Cardiology in Review
Volume 11, Number 2, pp. 60–72

Risk Assessment by Myocardial Perfusion Imaging for Coronary Revascularization, Medical Therapy, and Noncardiac Surgery

GEORGIOS I. PAPAIOANNOU, MD*, and GARY V. HELLER, MD, PhD, FACC†

Stress myocardial perfusion imaging (MPI) has become an important tool in risk stratification of patients with known coronary artery disease. A normal myocardial perfusion scan has a high negative predictive value and is associated with low annual mortality rate (< 1%). Patients with extensive ischemia (> 20% of the left ventricle), defects in more than 1 coronary vascular territory, transient or persistent left ventricular cavity dilation, and ejection fraction less than 45% have a high annual mortality rate (> 3%). Those patients should undergo coronary revascularization whenever feasible, as the cardiac event rate increases in proportion to the magnitude of the jeopardized myocardium. Stress MPI can be used to demonstrate ischemia in patients with symptoms early after coronary artery bypass surgery (< 5 years) or in those without symptoms late (≥ 5 years) after coronary artery bypass surgery. With respect to patients who underwent percutaneous interventions, stress MPI can help detect in-stent restenosis early after the intervention (3–6 months) or assess the progression of native coronary disease afterward. Since preliminary data suggest that a reduction in the perfusion defect size may translate to a reduction of coronary events, stress MPI can help assess the efficacy of medical management of coronary disease. Finally, stress MPI is indicated for perioperative cardiac risk stratification for noncardiac surgery in patients with intermediate risk predictors (mild angina, prior myocardial infarction or heart failure symptoms, diabetes mellitus, renal insufficiency) and poor functional capacity or in those who undergo high-risk surgery with significant implications in further preoperative management.

Key Words: Coronary artery disease, Myocardial perfusion imaging, Risk assessment

Concept of Risk

Ischemic heart disease and its manifestations remain a major health problem. Despite remarkable achievements in the diagnosis and treatment, coronary artery disease (CAD) remains the single leading cause of death in the United States (1). Appropriate management of known CAD involves assessment of the individual risk of future cardiac events, including death and myocardial infarction. High-risk patients (eg, those with left main disease, 3-vessel disease, or both) benefit from an aggressive approach with coronary angiography and revascularization. In contrast, the vast majority of individuals with low annual risk for cardiac events can be managed conservatively (2).

Stress myocardial perfusion imaging (MPI) with thallium-201 isotope (^{201}Tl) or technetium-99 meter isotope (^{99m}Tc) agents has the ability to distinguish patients at high risk (> 3% annual mortality rate) from those at low risk (< 1% annual mortality rate) and currently plays an important role in the management of patients with known or suspected coronary disease (3). A normal ^{201}Tl or ^{99m}Tc-sestamibi scan is generally associated with low risk of future cardiac events (4–6). This low event rate approaches that of a normal age-matched population and also of patients with normal coronary angiograms (7). The same benign prognosis appears to persist even in patients with strongly positive exercise electro-

*Cardiovascular Fellow, and †Director, Nuclear Cardiology Laboratory, Program Director, Cardiovascular Fellowship, and Professor of Medicine and Nuclear Medicine, Hartford Hospital, University of Connecticut Medical Center, Hartford, Connecticut.

Address reprint requests to: Gary V. Heller, MD, PhD, FACC, Hartford Hospital, Nuclear Cardiology Division, 80 Seymour Street, Hartford, CT 06102. E-mail: gheller@harthosp.org.

cardiograms (ECGs) or angiographically significant coronary disease (8,9). The extent and severity of ischemic zones measured by MPI quantify the magnitude of myocardium at risk during exercise or pharmacological stress testing (10). Studies demonstrating high-risk features (extensive ischemia more than 20% of the left ventricle, defects in more than 1 coronary vascular supply region, reversible ischemia in multiple segments, transient or persistent left ventricular cavity dilation, increased ^{201}Tl lung uptake) (11–13) predict an increased risk of cardiac events (Table 1, Fig. 1).

The introduction of the newer ^{99m}Tc-agents and the high count density achieved with them lead to both a higher quality of myocardial perfusion images and stable myocardial distribution with time (14). By the use of electrocardiographic gating during acquisition of tomographic perfusion images, functional important information of the left ventricle is obtained (wall motion, wall thickening, cavity volumes, and ejection fraction). Gated single photon emission computed tomography (SPECT) provides important additional information beyond MPI alone, with major implications for optimal patient care (15,16). Patients with an ejection fraction less than 45% and mild, moderate, or severe perfusion abnormalities have a high mortality rate, whereas patients with an ejection fraction of 45% or greater have a cardiac death rate of less than 1% per year, regardless of the degree of the perfusion abnormality (17).

The use of MPI as a means of risk assessment can be applied to a wide variety of patients, beginning with the initial evaluation of patients without CAD. This review focuses on patients already diagnosed with CAD, including those undergoing revascularization procedures or medical therapy. In addition, we will examine the role of MPI in assessing cardiac risk prior noncardiac surgery.

Myocardial Perfusion Imaging Before and After Revascularization (Percutaneous Transluminal Coronary Angioplasty, Coronary Artery Bypass Grafting)

Before Revascularization

Over the years, myocardial perfusion scintigraphy has evolved as an essential tool in the evaluation and assessment of patients before coronary revascularization. It has a dual role: before coronary angiography, MPI is extremely useful in documenting ischemia and determining the functional impact of single or multiple lesions identified subsequently. After coronary anatomy is known, despite some limitations in the setting of multivessel disease (18), MPI remains the test of choice for identifying the lesion responsible for the ischemic symptoms or so-called "culprit lesion." (19) The ability of MPI to demonstrate the presence of ischemia is desirable when considering revascularization for the relief of anginal pain, since the presence and extent of ischemia may be delineated (20). With respect to identification of the culprit lesion, Hirzel et al. (21) first examined the value of perfusion imaging before and after revascularization. Planar exercise ^{201}Tl imaging was able to identify the ischemic zone that corresponded to a coronary stenosis in 88% of lesions. Other studies have confirmed that MPI identifies the culprit stenosis in 80 to 93% of patients (22).

