been shown that some continuation of blood flow allows the radiotracer to get to the area for binding and improves thrombi detection.[27] Figure 1 is an example of thrombus detection using an antifibrin antibody in a dog model.

To image older thrombi, efforts have been directed at developing antibodies to components of the fibrinolytic cascade that appear later to enhance imaging of thrombi several days old, especially in the presence of anticoagulation. One of these later

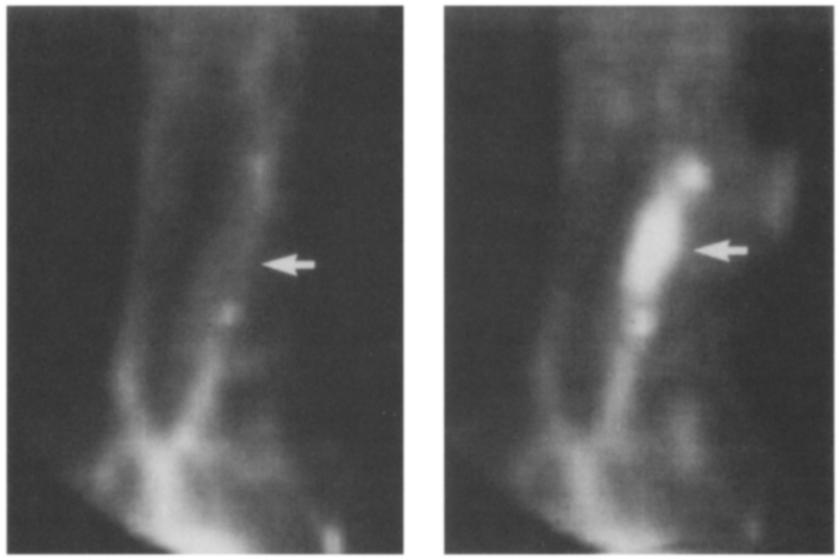

Fig 1. Anterior indium-111 labeled platelet scans of multiple left ventricular thrombi at 24 and 96 hours after injection. At 24 hours there is a single focus (*arrow*) of increased platelet accumulation. By 96 hours, multiple foci are evident along the septum and the anterior walls of the left ventricle. The liver and spleen activity are present in the lower left and right, respectively, of the images. (Courtesy of JR Stratton, MD.)

components is GC4. It is a monoclonal antibody specific for an epitope exposed on fragment D of human fibrin after plasmin digestion.[27] As the levels of the epitope for the early formed T2G1s antibody decrease owing to thrombin degradation of the beta chain of fibrin, there is an increase in the number of binding sites available for the GC4 antibody. In animal experiments, GC4 uptake was greater than T2G1s during heparinization and in 3-day-old versus 3-hour-old thrombi.[27] Because patients being evaluated for the presence of thrombi are usually anticoagulated, the high uptake observed during heparinization makes GC4 a potentially useful imaging agent.

Another molecule with potential for imaging thrombi is fragment E.[28] It is a plasmin degradation product from cross-linked fibrin, which binds specifically to fibrin polymers. It has been radiolabeled with ^{99m}Tc and shown in animal models to have very high uptake ratios in areas of thrombosis. An important feature of this molecule is that it provides diagnostic images in 20 to 60 minutes.

Although fibrin accumulation is highest in venous thrombi, antifibrin antibodies have been used to image carotid arterial thrombi in a dog model.[8] Excellent uptake ratios were present in the thrombi and all could be imaged and visualized by 3 hours and the majority were seen within the first hour.

Detection of Thrombi in Man

Despite this promising animal work, only a few potential thrombus imaging agents have progressed to studies in humans and all of them were focused on imaging venous thrombi. There have been 5 published studies enrolling 405 patients using various antifibrin antibody components to image venous thrombi. A summary of these studies is shown in Table 5.[29-33] The largest study of 256 patients was presented as an abstract.[32]

The first published study showed a very good overall sensitivity and specificity for detection of thrombophlebitis using the ^{111}In labeled monoclonal antibody Fab fragment directed at the 59D8 antigen.[29] All the patients presented with a very high clinical suspicion for deep vein thrombophlebitis and contrast venography was performed in all

Table 5. Detection of Venous Thrombosis in Humans Using Antifibrin Antibodies

Author	Epitope	No. Patients	Sensitivity, %	Specificity
Bautovich[33]	DD3B6/22	20	100	NT
Schaible[32]	T2G1s	256	79	91%
De Faucal[30]	T2G1s	44	85	100% (n = 10)
Alavi[31]	T2G1s	33	97	NT
Jung[29]	59D8	52	84	81%

Abbreviation: NT, not tested.

