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The Use of Nuclear Cardiology in Clinical Decision Making

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Extensive data exist to support the role of myocardial perfusion single-photon emission computed tomography (MPS) in risk stratification. Normal MPS studies usually are associated with very low risk, and patient risk increase significantly as a function of MPS results. Ventricular function measurements from gated single-photon emission computed tomography further augment risk stratification, particularly with respect to identifying patients at risk of cardiac death. Ancillary findings are prognostically important, particularly in the setting of normal or near-normal MPS results. Recent data suggest that MPS results can identify which patients will benefit from revascularization versus medical therapy and have expanded the understanding of how stress MPS is helpful in the identification of risk, enhanced the means of identifying risk, and improved its use as a means to identify optimal posttest treatment.

During the past decade, the most rapidly growing area of nuclear cardiology has been in the application of stress myocardial perfusion single-photon emission computed tomography (MPS) for prognostication in patients with known or suspected coronary artery disease (CAD). This growth has been stimulated by a wealth of studies in large patient groups, as well as a basic shift in the clinical approach to patient management toward strategies based on patient risk rather than coronary anatomy as an endpoint.

Risk-Based Approach to Patient Care

A new paradigm in patient management is that of a risk-based approach to patients with suspected CAD without limiting symptoms.[1] With a risk-based approach, the focus is not on predicting which patient has anatomic CAD but on identifying patients at risk for specific adverse events, ie, cardiac death or nonfatal myocardial infarction (MI), and on post-MPS management strategies that might reduce the risk of these outcomes. Catheterization and revascularization can be limited to those patients who may benefit from these procedures using this approach. It appears better suited to the modern environment of cost containment and dramatic improvements in medical therapy than an anatomic approach based on simple diagnosis, in which the patient with suspected disease undergoes coronary angiography and the presence of any anatomic CAD triggers revascularization.

Incremental Prognostic Value

Another concept underlying the prognostic use of stress MPS is that of incremental prognostic value.[1] Given the constraints placed on physicians and the health care system to practice clinically effective and cost-effective medicine, it is generally accepted that all diagnostic modalities must be judged by the added or incremental information they contribute over that provided by the information known about the patient before the test. Hence, the clinical value of MPS for prognostic in CAD depends on the incremental or added prognostic information yielded by this modality over all data available before the test (eg, clinical, historical, and data from the nonimaging components of stress testing). This approach was first demonstrated with planar myocardial perfusion scintigraphy by Ladenheim and coworkers[2] in a cohort of patients undergoing exercise stress. This analytic approach permits clinicians to determine the true prognostic value of a test and its actual clinical contribution. Historically, incremental value was determined by by means of multivariable modeling to demonstrate increased prognostic information with the addition of test information. First, information available without consideration of the myocardial perfusion im-

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aging data was modeled with respect to an endpoint of interest. Subsequently, after adjusting for the components comprising the prescan model, data from the test in question are considered and, if it is predictive of the endpoint after adjusting for the initial data, incremental value is said to be present. Several large studies reporting prognostic analyses of MPS in cohorts using exercise, vasodilator, or both types of stress and in various clinical settings have extended these results.[3-10]

Added Value of Gated Single-Photon Emission Computed Tomography (SPECT)

Since gated SPECT has become routine only recently, there are few reports of its incremental value over perfusion imaging in assessing prognosis. Left ventricular ejection fraction (LVEF), when measured by other modalities, has been shown to risk-stratify patients for risk of subsequent cardiac death. Sharir and coworkers,[11] demonstrated that poststress LVEF, as measured by gated SPECT, provided significant information over the extent and severity of perfusion defect in the prediction of cardiac death. LV end-systolic volume provided added information over poststress LVEF for prediction of cardiac death.[12] Sharir and coworkers demonstrated a relatively low cardiac death rate in patients with abnormal perfusion and normal LV function, which was subsequently shown to be caused by a referral bias in which patients with greatest ischemia by assessment of global stress perfusion abnormality using the summed stress score (SSS) were sent preferentially for early revascularization and thus censored from assessment of the prognostic value of the test.[13] The prognostic value of gated SPECT was further confirmed other populations, including a study in a cohort from a community setting.[14,15]

What Is Adequate Risk Stratification?

It is widely appreciated that although the concepts underlying incremental prognostic value are important, incremental prognostic value does not form the basis of daily application of MPS results. Physicians cannot make a patient management decision by knowing a χ^2 value of a test. However, risk stratification is both conceptually important in its ability to ascertain the added value of testing and clinically important by providing a means by which the test results can be applied in daily practice. For MPS, optimal risk stratification derives from the ability of a normal scan to identify a cohort of patients as being at exceedingly low risk, hence not in need of consideration of revascularization, and that of the abnormal scans to identify patients at greater risk, who are thus potential candidates for intervention.[16]

Risk of Adverse Events After a Normal Scan

There are extensive literature examining risk after a normal stress MPS with most studies reporting rates of hard events (cardiac death or nonfatal MI) of <1% per year of follow-up.[1,17] The American Society of Nuclear Cardiology published a position statement in 1997 stating that a normal MPS study predicts a very low likelihood (<1%) of adverse events