Although the presence of angiographically detected coronary disease increases with age (23), the prognosis of intermediate lesions in such a population is determined by the extent and severity of reversible ischemia (24). Therefore, in a population with known coronary disease and persistent symptoms despite medical therapy, myocardial perfusion scintigraphy may identify objective evidence of stress-induced ischemia. Although less important before coronary artery bypass grafting (CABG), in which typically all lesions with 50% or greater stenosis are bypassed, this is extremely useful for further management decisions with respect to percutaneous interventions (25). The absence of reversible ischemia in patients with known CAD is an excellent prognostic marker and predicts a low annual event rate (26). Unfortunately, in these patients, who represent a considerable proportion of the percutaneous transluminal coronary angioplasty (PTCA) population, the decision to perform PTCA is often based on the information obtained by coronary

Table 1. Predictors of stress-induced ischemic extent and severity with myocardial perfusion SPECT

- Number and/or location of reversible defections
- Magnitude (severity and extent) of stress defects
- 201-T1 uptake of isotope*
- Transient ischemic left ventricle cavity dilatation after exercise*
- Delayed redistribution

Best assessed by obtaining a 5-minute poststress and 4-hour redistribution or rest anterior planar scintigram before the initiation of SPECT imaging. (Adapted and reprinted with permission from reference 3).

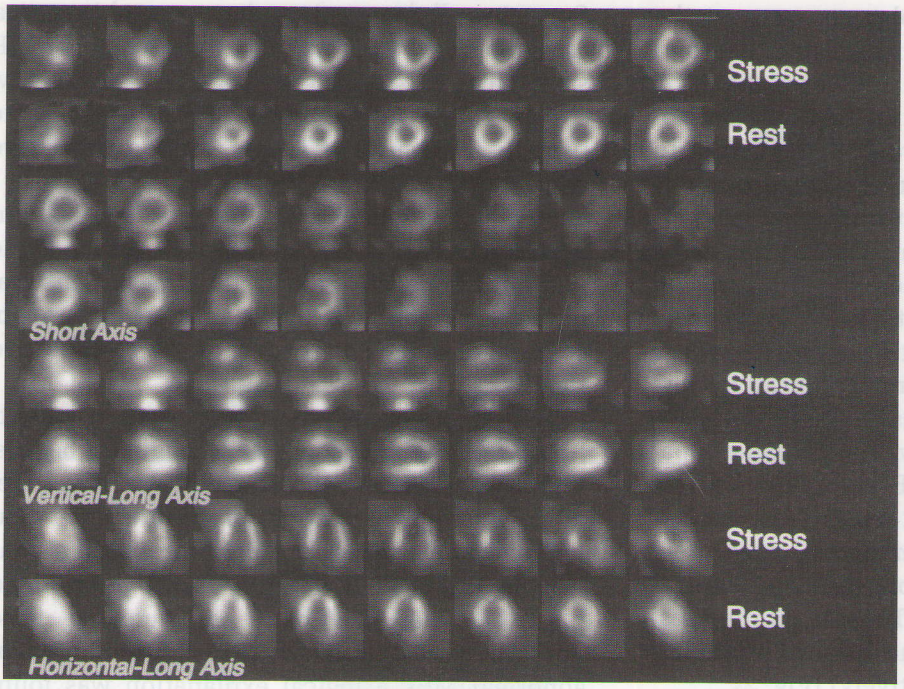

Figure 1. High-risk scan. Demonstration of exercise technetium-99 meter isotope (^{99m}Tc)-sestamibi myocardial perfusion imaging in multiple views (short axis, vertical-long axis, horizontal-long axis; stress images on top of each row with rest images on the bottom). Stress images demonstrate transient cavity dilation and extensive ischemia involving the anterior, anteroseptal, anterolateral, and anteroapical distribution. Rest images reveal normalization of the cavity size and elimination of the perfusion abnormalities. These findings predict a high risk for future cardiac events for the patient.

angiography alone, and its benefit is unproven (27,28).

After Revascularization

Recent figures estimate that 598,000 CABG procedures are performed annually in the United States (29). The long-term effectiveness of this now common procedure is limited by graft stenosis and progression of native disease. MPI may be used in patients after CABG surgery to (1) document intraoperative cardiac injury (2), document improvement in perfusion or function (3), demonstrate graft disease and stenosis, and (4) predict subsequent cardiac events (22). However, the primary value of MPI lies in the ability for identification of graft disease or occlusion. Recently published angiographic data in a cohort of 1388 patients reported a graft occlusion rate of 2.1% per year; at 5 years, 48% of patients had significant graft disease, and at 15 years, 81% (30). Evaluation of post-CABG patients with stress MPI depends on the presence or absence of symptoms as well as timing from the surgical procedure. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines argue against routine testing of asymptomatic patients but do allow the "assessment of selected symptom-free patients" (19), such as patients with an abnormal ECG response to exercise or those with rest ECG changes precluding identification of ischemia during exercise.