Table 6. Sensitivity for Imaging DVT in Different Locations and Duration of Symptoms

Location	All Patients (n = 52)	Symptoms <10 Days (n = 44)
Calf	92%	100%
Popliteal	82%	94%
Thigh	63%	71%
Pelvis	18%	13%

patients. Thus, this was a group with a high pretest probability of having DVT. Table 6 shows the sensitivity for various locations of DVT in the leg for the entire group and in 44 patients in which the DVT symptoms were present for less than 10 days. Detection is best in the calf and popliteal areas and in patients with symptoms less than 10 days. In the thigh and pelvis, overall detection is lower regardless of thrombus age.

Subsequent studies in man have all shown similar or better sensitivity. The results by Schaible are probably the most indicative of the diagnostic accuracy of the technique.[32]

As discussed earlier, the histological composition of arterial and venous thrombi differs. There has only been 1 study in which a platelet-specific agent was compared in a patient population with abdominal aortic aneurysms with an antifibrin compound for detection.[34] ^{99m}Tc antifibrin antibody was less sensitive than ^{111}In labeled platelets for imaging arterial thrombi. Because these were chronic thrombi, the results can be explained most readily on the basis of continued platelet deposition, but there was little active fibrin deposition in these very old thrombi.

PLATELET IMAGING

Most of the work on developing new imaging agents for detection of thrombi has focused on the use of specific agents for arterial thrombi. This is owing to the greater frequency and the severe clinical consequences of acute arterial syndromes involving the heart and the brain. The greatest attention has focused on agents that target activated platelets, as they are the most specific for thrombi and have the largest number of binding sites. The early studies were performed by taking platelets from patients, labeling them with ^{111}In, reinjecting them into the patient, and following-up accumulation levels over time. It was shown that thrombi were accurately detected using this technique, in comparison with other diagnostic methods and that identification of active platelet accumulation had prognostic value.[4] Figure 2 demonstrates a strongly positive study. Unfortunately, the complicated and prolonged time required to label the platelets and the need to perform serial imaging at 24, 48, and even 72 hours limited the clinical use of this method for initial evaluation of acute vascular syndrome patients. As a result of these limitations, ^{111}In platelet labeling is not being performed on a clinical basis and is performed exclusively as a research tool.

Platelet imaging has been shown to provide excellent prognostic information in patients with chronic left ventricular thrombi.[35] In patients with chronic left ventricular thrombi seen on echocardiography embolic events occurred in 7 of 34 (21%) patients of those with positive platelet uptake and

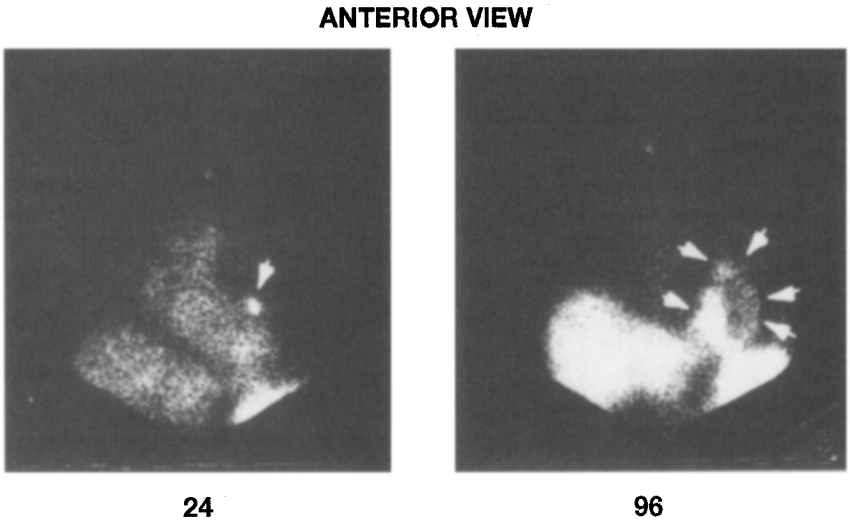

Fig 2. Anterior Tc-99m antifibrin antibody images in an animal model of a left carotid thrombus. On the immediate images, the central area of thrombus formation (*arrow*) has less intense uptake than the 2 ends where there is greater access of the radiotracer. By 2 hours, the central portion of the thrombus has very intense uptake (*arrows*). (Courtesy of MD Cerqueira, MD.)