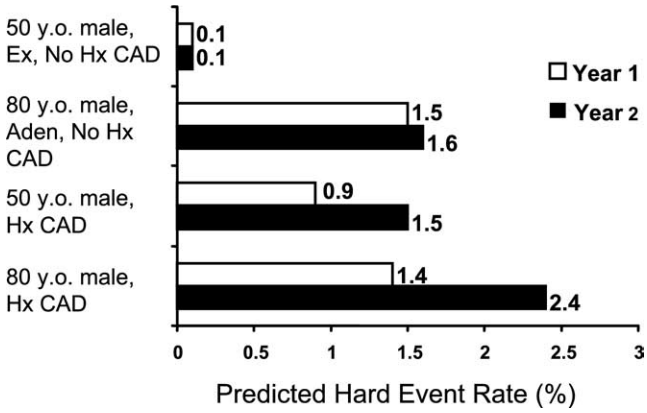


Figure 1 Examples of predicted event rates in the first and second years after a normal stress MPS study. The top pair of bars represents first and second year event rates in a 50-year-old male with no known CAD undergoing exercise stress. In comparison, an 80-year-old male with no known CAD undergoing adenosine stress would have significantly greater first- and second-year event rates. Of note, although the risk increases, the rates in the first and second years are not different. However, the counterparts of these 2 patients with CAD, as shown in the bottom 2 pairs of bars, would have significantly greater risk, the rate in the second year would exceed that in the first year and the change in risk between years 1 and 2 would increase as a function of age in the setting of known CAD (adapted with permission[25]).

such as cardiac death or myocardial infarction for at least 12 months and that this level of risk is independent of gender, age, symptom status, past history of CAD, presence of anatomic CAD, imaging technique or isotope (^{201}Tl or ^{99m}Tc sestamibi).[18] However, published prognostic studies performed in patients undergoing pharmacologic stress, considered a population at higher risk and with more comorbidity than patients undergoing exercise stress, have reported hard event rates of 1.3% to 2.7% per year, suggesting that underlying clinical risk and prior CAD may influence event rates after a normal MPS.[19-24]

More recently, an analysis of 7376 patients with normal stress MPS addressed predictors of risk and its temporal characteristics.[25] This study identified a number of variables, including the use of pharmacologic stress, the presence of known CAD, diabetes mellitus (in particular, female diabetics), and advanced age as markers of increased risk and shortened time to risk (eg, risk in the first year of follow-up was less than in the second year). Baseline patient risk after a normal MPS varied widely as a function of the patient's clinical characteristics. In certain patients, for example, elderly patients who were unable to exercise with known CAD or diabetes mellitus, the risk of cardiac death or myocardial infarction exceeded 1% even in the first year of follow-up. It is important to note that the increased baseline risk of patients after normal MPS is limited to a subset of patients. As a whole, patients with a normal MPS are at very low risk. This study also showed that in patients with known CAD who had normal MPS, the temporal component of risk increased rapidly, as shown in Figure 1. Hence, even patients who had low risk in the first year after normal MPS may no longer be at low

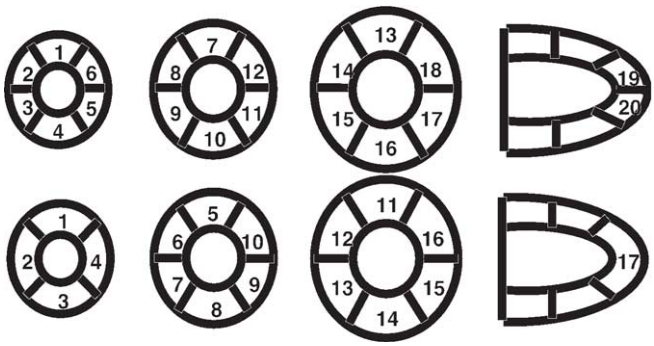


Figure 2 Seventeen-segment and 20-segment models of the left ventricle.[26]

risk in the second year. Little is known regarding this concept of accelerated risk over time, and further studies are needed to further delineate the 'warranty period' after a normal MPS. Thus, while the risk of a hard event after a normal scan is generally low, there is little information currently available to guide the need for and timing of retesting after a normal scan.

Expressing the Extent and Severity of Perfusion Results

Summed Scores

To glean the full prognostic information from MPS, it is essential that scans not be simply interpreted as normal or abnormal but that the extent and severity of perfusion abnormalities be taken into account. We initially described a summed segmental scoring approach using 20 segments.[3,4] Recently, committees of the American College of Cardiology and the American Heart Association have recommended a 17-segment approach.[26] Each segment is scored from 0 to 4, with 0 = normal, 1 = equivocal reduction, 2 = definite but moderate reduction, 3 = severe reduction of tracer uptake, and 4 = absent uptake of radioactivity. Figure 2 compares the 20 and 17 segment scoring systems. With the 17-segment system, the apex is considered 1 segment and the distal short axis contains 4 segments. This system is more appropriately weighted to the amount of myocardium contained in these regions.[27]

From the scoring of the 17 or 20 segments, it is possible to derive global scores that reflect the overall extent and severity of the perfusion defect. These scores are to myocardial perfusion as ejection fraction is to ventricular function. The SSS, summing the scores of the 17 to 20 segments at stress, yields the perfusion analog of the peak ejection fraction, representing ischemic and infarcted tissue. The summed rest score is analogous to the resting ejection fraction and is related to the amount of infarcted or hibernating myocardium, and the summed difference score expresses the amount of perfusion defect reversibility. As a single overall prognostic variable, the summed stress score has been shown to be the single most important predictor of hard events.[5]