A number of studies (31–36) have shown that stress MPI can accurately detect graft stenosis, even in patients with atypical symptomatology, and can effectively localize stenosis, especially if gated SPECT imaging is performed. Lakkis et al. (34) performed SPECT ^{201}Tl imaging in 50 patients at approximately 51 months after surgery. All patients developed chest pain, although 40% of them had atypical symptoms. The sensitivity, specificity, and diagnostic accuracy were 80%, 87%, and 82%, respectively. Although these numbers did not differ from previous reports with planar imaging (35), the sensitivity for individual vascular territories was substantially higher with SPECT MPI—82% for the left anterior descending artery territory, 92% for the right coronary artery territory, and 75% for the left circumflex artery territory (localization of the occluded graft was correct in only 61% of patients with planar imaging) (35). Recent literature supports the notion that a cutoff point of 5 years can be applied to patients post-CABG. In patients late (> 5 years) post-CABG, irrespective of symptoms, myocardial perfusion SPECT has been an effective method for risk stratification. Palmas et al. (36) studied 294 patients 5 years or more post-CABG. During the 31-month follow-up, the event rate (death or nonfatal myocardial infarction) was 14%. The ^{201}Tl reversibility score (a global measure of ischemic index) and the presence of increased lung uptake added significant prognostic information to a clin-

ical model; when these variables were present, the odds of a cardiac event increased by 80% and 10%, respectively. Similarly, Zellweger et al. (37) identified 1765 patients who underwent dual-isotope SPECT MPI 7.1 ± 5.0 years post-CABG and followed them for 1 year or more after testing. A total of 53 cardiac deaths occurred, and there was a significant increase in annual death rates as a function of ischemia (summed stress score). Patients more than 5 years post-CABG, irrespective of symptoms, and symptomatic patients 5 years or less post-CABG benefitted from nuclear testing, because the assessment of ischemia provided a guide to appropriate therapy. Asymptomatic patients 5 years or less post-CABG had a low cardiac death rate (1.3%) and did not benefit from nuclear testing. In both groups, a moderate or severely abnormal summed stress score (based on the interpretation of the stress ^{99m}Tc-sestamibi images) predicted a significant higher annual mortality rate (2.1% and 3.1%, respectively) (Fig. 2).

After Percutaneous Coronary Intervention

The explosion of PTCA and stent placement in patients with single or multivessel disease has created a necessity for early detection of restenosis. A number of clinical studies have documented the usefulness of stress myocardial SPECT for identifying restenosis in patients after coronary angioplasty, stent placement, or both (38,39). In one of the first studies of coronary flow after PTCA, Hirzel et al. (21) examined patients with single vessel disease who underwent successful PTCA. Significant improvement in perfusion was noted in 28 of the 30 patients. The only patients with abnormal MPI 6 months after angioplasty were shown to have restenosis. Hecht et al. (38) compared exercise stress testing with and without MPI in 116 patients; almost half of them had multivessel disease. The sensitivities for exercise stress testing and MPI were 53% and 93%, respectively ($P < 0.001$). Specificity of MPI was also higher (77%) compared to exercise stress testing (64%, P = NS). However, many studies showed that not all patients have normalization of perfusion. Partially reversible or persistent defects have been noted in many patients shortly after (within 1 month of) a successful PTCA (22). In fact, reversible defects consistent with ischemia were reported to be found in 18 to 47% of patients after PTCA (40,41). Resolution of these perfusion defects is noted to some extent in subsequent stress tests (21,42), raising the question of a high rate of false-positive transient results (42). Summing all the previous data, several investigators expressed concern about the value of MPI soon after PTCA. On the contrary, others have shown that early MPI after PTCA is accurate, usually confirms the success of the procedure, and may predict late restenosis (40,43,44). It should also be pointed out that most studies were performed during an era of angioplasty alone, without the benefit of stent placement. This may have contributed to a higher false-positive rate by such mechanisms as inappropriate vasoconstriction.

This ability of MPI to perform early risk stratification has obvious potential benefits, because high-risk patients may be considered for altered medical treatment or additional efforts of revascularization. Iskandrian et al. (44) proposed a pharmacological SPECT strategy early after angioplasty (1 week) without an increased false-positive rate. Although 35% of patients had abnormal MPI, a logical explanation was found for the majority of them (dissection, myocardial infarction, residual stenosis). Current consensus is to obtain an exercise myocardial perfusion study 4 to 6 weeks after intervention (3,19) whenever indicated; however, the proper timing for use of myocardial perfusion SPECT remains to be determined. Based on existing knowledge about the timing interval of subacute thrombosis (45) (less than 4 weeks) and in-stent restenosis (46) (3–6 months), we propose an algorithm as guidance for the management of patients with known CAD after percutaneous coronary intervention (PCI) (Fig. 3). Asymptomatic patients may be considered for stress MPI 4 to 6 weeks after intervention to assess the functional results of PCI and establish a new baseline (19). Subsets of patients who benefit from this approach include those at high risk after PCI (patients with decreased left ventricle function, multivessel disease, proximal left anterior descending disease, previous sudden death, diabetes mellitus, hazardous occupations, and suboptimal PCI results) (47). Stress MPI is also recommended in patients who develop atypical symptoms after PCI, and it is necessary to assess whether these symptoms represent ischemia. Patients with symptoms typical of ischemia less than 6 months after intervention should proceed with coronary angiography as a first step, unless contraindicated. If angina occurs later (more than 6 months after PCI), stress MPI can be used to assess the degree and area of ischemia, since progression of native coronary disease rather than in-stent restenosis is more likely.