in 2 of 69 (3%) patients without evidence of platelet uptake. These results suggest that ongoing platelet uptake is indicative of less well organized thrombi with physiologically reactive surfaces and continued platelet accumulation and turnover on the surface of the thrombi identifying increased embolic potential. It will be important to perform studies with potential platelet-specific imaging agents to determine if this prognostic information on embolic events is retained. None of the other anatomic diagnostic imaging modalities provides this type of physiological information.

IIB/IIIA Receptors

Antibodies

Multiple epitopes related to the IIB/IIIA complex appearing in large numbers on activated platelets has been identified as potential targets for imaging thrombi. These include 7E3, 50.H.19, P256, 10E3, and B59.2.[3,4] The 7E3 and P256 antibody have been the most extensively evaluated in animal studies and shown to be capable of excellent imaging of both venous and arterial thrombi.[36-38] Important for clinical diagnosis and management is that uptake and retention in the thrombus is not influenced by the use of aspirin or heparin.[39] This allows effective treatment to be initiated while performing diagnostic studies without altering the overall diagnostic accuracy. Despite all the promising animal studies, there have been very few studies performed in humans. Peters et al[37] studied a total of 8 patients with assorted thrombi using P256. In the 3 patients with documented DVT, 2 patients had detection of the thrombus using this agent.

Developmental efforts using antibody components have been mostly abandoned owing to the availability of small molecular weight peptides, which offer the best opportunities to achieve all the characteristics listed for the ideal thrombus imaging agent in Table 4.

Peptides

The approach most likely to result in successful imaging of thrombi involves the use of short synthetic peptides containing a specific binding site for components or epitopes found in the thrombus. The desirable properties of these molecular recognition units are shown in Table 7. Being chemically synthesized, peptides are less expensive to produce than antibodies and can be more readily altered to meet specific requirements for binding. Whole antibodies or fragments are produced in murines or mouse-derived cell systems. With repeat administration in humans, human antimouse antibodies (HAMA) may be generated and this limits repeat administration owing to concerns about allergic reactions. The chemically synthesized peptides do not cause formation of HAMA and repeated administration for diagnostic testing or therapy can be safely performed without the need to measure HAMA levels.

Table 7. Properties of Peptide Molecular Recognition Units

Chemically synthesized, less expensive to produce
Nonantigenic, multiple injections possible
Low molecular weight, rapid blood/background clearance
Better penetration into thrombus
Short serum half-life
^{99M}Tc label, widely available, less expensive, optimal imaging characteristics

The low molecular weight of peptides and small size improves penetration into the area of thrombosis and at the same time allows rapid renal clearance resulting in a low background activity in minutes, instead of hours. Most of the peptides developed for thrombus imaging have targeted the large number of IIB/IIIA platelet receptor epitopes.[40-42] A 3 amino acid binding sequence, Arg-Gly-Asp (RGD), to the glycoprotein IIB/IIIA receptor ligand mediates binding and is the most frequently used amino acid sequence for these peptides. There are usually multiple repeat sequences of this 3 amino acid chain to increase the probability of binding. Separate amino acid sequences are added to facilitate radiolabeling. The final molecular complex retains all the biological features of binding and clearance.

Despite all these favorable characteristics of the RGD peptides, animal studies have shown variability in the uptake and retention at sites of thrombosis.[40,42] Knight et al[42] found that a repeating RGD sequence attached to ^{99m}Tc was cleared rapidly from the blood, but uptake ratios in rabbit model thrombi were no better than the nonspecific binding of fibrinogen. It was postulated that the rapid serum clearance decreases the background activity but does not stay in the circulation long enough to allow binding between the peptide and the binding sites. A series of naturally occurring peptides found in snake venom also bind to the IIB/IIIA receptor and have been evaluated for their ability to bind to thrombi in animal models. Several of the compounds were shown to have very high binding and allow thrombus detection within 1 hour of injec-

tion. Further work is required to confirm the ability to allow imaging.