Percent Myocardium With Abnormal Perfusion

In a recent work, we reported what we considered an improvement over the summed scores. The visual semiquantitative summed scores are converted into percent abnormal myocardium by normalizing to the maximal possible score (80 for a 5-point, 20-segment system or 68 for a 5-point, 17-segment system).[28] The benefits of this approach include that the % abnormal myocardium provides a measure with intuitive implications not possible with the unit-less summed scores and that it can easily be applied with scoring systems using varying numbers of segments (eg, 20 [previous Cedars-Sinai system], 17 [American College of Cardiology/American Heart Association system], 14 [Mayo Clinic system], 12 [Duke University system]). It also is applicable to quantitative methods that directly measure these abnormalities as % myocardium. We now use this % abnormal myocardium approach with all of our prognostic studies as well as in our clinical reports. In a large study, we recently demonstrated that the 20- and 17-segment systems perform essentially equally well for predicting cardiac death when expressed as % abnormal myocardium at stress.[27]

Event Risk With Abnormal Scans

Numerous studies to date have described a close relationship between increasing extent and severity of scan abnormality and increasing patient hard event or cardiac mortality risk.[1,2,4,5,7-11,14,15,19,23,29,30] This relationship, illustrated conceptually in Figure 3, has been shown to be present irrespective of the type of stress performed, the patient cohort examined (with respect to clinical characteristics or history of CAD), and the type of isotope used. The decreased slope of the increase in mortality with increasing extent/severity of perfusion defect probably is primarily related to the referral of the most ischemic patients to revascularization, resulting in their being censored from the prognostic evaluation as a unique contribution.[31] Variation in this relationship, however, increasingly is appreciated. For example, the precise level of risk for any scan abnormality has been shown to vary with underlying clinical characteristics of the patients examined. In a large follow-up study, for any defect extent and

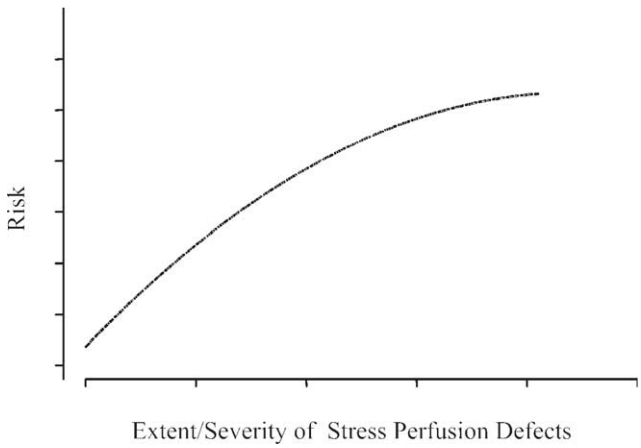


Figure 3 Relationship between extent and severity of stress perfusion defects on MPS and subsequent patient risk of cardiac death or hard event (cardiac death and nonfatal myocardial infarction). This relationship depicted is generalization of this relationship based on numerous studies.

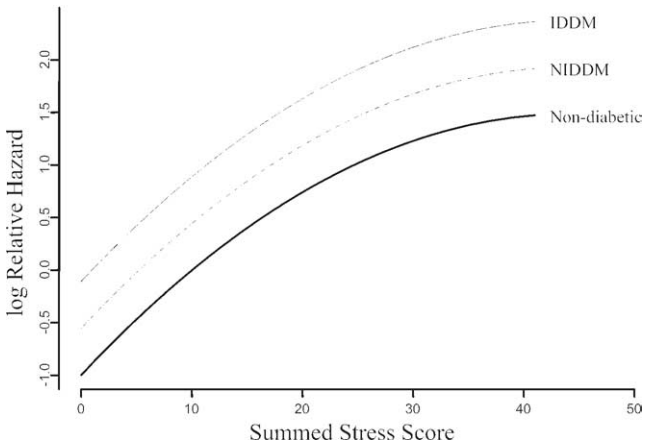


Figure 4 Relationship between log relative hazard for predicted cardiac mortality and summed stress score in insulin-dependent diabetes mellitus (IDDM), noninsulin-dependent diabetes mellitus (NIDDM), and nondiabetics. $P < 0.001$ (adapted with permission[32]).

severity, risk was greater in patients with insulin-dependent diabetes mellitus than those with noninsulin-dependent diabetes mellitus than in nondiabetics (Fig. 4).[32] Furthermore, the type of event likely to occur on follow-up varies as a function of the type of defect found, with myocardial infarction more likely in the setting of reversible defects and cardiac death more likely in the setting of fixed defects.

Mildly Abnormal Perfusion Scans

As shown in Figure 5, a large study evaluating risk after MPS showed patients with moderately and severely abnormal scans to be at intermediate risk for both cardiac death and MI.[5] Importantly, patients with mildly abnormal scans were at intermediate risk for MI but at low risk for subsequent mortality (2.7% versus 0.8% risk per year, respectively); hence, they could be considered as having "flow-limiting" CAD but were unlikely to die from their disease. We hypothesized that if not limited by their symptoms, these patients would be candidates for aggressive medical therapy/risk-factor modification on the basis of this low mortality rate and the observation that medical therapy, but not revascularization, lowers the risk of MI, acute ischemic syndromes or cardiac hospitalizations,

Several studies have now shown that for any extent and severity of any type of scan abnormality, risk varies as a function of underlying patient risk, as determined by history of CAD, clinical risk factors, type of stress performed, response to stress testing and, if known, coronary anatomy.[4,6,25] Hence, not only do scan data provide incremental prognostic information over prescan information, but prescan data also yield incremental prognostic information over MPS results.[4,6,25,32] Thus, although patients with mildly abnormal MPS results generally are at low risk of cardiac death, this is not the case in those with significant comorbidity (eg, advanced age, prior CAD, diabetes mellitus, atrial fibrillation,[33] pharmacologic stress).