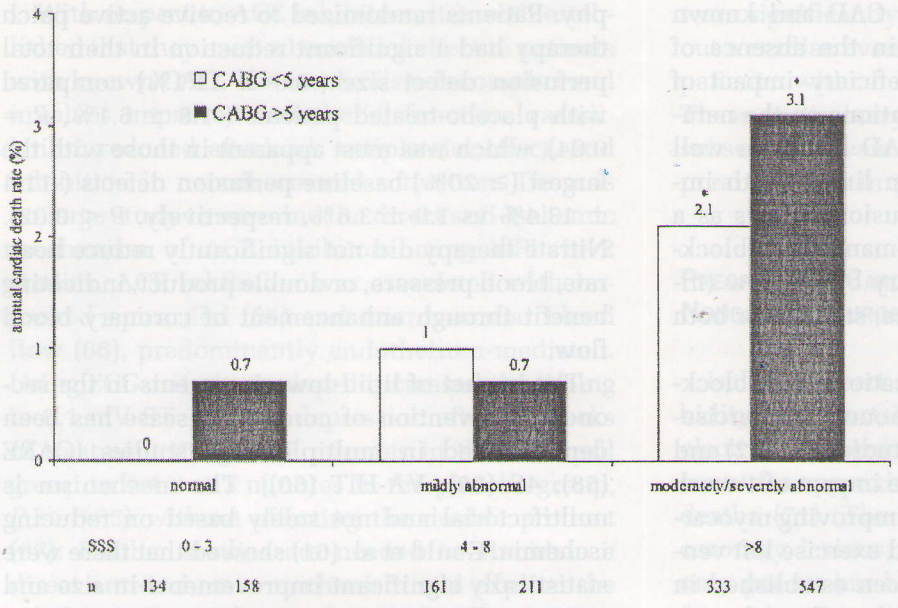

*Figure 2. Annual cardiac death (CD) rates as a function of summed stress score (SSS) in patients 5 years or less and more than 5 years after coronary artery bypass graft (CABG) surgery (n = 1544). *Statistically significant increase as a function of SSS (P = 0.049, 0.005 for ≤ 5 years and > 5 years, respectively. Reprinted with permission (37).*

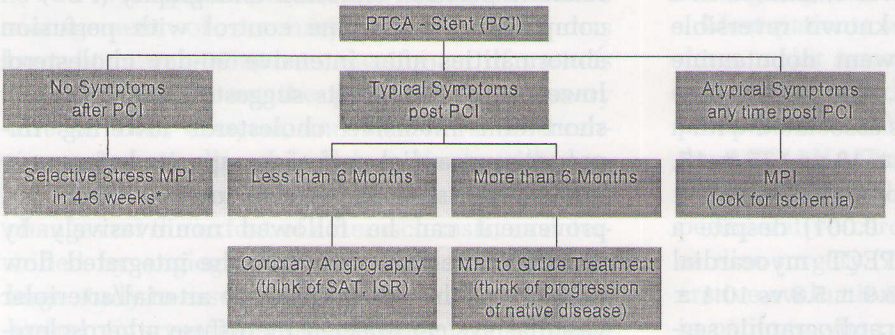

*Figure 3. Proposed algorithm for management of patients after percutaneous intervention (PCI) with respect to nature and timing of symptoms. *ACC/AHA practice guidelines favor selective evaluation in patients considered to be at particular high risk (eg, patients with decreased left ventricle [LV] function, multivessel coronary artery disease [CAD], proximal left anterior descending disease, previous sudden death, diabetes mellitus, hazardous occupations, and suboptimal PCI results) (47). ISR, in-stent restenosis; MPI, myocardial perfusion imaging; PTCA, percutaneous transluminal coronary angioplasty; SAT, subacute thrombosis.*

Assessment of Efficacy of Medical Management of Coronary Artery Disease

Intensive medical therapy with risk factor modification is essential in the management of patients with CAD. While high-risk patients demonstrate a survival benefit from CABG, low-risk and moderate-risk patients have equivalent outcomes with respect to mortality with either approach (medical management or revascularization) (2). The exact definition of what constitutes appropriate medical therapy can be debated, but it would surely include aspirin, beta-blockers, lipid-lowering agents, and probably angiotensin-converting enzyme (ACE) inhibitors in diabetics or patients with impaired left ventricular function (48). Since the degree and extent of ischemia predicts future events (11), MPI has been used to assess the impact of medical management on the ischemic zones in patients with known coronary disease. In fact, Mahmarian et al. (49) demonstrated that quantitative exercise ^{201}Tl tomography is highly reproducible and can be used to interpret temporal changes accurately in myocardial perfusion in individual patients. In 18 patients with baseline tomographic perfusion defect involving 5% or more of the left ventricle after treadmill exercise MPI, the study was repeated using the same exercise protocol and without significant differences in exercise parameters. Seventeen of 18 patients (94%) had an abnormal repeat exercise perfusion scan, and 96% of initially abnormal vascular territories remained abnormal. The mean tomographic perfusion defect size was not significantly different between the 2 studies, and the components were not defined as scar and ischemia.

There are no data or recommendations regarding routine evaluation and follow-up with perfu-

sion imaging of patients with CAD and known myocardial perfusion defects in the absence of symptoms. However, the beneficiary impact of various pharmacologic interventions on the natural history of patients with CAD has been well established (48). This has been linked with improvement in myocardial perfusion defects as a result of decreased oxygen demand (beta-blockers) (50–54), improved coronary blood flow (nitrates, calcium-channel blockers, statins), or both (55,56).

Among the antianginal medications, beta-blockers markedly decrease the amount of exercise-induced ischemia in multiple studies (50–52) and may normalize the test (52). The impact of 1-week treatment with propranolol on improving myocardial blood flow distribution and exercise left ventricular ejection fraction has been established in men with CAD (50). Similarly, the effect of acute administration of propranolol was examined in a small series of patients with known reversible perfusion defects who underwent dobutamine MPI with ^{99m}Tc-sestamibi (53). The dobutamine stress test after propranolol was associated with a lower maximum heart rate (83 ± 18 vs 125 ± 17, $P < 0.001$) and rate pressure product (14,169 ± 4248 vs 19,894 ± 3985, $P < 0.001$) despite a higher infusion dose. The SPECT myocardial ischemia score was also lower (6.9 ± 5.8 vs 10.1 ± 7.1, $P = 0.047$), and fewer echocardiographic segments were abnormal (3.4 ± 3.0 vs 4.6 ± 3.4, $P = 0.042$). These data suggest that the anti-ischemic effect of beta-blockers works primarily by decreasing the heart rate and myocardial oxygen demand. However, recent evidence supports the idea that beta-blockers may increase coronary flow reserve and myocardial oxygen supply (57). Improvement in myocardial ischemia with beta-blockers was recorded as early as 1 week after oral treatment, and acutely with intravenous administration.