The P280 peptide contains 26 amino acids with an RGD sequence binding to activated platelets. It has been approved by the Food and Drug Administration for imaging of DVT and there is optimism that it will work for detection of pulmonary emboli. There are published reports of human use in 9 patients with clinical suspicion and diagnostic evidence of DVT.[41] In 8 of the 9 patients, thrombi were visualized in less than 1 hour and in 2 patients pulmonary emboli were also identified. The single patient who did not have visualization had the diagnosis of DVT made 42 days earlier and it is possible that this far out from the acute event there were not enough binding sites present. Imaging of arterial thrombi with this agent in the heart or arterial circulation has not been shown and further work is required.

GMP-140. Another activated platelet-specific epitope that has been used for imaging is an antibody targeting the GMP-140 protein present on platelet membranes. This protein is part of the platelet alpha granule membrane. In quiescent circulating platelets these granules are intracellular and not exposed on the external surface membrane. When platelets are stimulated and undergo degranulation, the alpha particles fuse with the plasma membrane and the GMP-140 is exposed directly on the outer membrane. Thus antibodies or peptides that target this complex will bind in high numbers and allow detection. The binding characteristics of a GMP-140 antibody fragment after angioplasty-induced vascular injury has been evaluated in animal models and in humans.[43,44] Studies were performed in 11 patients after percutaneous transluminal coronary angioplasty (PTCA) of 23 peripheral extremity arterial lesions. Seventy-eight percent of the dilated lesions were detected visually by imaging. Complicated procedures consistently had higher uptake and this was related to the greater number of platelets that accumulated. It was postulated, but not proven by the data, that high uptake and visualization after procedures indicated high platelet turnover at the site and might predict restenosis at the site. This was mediated by release of growth factors by the degranulation of platelets. Long-term follow-up studies are needed in such patients. This same group attempted unsuccessfully to use the GMP-140 compound after PTCA in the coronary circulation. Failure to visualize thrombi probably relates to the smaller size of the arteries, motion of the heart during contraction, and the large amount of blood pool activity in the adjacent cavity of the left ventricle.

Annexin-V. Annexin-V is a naturally occurring human protein with multiple properties that has a very high binding affinity for phosphatidylserine.[45] Phosphatidylserine is present in very small concentrations on the external membrane surface of quiescent platelets, but increases to more than 100,000 binding sites when platelets are stimulated by collagen and thrombin. With this many binding sites, this epitope is specific for areas of thrombi and has a higher concentration than the IIB/IIIa receptor. Iodinated annexin-V showed favorable clearance, uptake, and retention in fresh thrombi in an in vitro testing system.[45]

It has been possible to label this compound with a ^{99m}Tc label without altering the binding characteristics. Fresh atrial thrombi in a pig model were detected using ^{99m}Tc labeled annexin-V and using both planar and SPECT imaging.[46] In 12 pigs with preformed atrial thrombi, imaging was positive in 10 pigs and equivocal in 2 pigs. In 10 control pigs without atrial thrombi, there was no increase in uptake at the site of sham operation. These results are encouraging because this protein can be readily made by recombinant technology, which would make it widely available and relatively inexpensive. Studies in humans are currently being conducted.

Atherosclerosis Imaging

The ability to detect, quantitate, and monitor atherosclerotic plaque formation is of major clinical importance owing to the progression of these plaques to stable coronary artery disease, in some ways a good outcome, or the occurrence of acute ischemic syndromes caused by the rupture of vulnerable plaques, a bad outcome. Myocardial perfusion imaging has an established role for the detection of high-grade coronary artery stenosis in the stable or chronic clinical setting of atherosclerosis. However, the ability to identify and perhaps quantitate the presence and extent of vulnerable atherosclerotic plaques offers the unique opportunity to provide information not available by any other diagnostic imaging modality.[2] Thus, the ability to differentiate between stable and unstable plaque is very important. There are several potential targets that can be used to selectively radiolabel vulnerable plaques. These are listed in Table 8.