Moderately to Severely Abnormal Perfusion Scans

Although both reversible and fixed stress perfusion defects are predictors of prognosis, those at highest risk of cardiac events are patients with extensive stress-induced abnormalities. Multiple studies have described the highest event rates to be present in patients with moderate to severely abnormal perfusion defects. These results extend to both ^{201}Tl,[2,9] ^{99m}Tc sestamibi[14,19] and, more recently, ^{99m}Tc tetrofosmin,[34] as well as dual-isotope approaches.[3-5,10,23,30] Prognosis has been shown to be dependent on both the severity and extent of perfusion defects, correlates of the stenosis magnitude and the amount of myocardium subtended by the stenosed vessels.[35]

Nonperfusion MPS Markers of Risk

Transient Ischemic Dilation (TID) of the Left Ventricle

TID is considered present when the LV cavity appears to be significantly larger in the poststress images than at rest[36,37] and may often represent apparent cavity dilation due to diffuse subendocardial ischemia (obscuring the endocardial border). TID is considered to represent severe and extensive ischemia and has been shown to be highly specific for critical stenosis (greater than 90% narrowing) in vessels that supply a large portion of the myocardium (ie, proximal left anterior descending or multivessel lesions 90%).[36,37] TID in the setting of vasodilator stress has been found to have similar implications as that associated with exercise.[38] Although TID has been known to be a marker of risk,[1] only recently has it been found to add incrementally over perfusion data for prediction of risk.[15,39] The prognostic value of TID as observed on MPS has recently been reported by Abidov and coworkers, who evaluated 1560 patients with normal stress MPS (436 vasodilator and 1124 exercise) with no LV enlargement who were followed up for 2.3 years for hard and soft cardiac events.[39] They demonstrated that in patients with otherwise normal MPS, TID is an independent and incremental prognostic marker of total events even after significant clinical variables, eg, age, typical angina and diabetes, are factored.

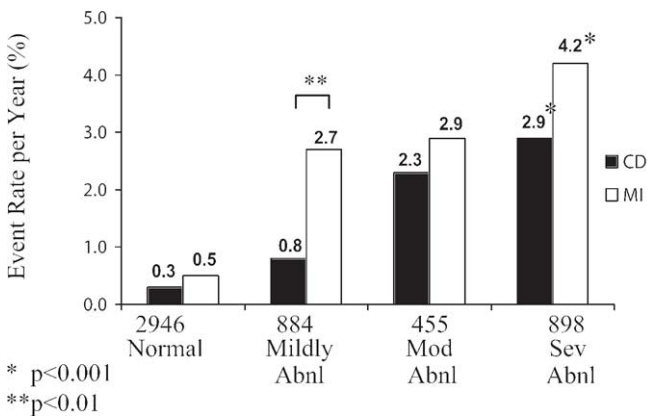


Figure 5 Annualized frequencies of cardiac death and myocardial infarction as a function of scan result (normal, mild, moderate, and severely abnormal scans; adapted with permission[5]). $*P < 0.001$ for each endpoint across scan categories; $**P < 0.01$ for cardiac death versus myocardial infarction in mildly abnormal scans.

The findings suggest that when TID is present, caution in making low-risk prognostic statements may be warranted, especially in patients with typical angina, the elderly, and diabetics.

Increased Lung Uptake of Perfusion Tracers

It is generally accepted that the finding of increased pulmonary uptake of ^{201}Tl reflects increased pulmonary capillary wedge pressure because of either ischemia or nonischemic etiologies. Increased thallium lung uptake after exercise has been shown to have incremental prognostic information over myocardial perfusion defect assessment.[40] Limited studies have examined the implications of increased pulmonary uptake of ^{99m}Tc sestamibi with inconclusive and mixed results.[41-44] The correlation between LV TID and lung uptake is weak, suggesting that there may be different pathophysiologic mechanisms for each, and their measurements may be complementary in assessing the extent and severity of CAD for risk stratification.[45] In general, there is a consensus that increased lung uptake is of prognostic value with both pharmacologic and exercise thallium MPS; however, the finding of increased lung uptake appears to be far less common with the ^{99m}Tc agents, and the prognostic implications of increased lung uptake of these agents has not yet been defined for either exercise or pharmacologic stress.

Nonperfusion Markers in the Setting of Pharmacologic Stress

The clinical implementation of the results of pharmacologic stress MPS is challenging because of the absence or lowered accuracy of conventional markers of ischemia such as three times per day ischemic symptoms and ST segment response and exercise time.