Although nitrates and calcium-channel antagonists are not first-line agents in patients with coronary disease, they do have an impact on existing ischemia. Either in conjunction with beta-blockers (54), or alone (55,56), both of these agents decrease the size of reversible defects (particularly in patients with large ischemic perfusion defects), and appear to have a favorable impact on the deleterious prognostic effect of exercise-induced ischemia. Mahmarian et al. (56) evaluated prospectively whether short-term (6.1 ± 1.8 days) transdermal nitroglycerin patches could limit the extent of exercise-induced left ventricular ischemia as assessed by quantitative ^{201}Tl tomography. Patients randomized to receive active patch therapy had a significant reduction in their total perfusion defect size (-8.9 ± 11.1%) compared with placebo-treated patients (-1.8 ± 6.1%, $P = 0.04$), which was most apparent in those with the largest (≥ 20%) baseline perfusion defects (-11.4 ± 13.4% vs 1.0 ± 3.6%, respectively, $P < 0.02$). Nitrate therapy did not significantly reduce heart rate, blood pressure, or double product, indicating benefit through enhancement of coronary blood flow.

The impact of lipid-lowering agents in the secondary prevention of coronary disease has been demonstrated in multiple large studies (CARE (58), 4S (59), VA-HIT (60)). The mechanism is multifactorial and not solely based on reducing ischemia. Gould et al. (61) showed that there were statistically significant improvements in size and severity of perfusion abnormalities by rest-dipyridamole positron emission tomography (PET) on comparison of baseline control with perfusion abnormalities after intensive 90-day cholesterol lowering. These results suggested that relatively short-term intensive cholesterol lowering improves myocardial perfusion capacity before anatomic regression of stenosis occurs. Such improvement can be followed noninvasively by dipyridamole-PET, reflecting the integrated flow capacity of the entire coronary arterial/arteriolar vascular system affected by diffuse atherosclerosis. Other investigators (62) used SPECT MPI in patients with CAD and hypercholesterolemia to assess serial changes in myocardial perfusion associated with cholesterol reduction therapy. Following improvement in total cholesterol (pretreatment: 223 ± 51, posttreatment: 147 ± 33, $P < 0.001$), the stress defect score (defined as % left ventricular mass hypoperfused) was significantly improved (pretreatment: 19 ± 16, posttreatment: 9 ± 13, $P = 0.022$). The same investigators studied the effect of short-term (6 weeks) or long-term (6 months) pravastatin in dyslipidemic patients with baseline MPI ischemic defects (63). Despite a significant reduction of LDL at 6 weeks (33%, $P < 0.001$), myocardial perfusion scores were reduced only at 6 months (12.6 ± 5.7 at baseline, 9.4 ± 6.2 at 6 months, $P < 0.01$). The time course of reduced perfusion abnormalities paralleled documented clinical benefit (58–60) rather than LDL reduction. Whether stress MPI may identify effective clinical response to statin therapy and facilitate optimal medical or revascularization therapy strategy or both needs to be determined by larger scale trials in the future (64).

With respect to ACE inhibitors, it is well established that they exert a beneficial effect in patients with known CAD. The mechanism is complex and involves improved endothelial function, vasodilation, reduced afterload, antiplatelet effect, and inhibition in neurohormonal activation. There is no large study to examine the direct anti-ischemic mechanism of ACE inhibitors using MPI. In 2 studies, ACE inhibition was associated with improved epicardial (65) and microvascular blood flow (66), predominantly endothelium-mediated. Using ECG criteria, enalapril increased the timing to 0.1 mV ST segment depression after 12 weeks of treatment (5.6 ± 1.9 minutes in the enalapril group vs 4.4 ± 1.3 minutes in the placebo group, $P < 0.05$) without affecting the double product (67). Further studies are needed to elucidate a direct anti-ischemic mechanism and explore the role of MPI in monitoring such an effect.

The widespread interest in the noninvasive management of coronary atherosclerosis has brought new attention to the impact of various lifestyle changes on the prognosis of coronary disease. Diet, exercise, and behavioral interventions are generally advised in patients with documented coronary disease. The impact of these changes on the extent of atherosclerosis, as determined by angiography, is modest. There is no large study to assess the impact of nonpharmacological interventions on ischemic zones using MPI. However, the size and severity of perfusion abnormalities on rest-dipyridamole PET imaging in an experimental group was decreased (improved) compared to controls after 5 years of intensive risk factor modification (68).

Despite the fact that all the above interventions aim to improve the ischemic zones, one important question remains: does the reduction in the perfusion defect size translate to an actual reduction in risk for subsequent cardiac events? In the ACME study (69), patients who normalized a previously ischemic planar ^{201}Tl perfusion scan with either medical therapy or PTCA had a significantly higher survival rate (92%) compared to those who continued to have exercise-induced ischemia (82%, $P = 0.02$). Dakik et al. (70) studied 42 patients after myocardial infarction with large total (≥ 20%) and ischemic (≥ 10%) zones as assessed by adenosine ^{201}Tl SPECT MPI. Patients were treated with either intensive medical therapy or PCI. Repeat imaging was performed in 42 ± 26 days, and clinical events were recorded 11 months after enrollment. The respective reductions in total and ischemic perfusion defect size were significantly greater in the 35 patients without a cardiac event (-15% and -14%) than in the 7 patients with a cardiac event (-6% and -5%). These preliminary data suggest that the risk for a subsequent event is strongly influenced by temporal changes in perfusion defect size.

Preoperative Cardiac Risk Stratification for Noncardiac Surgery

Ischemic heart disease is a major cause of morbidity and mortality among patients undergoing elective noncardiac surgery; cardiac deaths account for approximately one half of perioperative deaths (71). The physiologic importance of the coronary lesions, rather than the coronary anatomy per se, has been established as the standard for evaluating cardiac risk in patients with CAD undergoing elective noncardiac surgery.