Table 8. Potential Targets for Vulnerable Plaque Imaging

LDL cholesterol
Proliferating smooth muscle cells
Up-regulated Receptors
Tyrosine kinase-Endothelin-1: ^{99m}TC ZK 167054
G-protein signaling-Purines: ^{99m}TC Ap4A
Surface antigenic moieties: Z2D3
Macrophage infiltration in atherosclerotic plaques
Large lipid cores in atherosclerotic lesions

Similar to the developmental efforts that have been undertaken for thrombus imaging, attempts to image areas of active atherosclerosis started with the labeling of one of the major but nonspecific components of atheroma, radiolabeled low density lipoprotein (LDL), and have progressed to the use of smaller antibody fragments and peptides directed at specific components of the vulnerable plaque.[47-50] There are fewer studies published in this area, especially in humans, than there are for imaging of thrombi, but there is increasing interest as the evidence continues to accumulate on the risk reduction associated with cholesterol control for primary and secondary prevention of ischemic events and the belief that even regression may occur in established coronary artery disease. To be able to identify and monitor changes in the quantity of vulnerable atherosclerotic plaque would serve an important clinical role.

LDL Detection

Detection of atheroma in the carotid system in man was first performed using radiolabeled LDL.[51] In this initial study, a total of 3 patients and 1 normal patient were studied using ^{125}I radiolabeled autologous plasma LDL. In the 3 patients with angiographically documented disease in the carotid arteries, there was increased tracer uptake detected. Uptake was not present in the normal carotid system. Subsequent studies using LDL have been performed in animal models exploring the use of ^{111}In and ^{99m}Tc radiolabel, which allow not only detection, but excellent imaging to be performed.[52,53] Uptake has also been shown in man and in animal models.[54,55] It is unlikely that additional efforts will be made to develop LDL as an imaging agent as the molecule is too large to allow rapid background clearance and the uptake is not specific for reactive areas of atheroma formation. There is the possibility that oxidized LDL, which is specific for the formation of plaques, may be used to image vulnerable plaques.[56]

Proliferating Smooth Muscle Cells

Proliferating smooth muscle cells increase in number in areas of endothelial injury or active atheroma formation and express several unique markers that can be used to target reactive or vulnerable plaques. These include 2 distinct surface receptors that are up-regulated after stimulation by growth factors: receptors that show tyrosine kinase activity and receptors that are coupled with the G-protein-signaling pathway.[57,58] In addition, there are also new antigenic proteins that appear on the cell surface to which specific antibodies can be produced. One of these is ^{99m}Tc Z2D3.[59-62]

Endothelin-1 derivatives selectively bind to tyrosine kinase receptors present in high concentrations on transformed smooth muscle cells in areas of atherosclerosis. One of these endothelin derivatives has been labeled with ^{99m}Tc and used to image areas of ongoing atherosclerosis in the aorta induced by endothelial injury in a rabbit model.[57] All the areas of active atherosclerosis were detected within 15 minutes of injection using this agent. A second type of growth factor receptor that has been targeted for potential imaging is the G protein–signaling pathway that binds purines in areas of atherosclerosis. In a rabbit aorta model of atherosclerosis, 2 ^{99m}Tc radiolabeled purine analogs produced excellent images in less then 30 minutes.[58]

Another antigenic marker of proliferating neointimal smooth muscle cells that allows differentiation from quiescent medial smooth muscle cells has been identified and a specific antibody, Z2D3, has been developed. An $F(ab')_2$ fragment has been developed, radiolabeled with ^{111}In and both animal experimental lesions, as well as lesions in the carotid system in man, have been identified by imaging.[59-62] The human studies were performed in 11 patients before carotid endarterectomy. All the lesions in the carotid system were correctly identified within 4 hours using planar and SPECT imaging. In addition, histological analysis of the endarterectomy specimens localized the uptake in the surgically removed plaques to smooth muscle cells. That specific areas of atherosclerosis can be successfully imaged is encouraging.[48]

Macrophage Infiltration in Atherosclerotic Plaques

Other specific targeting components with the potential for identification of active plaques include monocytes and other inflammatory cells that accu-

mulate in lipid-laden reactive plaques. To date, there have not been any successful imaging attempts using this approach.[47]

Large Lipid Cores in Atherosclerotic Lesions

In addition to the LDL and oxidized LDL techniques listed above, efforts have also focused on the use of a fragment of apolipoprotein B (SP-4) that binds in a distribution similar to cholesterol in areas of balloon vascular injury. It has been studied in Watanabe heritable hyperlipidemic rabbits that develop spontaneous arterial atherosclerotic lesion in a fashion similar to humans.[63] In these studies, there was excellent correlation between the images and the histological changes observed. These studies show promise, but major work remains to be performed before these agents can be applied directly in a clinical setting.

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