The Role of ST Segment Change in Pharmacologic Stress

A number of investigators have shown an association between ST depression during pharmacologic stress with future adverse outcomes. Marshall and colleagues[46] found that although ST depression was infrequent—only 17% of patients had at least 1 mm of ST depression and 5.3% had at least 2 mm of ST depression—it was both a univariate and multivariable predictor of adverse outcomes, hence providing incremental value over perfusion data alone. Subsequent studies in larger populations confirmed both the independent value of ST depression and its incremental value over perfusion variables for prediction of cardiac death and MI,[47] although other studies had mixed results. Some studies, including larger studies using cardiac death as a solitary endpoint,[32] have not found ST depression during adenosine stress to be predictive of outcome,[19,21,48-50] whereas other studies have.[51] This may be attributable to ST depression being more of a predictor of MI than cardiac death or the possibly to the inclusion of patients with uninterpretable resting electrocardiograms. However, recent data suggest that ST segment changes with vasodilator stress are predictive of adverse outcomes after a normal MPS, albeit an uncommon phenomenon.[52,53] Calnon and colleagues demonstrated the relationship between ST depression during dobutamine stress and perfusion results for optimal risk stratification of patients.[22]

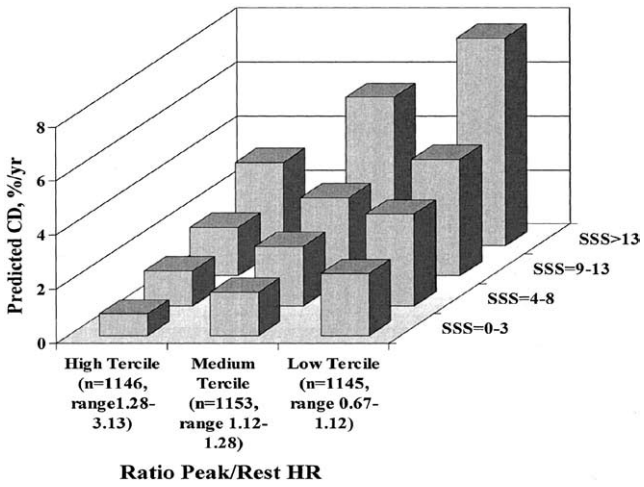


Figure 6 Observed CD rate distribution by tertiles of peak/rest HR and SSS categories (adapted with permission[55]).

Clinical and Hemodynamic Responses to Vasodilator Stress

Normally, there is a mild rise in heart rate and fall in blood pressure, particularly systolic blood pressure, with adenosine or dipyridamole infusion. However, the failure of heart rate or blood pressure to change with adenosine stress does not imply lack of myocardial perfusion response.[54] Amanullah and colleagues found both a higher heart rate at rest and a blunted heart rate increase during adenosine infusion to be univariate predictors of severe or extensive CAD in women.[54] The former also was found to be a multivariable predictor of adverse outcomes. The clinical significance and prognostic importance of different patterns of hemodynamic responses during vasodilator stress were recently described.[55] Abidov and colleagues investigated 3444 patients (54% women, mean age 74.0 ± 8.4 years) who underwent adenosine MPS with no additional exercise as an adjunct and were followed up for 2.0 years. During this follow-up, 224 cardiac deaths occurred (6.5%). Cox proportional hazards analysis was used to examine the prognostic implications of rest and peak adenosine stress heart rate and blood pressure after adjusting for other factors. After risk-adjustment, the ratio of peak to rest heart rate demonstrated the strongest relationship for either observed or predicted mortality rate in both genders, with the greatest risk being present in the lowest tertile of this ratio, ie, a failure to increase heart rate during adenosine infusion is associated with a worse prognosis. Even within each category of MPS result, risk of cardiac death decreased markedly across tertiles of this ratio (Fig. 6). Interestingly, Cox proportional hazards analysis also revealed a significant interaction to be present between gender and peak systolic blood pressure, in which there was an increased risk associated with a low peak systolic blood pressure (<90 mm Hg) in men but not in women. These findings will allow a considerable improvement in the estimation of risk in patients following vasodilator stress MPS.

Post-MPS Patient Management and Its Prognostic Implications

Two important points must be made regarding abnormal scans. First, the relationship between scan results and physician action must be understood. Further, the subsequent impact on observed survival rates after MPS due to physician action, and their implications for future research, must also be considered.

Scan Results and Physician Action

Multiple studies to date have examined post-MPS resource utilization using referral rates to early catheterization and revascularization as measures of physician action (early defined as occurring within the first 60 to 90 days post-MPS.[56,57] Among patients with normal scans, only a small proportion undergo early post-MPS cardiac catheterization, usually as a result of clinical symptoms.[3] Subsequent results demonstrated that the extent and severity of reversible defects shown by the MPS result are the dominant factor driving subsequent resource utilization.[4] In addition, for any amount of ischemia present, a variety of clinical factors, most importantly anginal symptoms, further influence referral rates. The presence of anginal symptoms results in the highest referral rates, while asymptomatic patients have the lowest referral rates.[6] Hence, whereas risk is driven by defect extent and severity, post-MPS resource use is driven by clinical evidence of ischemia. These results were subsequently confirmed by other investigators.[58,59]

This referral pattern is clinically appropriate, as it is driven by referral to revascularization in patients who are either symptomatic or have CAD potentially amenable for either coronary artery bypass grafting or percutaneous coronary intervention. Clearly, patients undergoing revascularization procedures performed early after MPS often will have the natural history of CAD altered. It is for this reason that prognostic studies of noninvasive testing have been in large part limited to patients undergoing medical therapy after testing as patients undergoing early revascularization are censored from analyses since ischemia on noninvasive testing prompts patient referral to early revascularization.[56,57] In turn, as MPS has become increasingly used, an increasing posttest referral bias has developed, leading to an underestimation of the prognostic value of noninvasive testing because of the revascularization of the highest risk patients.[1,16,31] That is, because the highest-risk patients are selectively revascularized and thus removed from survival analyses, the observed event rates in these highest risk patients are reduced and the prognostic value of the test appears to decline. This phenomenon has been recently studied and the potential reduction in event rates by early revascularization quantified.[31] Thus, the pattern of clinical use of MPS has created a referral bias that has resulted in potential underestimation of the prognostic value of MPS, a phenomenon that will need to be considered and taken into account in future studies.