Most patients with known CAD can safely undergo major noncardiac surgery. Thus, the major question is which subpopulations benefit from preoperative cardiac risk stratification. Recently, the ACC/AHA Task Force on Practice Guidelines published an update on the recommendations for perioperative cardiovascular evaluation for noncardiac surgery (72). In general, additional preoperative evaluation should not be performed either in patients who require emergent noncardiac surgery or in those who had coronary revascularization within the last 5 years and are asymptomatic. In patients with major clinical predictors of poor outcome (unstable coronary syndrome, decompensated congestive heart failure, significant arrhythmias, severe valvular disease), consideration of delaying or canceling the surgical procedure with further evaluation with coronary angiography is appropriate. The approach to stable patients with intermediate risk predictors (mild angina, prior myocardial infarction, compensated or prior heart failure symptoms, diabetes mellitus, renal insufficiency) is based on consideration of functional capacity and the risk of the surgical procedure. Patients with poor functional capacity (< 4 METs) benefit from further noninvasive risk stratification, while patients with moderate or excellent functional capacity can safely undergo surgery unless the surgical procedure is considered high-risk. Patients with minor risk predictors do not need noninvasive risk stratification unless both their functional capacity is poor (< 4 METs) and they undergo a high-risk surgical procedure. The results of noninvasive testing can be used to

determine further preoperative management, such as cardiac catheterization, coronary revascularization, or both; intensive medical therapy; or delay or cancellation of an elective noncardiac operation.

It is well appreciated that clinical indexes alone (such as the Goldman index) are insufficient in predicting perioperative cardiac events in patients with known CAD (11,73). Stress MPI appears to be the most accurate method for preoperative risk stratification as well as prediction of late cardiac events (3,11). Because many preoperative patients are unable to exercise, pharmacological MPI plays a predominant role in the evaluation and risk stratification of those individuals. Many studies in various patient cohorts have demonstrated that the risk of cardiac events is not related only to the absence or presence of jeopardized myocardium, but is rather directly proportional to the extent of myocardium at risk (74). This perception applies to risk stratification of patients before noncardiac surgery as well. Based on the number of myocardial segments with transient defects, Lette et al. (75) was able to divide 355 patients undergoing major surgery, into high-risk, medium-risk, and low-risk subgroups. The cardiac event rate was 1% in the 225 patients with a normal dipyridamole MPI, 8% in patients with reversible defects localized to one-vessel territory, 20% in those with reversible ischemia in 2-vessel territory, and 52% in those with extensive ischemic changes (Fig. 4). Brown and Rowan (76) reported that the risk of perioperative cardiac death or myocardial infarction in patients undergoing noncardiac surgery is directly proportional to the extent of jeopardized myocardium reflected in the number of myocardial segments with transient defects on dipyridamole ^{201}Tl MPI. The probability of a perioperative cardiac event was 1% in patients with only 1 segment with transient ^{201}Tl defect, 8% in those with 4 segments involved, and 49% in those with 7 segments with transient defects. Eagle et al. (77) demonstrated the incremental value of dipyridamole ^{201}Tl MPI in a series of 200 patients who underwent peripheral vascular surgery. After reviewing the hospital records for the occurrence of cardiac events (cardiac death, myocardial infarction, ischemic pulmonary edema, unstable angina), he identified 5 clinical variables (risk factors) that were significant predictors of perioperative events: (1) ECG Q waves, (2) a history of ventricular ectopy

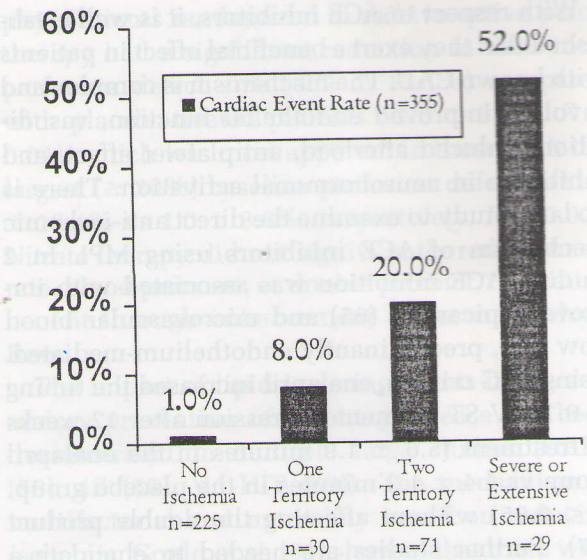

Figure 4. Perioperative rate of myocardial infarction, cardiac death, or both after the performance of major noncoronary surgery (vertical axis) for 355 patients stratified according to the magnitude of reversible defects during preoperative dipyridamole thallium-201 isotope (^{201}Tl) myocardial perfusion imaging (MPI). The frequency of perioperative events increased markedly in patients with a greater magnitude of ischemia. Adapted with permission (75).

requiring therapy, (3) diabetes mellitus, (4) advanced age, and (5) a history of angina. In patients with a very low-risk profile (i.e., none of the risk factors mentioned previously) and in those with a high-risk profile (3 or more risk factors), the cardiac event rates were low (3%) and very high (50%), respectively. However, in patients with 1 or 2 risk factors, dipyridamole ^{201}Tl MPI provided a striking differentiation of risk, heralding a 3% vs a 30% rate of perioperative events among the intermediate-risk patients having no reversible as opposed to reversible ^{201}Tl defects. All the above landmark studies suggest that among patients with an intermediate risk profile, stress MPI can be used preoperatively to predict cardiac events and is able to risk stratify patients based on the absence, presence, and extent of ischemia.