Survival With Medical Therapy Versus Revascularization After Stress MPS

A recent study of risk stratification in noninvasive imaging examined the relationship between the extent and severity of ischemia and the survival benefit associated with subsequent revascularization.[25] This study examined 10,627 patients without previous MI or revascularization who underwent stress MPS and were followed up for a mean of 1.9 years (<4% lost to follow-up). During this time period, 146 patients died of cardiovascular causes (1.4% mortality). The authors defined patient treatment on the basis of that received within 60 days post-MPS (revascularization [671 patients, 2.8% mortality] versus medical therapy [9956 patients, 1.3% mortality; $P = 0.0004$]) and used a risk-adjusted approach that included a propensity score to adjust for nonrandomization of treatment assignment. This propensity score was used to adjust survival analyses and was based on a logistic regression model that defined the predictors of referral to revascularization. As shown in Figure 7, ischemia was by far the most powerful driver of referral to revascularization, with other clinical parameters such as presenting symptoms also influencing treatment.

Based on the Cox proportional hazards model most predictive of cardiac death ($\chi^2 = 539$, $P < 0.0001$), in the setting of no or mild ischemia, patients undergoing medical therapy as their initial treatment had superior survival to those patients referred to revascularization. However, in the setting of moderate-to-severe ischemia (>10% of the total myocardium ischemic) by MPS, patients undergoing revascularization had an increasing survival benefit over patients undergoing medical therapy (Fig. 8). As previously shown in prospective randomized clinical trials comparing medical therapy to revascularization, the absolute benefit accrued with a particular treatment varied as a function of various markers of risk.[60] Similarly, in this study, patients with characteristics associated with greater clinical risk (the elderly, women, diabetics, and patients undergoing pharmacologic stress) were found to have the greatest increase in survival with revascularization over medical therapy in the setting of significant ischemia (Figs. 9-11).

The analytic methodology used in this current study also provided an alternative definition of a test's clinical incremental prognostic value—the ability to identify patients who for a given test result will benefit from a particular therapeutic approach as opposed to another. The advantages of this approach are twofold. It is less subject to posttest referral bias, a problem previously discussed, as it incorporates all patients. Also, it is defined in a more clinically applicable manner than simple assessment of prognosis with medical therapy alone by providing prediction of benefit associated with a therapeutic option.

These results were extended to include data from gated SPECT results and were presented in preliminary form at a recent American Heart Association meeting.[61] In this study, gated SPECT EF and ischemia added incrementally to each other for prediction of cardiac death and assessing potential benefit from revascularization. Although EF was found to be a superior predictor of cardiac death, only inducible ischemia identified which patients experienced a short-term benefit from revascularization. However, as described above, the absolute benefit associated with revascularization varied with patient risk. Hence, for any degree of ischemia, the survival

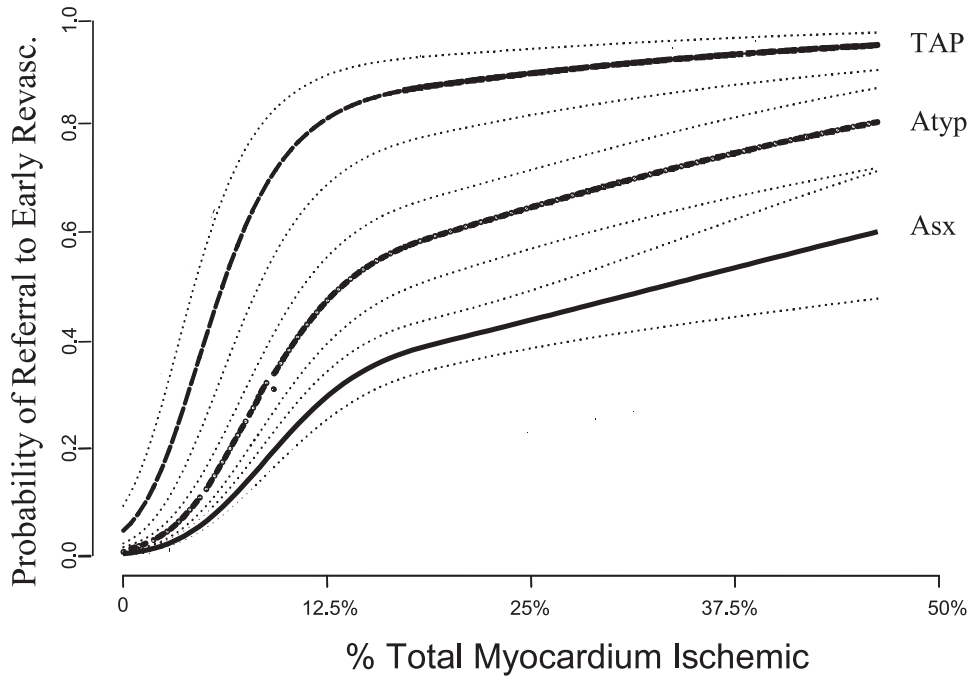


Figure 7 Likelihood of referral to revascularization as a function of percent myocardium ischemic based on logistic regression analysis. TAP, typical angina; Atyp, atypical angina pectoris; Asx, asymptomatic (adapted with permission[28]).

benefit associated with revascularization was greater patients with reduced EF.