In a recent review of the literature, Yao and Rozanski (3) summarized the results of 15 prognostic studies that used pharmacological ^{201}Tl MPI for the preoperative evaluation for patients undergoing noncardiac surgery. Two criteria for study selection were used: (1) scintigraphic results could be divided into those that were normal or showed fixed or reversible defects, and (2) the frequency of hard perioperative events (myocardi-

al infarction, cardiac death) was reported. Analysis of the results showed 3 principles. First, approximately 5% (90/1847) of surgical cases were cancelled as a response to an abnormal preoperative study. Second, a very low frequency of perioperative cardiac events (9/750, 1.2%) existed among patients who had a normal MPI study, similar to nonpreoperative patients with normal MPI SPECT studies. Third, the frequency of major cardiac events was 15.6% (114/730) among patients who manifested reversible myocardial perfusion defects on their preoperative study. In those patients with fixed defects, the cardiac event rate was 5.1% (14/277), which represents an intermediate risk. However, the majority of these studies had been performed before the routine evaluation of fixed myocardial perfusion defects with subsequent reinjection of ^{201}Tl at rest. Because approximately 30 to 50% of fixed defects can be expected to show redistribution with the reinjection technique (78,79), many of these studies may have been limited in this regard. Patients with small fixed defects could represent small myocardial infarcts, small areas of hibernating myocardium, or attenuation artifacts. By contrast, large fixed defects could represent either large areas of myocardial scar tissue or zones of hibernating and viable myocardium. Since both of them are potential causes of increased cardiac events, this may explain the intermediate likelihood of cardiac event rates in this particular patient population. The above data confirm the results of a previously reported review of the literature on dipyridamole ^{201}Tl MPI by Leppo (80). The negative predictive value of a normal MPI was recorded at 99%, and the sensitivity of a positive scan was 76%, with a specificity of 90%.

Historically, most preoperative studies were completed using ^{201}Tl as the imaging agent. Fewer data are available with ^{99m}Tc-labeled agents. The largest series of patients was reported by Stratmann et al. (81,82). Those investigators reported their experience with 229 patients who underwent dipyridamole ^{99m}Tc-sestamibi SPECT MPI before nonvascular surgery (82). In 89 patients undergoing minor procedures (eg, inguinal hernia repair), only 1 perioperative cardiac event occurred in 64 patients with abnormal studies, and none occurred in the 25 patients with normal images. Of the 140 patients who underwent major surgical procedures (eg, bowel resection, thoracotomy), 11 had perioperative events. Only 1 of the Goldman class I patients had a cardiac event, and MPI with ^{99m}Tc-sestamibi was not predictive of increased risk. Of the 60 patients (Goldman class II or higher), event rates were 4% for a normal MPI, 27% for an abnormal study ($P < 0.05$), 24% for a reversible defect ($P = 0.45$), and 37% for a fixed defect ($P < 0.01$). Thus, dipyridamole ^{99m}Tc-sestamibi MPI provided prognostic information for those patients at greater clinical risk (Goldman class II or higher). Similar data with ^{99m}Tc-sestamibi have been reported with the use of adenosine and dobutamine in smaller studies (83,84).

Preoperative risk stratification provides a unique opportunity for the clinician not only to predict the short-term risk for a particular patient but also to estimate late cardiac events. Indeed, Hendel et al. (85) described the perioperative and long-term outcome of 360 patients who underwent dipyridamole ^{201}Tl MPI before elective vascular surgery. During a mean follow-up of 31 months, transient defects had a significant univariate predictive value for late cardiac events. The best predictor of late cardiac events was the presence of fixed defects. Similar data were reported by Younis et al. (86). Patients with reversible defects had significantly greater incidence of death or myocardial infarction than patients with other test results ($P < 0.001$).

Finally, although myocardial SPECT imaging can successfully identify patients at high risk for perioperative and long-term cardiac events, the validity of a strategy of coronary revascularization, with its additional risk, before noncardiac surgery remains unclear. Studies that investigated this question are few and small (87,88). In one of them, Younis et al. (88) evaluated the impact of preoperative risk modification in patients undergoing major nonvascular surgery. Based on the results of dipyridamole ^{201}Tl MPI (reversible defects), preoperative coronary revascularization or medical interventions were instituted in 36 of 72 patients. The perioperative cardiac event rate was reduced from 47% to 8% ($P < 0.001$). In addition, this study confirmed that the presence of multiple (≥ 2) abnormal ^{201}Tl segments was the only independent predictor of cardiac death or nonfatal myocardial infarction by multivariate analysis.

In summary, MPI in conjunction with clinical predictors of risk, functional capacity, and surgery-specific risk can accurately assess the perioperative cardiac risk among selected patients (intermediate-risk group) undergoing noncardiac surgery. A normal study has a high negative predictive value, whereas a positive study predicts a higher event rate that appears to increase in pro-

portion to the magnitude of jeopardized myocardium.

Conclusion

Stress MPI has emerged as an important tool in the management of patients with known CAD and risk stratification. In conjunction with ^{201}Tl, the development of ^{99m}Tc-labeled agents with improved imaging characteristics and the ECG gated acquisition permits simultaneous assessment of myocardial perfusion and ventricular systolic function. This in turn translates to superior diagnostic accuracy and provides important prognostic information regarding cardiac events. A normal stress MPI is associated with a low risk for future cardiac events (<1% annual mortality rate). Studies demonstrating high-risk features such as extensive ischemia, reversible ischemia in multiple segments, transient or persistent cavity dilation, or ejection fraction less than < 45% predict an annual mortality rate greater than 3%. Those patients should undergo coronary revascularization, whenever feasible, as the cardiac event rate appears to increase in proportion to the magnitude of jeopardized myocardium. In patients with known CAD who underwent revascularization procedures, stress MPI can be used to demonstrate ischemia in those with symptoms early after CABG or without symptoms late (≥ 5 years) after CABG. In those who underwent PCI, stress MPI can be used for the detection of in-stent restenosis and can guide further treatment decisions. Since preliminary data suggest that a reduction in the perfusion defect size may translate to a reduction of cardiac event rate, stress MPI can be used to assess the efficacy of medical management of CAD. Finally, stress MPI can assess perioperative cardiac risk in patients with intermediate-risk predictors undergoing noncardiac surgery. A normal study has a high negative predictive value, while a positive study predicts a high perioperative event rate that appears to increase proportionally with the extent of ischemia.