A Paradigm Shift: Identification of Potential Risk Versus the Identification of Potential Benefit

Treatment Algorithms Based on Risk

Until recently, post-MPS treatment recommendations were based on the extent and severity of stress perfusion defects—the SPECT data most predicative of adverse outcomes. The underlying principle of this approach was to manage patients on the basis of risk, with those patients at intermediate-to-high risk of cardiac death being referred to catheterization with possible revascularization, and those patients at low risk of cardiac death referred to medial management. As patients with normal MPS are at exceedingly low risk, it has been recommended that they be treated with aggressive risk factor modification. Patients with moderate-to-severely-abnormal scans, given their intermediate-to-high risk of adverse events, were recommended to be referred to catheterization, with an eye to possible revascularization if suitable anatomy is found. In patients with mildly abnormal scans, we previously recommended medical management, as their risk for cardiac

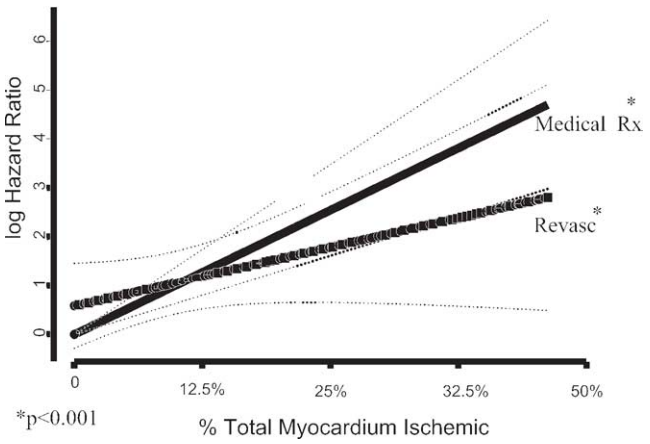


Figure 8 Log hazard ratio for revascularization versus medical therapy as a function of percent myocardium ischemic based on final Cox proportional hazards model. Revasc, revascularization. Model $P < 0.0001$, interaction $P = 0.0305$ (adapted with permission[28]).

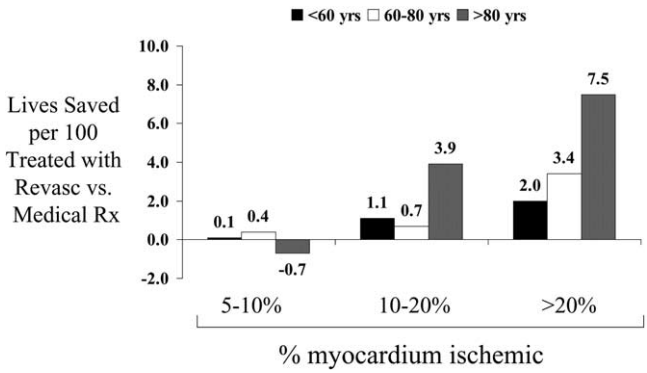


Figure 9 Lives saved per 100 treated with revascularization versus medical therapy in patients by age category (<60 years: black bars; 60-80 years: clear bars; >80 years; cross hatched bars) as a function of %myocardium ischemic (5-10%, 10-20%, >20%). Revasc, revascularization. Results based on Cox proportional hazards model. Statistical significance as per model.[28]

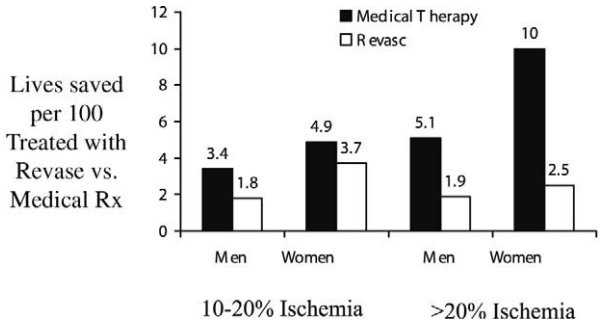


Figure 10 Lives saved per 100 treated with revascularization versus medical therapy in men and women *without diabetes mellitus* as a function of percent myocardium ischemic. Black bars, medical therapy; clear bars, revascularization. Revasc, revascularization. Results based on Cox proportional hazards model. Statistical significance as per model ($P < 0.0001$).[28]

death was low, and their intermediate risk for myocardial infarction could be best addressed with aggressive risk factor modification and medical therapy. In those patients with mildly abnormal scans in whom quality of life, symptomology or compromise of functional status is an issue, catheterization would be justified as a means to alleviate these nonprognostic factors. Finally, in patients with ancillary or nonperfusion abnormalities, such as TID lung uptake, ischemic ST segment changes, gated SPECT wall motion abnormalities, it may be advisable to pursue a more aggressive course of clinical action as the MPS results may underrepresent the amount of CAD and accompanying risk the patient faces. These recommendations were further altered in the face of gated SPECT outcomes data because the presence of a normal gated SPECT EF was associated with a very low risk of cardiac death, hence the possibility that even in the setting of significant ischemia, perhaps catheterization and revascularization were not needed. Conversely, in the setting of compromised LV function, a more aggressive course with referral to catheterization may be indicated despite relatively smaller amounts of inducible ischemia.

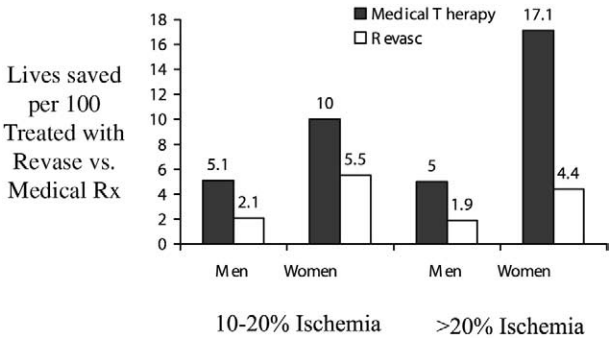
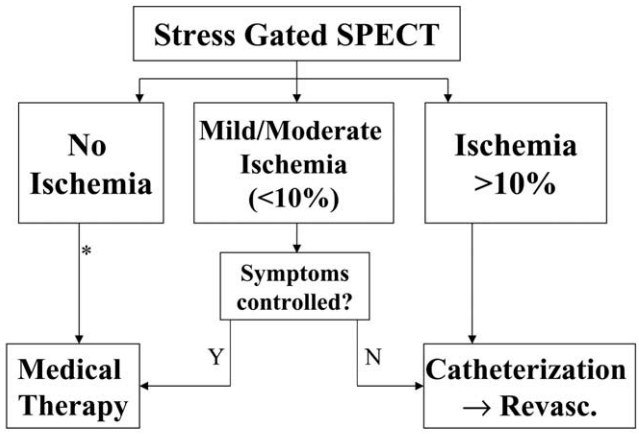


Figure 11 Lives saved per 100 treated with revascularization versus medical therapy in men and women *with diabetes mellitus* as a function of percent myocardium ischemic. Revasc, revascularization. Results based on Cox proportional hazards model. Statistical significance as per model ($P < 0.0001$).[28]



***EF < 30%, ancillary high risk findings?**

Figure 12 Schema for management of patients after stress-gated MPS. Patients without inducible ischemia are referred to medical therapy. The exceptions to this, as noted by the asterisk, would be patients with low ejection fractions or with ancillary high risk findings such as three times per day lung uptake or pot-stress wall motion abnormalities. Patients with significant ischemia (>10%myocardium ischemic) are referred to catheterization for evaluation as revascularization candidates. Patients with mild-to-moderate amounts of ischemia are referred to catheterization if issues are present regarding quality of life, functional status, or symptoms. However, if patients with small amounts of ischemia have no such issues, they can be managed with medical therapy and aggressive risk factor modification.

Treatment Algorithms Based on Potential Benefit

On the basis of recently published data[28] presented previously that demonstrate the close relationship between inducible ischemia and a survival benefit with revascularization, the focus of management algorithms can be shifted from decision making based on risk to decision making based on benefit. Importantly, the component of the MPS study that is scrutinized is the extent and severity of ischemia, rather than the total stress defect size.

Using this approach (Fig. 12), as described previously, patients with normal scans would still be managed medically and with risk factor modification because no potential survival benefit could be accrued with revascularization. In patients without previous CAD who have >10%-15% of their myocardium ischemic, the recommendation can be made to define coronary anatomy with an eye to revascularization since these patients have significant enhanced survival with this approach compared with medical therapy. Patients with mild to moderate amounts of inducible ischemia by MPS (clear cut reversible defects but involving less than 10%-15% of the total myocardium) would undergo medical therapy because there is insufficient ischemia for revascularization to achieve a survival benefit compared with medical management alone. As mentioned previously, because these recommendations are made on the grounds of potential survival benefit with revascularization versus medical therapy, patients in whom quality of life, recurring symptoms or functional status are an issue may justify catheterization and re-

vascularization despite insufficient ischemia to other wise justify intervention. Finally, the presence of ancillary markers indicative of severe or extensive underlying CAD, particularly in the setting of normal or near normal stress perfusion, would merit consideration for intervention.

Can We Prognosticate in Reports? A Future Direction of Survival Analyses

With the ongoing development of stress MPS, increasing numbers of variables are identified as being important prognosticators, and with the development of improving software, more information is being collected that may too be important for prognostication. The greatest challenge facing clinicians attempting to apply MPS results to patient care is to distill all information reported after MPS, eg, clinical, historical, stress test, perfusion, and function data, into an estimate of likelihood of CAD or risk of adverse events for an individual patient. Ideally, if in the future we wish to estimate patient risk on stress MPS reports, we will need to incorporate varied types of data to formulate this estimate. Because MPS and pre-MPS data add incrementally to each other, accurate final estimates of risk must also adjust for clinical data. Ideally, the development of validated scores will incorporate all available sources of information, including expressing MPS results in a manner independent of the scoring system used (eg, percent of total myocardium abnormal at stress, etc). Hence, by deriving the equivalent of the Duke Treadmill Score[62] for MPS results, accurate and reliable estimates of CAD likelihood or risk could be incorporated into MPS reporting. In light of recent data comparing survival benefits with different treatments, it may well be possible that formulas or scores to estimate risk may permit separate estimates for survival with different post-MPS treatment approaches. It must always be recognized, however, that clinical judgment is paramount in the application of these approaches due to imperfections in the data derived from populations in defining all of the variables that might be operative in determining the risk of an individual patient.

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