In conclusion, myocardial perfusion scintigraphy provides a functional assessment of the coronary circulation with important implications in optimal patient care. Extensive literature supports the notion that information obtained with radionuclide imaging can be used in a variety of patients with known CAD for both risk stratification and an ischemia-driven approach with respect to medical therapy or revascularization.

References

1. Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). Circulation 1999;99: 2829–2848.
2. Solomon AJ, Gersh BJ: Management of chronic stable angina: medical therapy, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery: lessons from the randomized trials. Ann Intern Med 1998; 128:216–223.
3. Yao SS, Rozanski A: Principal uses of myocardial perfusion scintigraphy in the management of patients with known or suspected coronary artery disease. Prog Cardiovasc Dis 2001;43:281–302.
4. Heo J, Thompson WO, Iskandrian AS: Prognostic implications of normal exercise thallium images. Am J Noninvas Cardiol 1987;1:209–212.
5. Pavin D, Delonca J, Siegenthaler M, et al: Long-term (10 years) prognostic value of a normal thallium-201 myocardial exercise scintigraphy in patients with coronary artery disease documented by angiography. Eur Heart J 1997;18: 69–77.
6. Raiker K, Sinusas AJ, Wackers FJT, et al: One-year prognosis of patients with normal planar or single-photon emission computed tomographic technetium 99m-labeled sestamibi exercise imaging. J Nucl Cardiol 1994;1:905–914.
7. National Center for Health Statistics: Vital Statistics of the United States, 1979: Mortality, part A. DHHS Publication No. (PHS) 84-1101. Washington, DC, US Government Printing Office, 1984; vol 2.
8. Brown KA, Rowen M: Prognostic value of a normal exercise myocardial perfusion imaging study in patients with angiographically significant coronary artery disease. Am J Cardiol 1993;71:865–867.
9. Schalet BD, Kegel JG, Heo J, et al: Prognostic implications of normal exercise SPECT thallium images in patients with strongly positive exercise electrocardiograms. Am J Cardiol 1993;72:1201–1203.
10. Ladenheim ML, Pollck BH, Rozanski A, et al: Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary disease. J Am Coll Cardiol 1986;7:464–471.
11. Brown K: Prognostic value of myocardial perfusion imaging: state of the art and new developments. J Nucl Cardiol 1996;3:516–537.
12. McClellan J, Travin M, Herman S, et al: Prognostic importance of scintigraphic left ventricular cavity dilatation during intravenous dipyridamole technetiun-99m sestamibi myocardial tomographic imaging in predicting coronary events. Am J Cardiol 1997;79:600–605.
13. Gill JB, Ruddy TD, Newell JB, et al: Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. N Engl J Med 1987;317:1485–1489.
14. Acampa W, Cuocolo A, Sullo P, et al: Direct comparison of technetium 99m-sestamibi and technetium99m-tetrofosmin cardiac single photon emission computed tomogra-

phy in patients with coronary artery disease. J Nucl Cardiol 1998;5:265–274.
15. Bavelaar-Croon C, Pauwels E, Van Der Wall E: Gated single-photon emission computed tomographic myocardial imaging: a new tool in clinical cardiology. Am Heart J 2001;141:383–390.
16. Borges-Neto S, Shaw L: The added value of simultaneous myocardial perfusion and left ventricular function. Curr Opin Cardiol 1999;14:460–463.
17. Sharir T, Germano G, Kavanagh PB, et al: Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999; 100:1035–1042.
18. Travin MI, Katz MS, Moulton AW, et al: Accuracy of dipyridamole SPECT imaging in identifying individual coronary stenosis and multivessel disease in women versus men. J Nucl Cardiol 2000;7:213–220.
19. Rithie J, Bateman T, Bonow R, et al: ACC/AHA guidelines for clinical use of cardiac radionuclide imaging: report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. J Am Coll Cardiol 1995;25:521–547.
20. Borges-Neto S, Watson JE, Miller MJ: Tc-99m-sestamibi cardiac SPECT imaging during coronary artery occlusion in humans: comparison with dipyridamole studies. Radiology 1996;198:751–754.
21. Hirzel HO, Nuesch K, Gruentzig AR, et al: Short and long term changes in myocardial perfusion after percutaneous transluminal coronary angioplasty assessed by thallium-201 exercise scintigraphy. Circulation 1981;63:1001–1007.
22. Hendel R: Assessment of revascularization. In: Zaret BL, Beller GA, eds. *Nuclear Cardiology: State of the Art and Future Directions*. 8th Edition. St. Louis, MO: Mosby; 1999:398–426.
23. Maseri A: The variable chronic atherosclerotic background. In: Maseri A. *Ischemic Heart Disease*. 1st Edition. New York, New York: Churchill Livingstone; 1995:193–235.
24. Beller G, Zaret B: Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000;101:1465–1478.
25. Smith SC, Dove JT, Jacobs AK, et al: ACC/AHA guidelines for percutaneous coronary interventions: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 2001;37:2215–2238.
26. Gibbons RS: American Society of Nuclear Cardiology project on myocardial perfusion imaging: measuring outcomes in response to emerging guidelines. (Editorial) J Nucl Cardiol 1996;3:436–442.
27. Topol EJ, Ellis SG, Delos M, et al: Analysis of coronary PTCA practice in the United States with an insurance-claims data base. Circulation 1993;87:1489–1497.
28. Pitt B, Waters D, Brown BW, et al, for the Atorvastatin versus Revascularization Treatment Investigators: Aggressive lipid lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 1999;341:70–76.
29. American Heart Association: *2001 Heart and Stroke Statistical Update*. Dallas, TX: American Heart Association; 2000.
30. Fitzgibbon GM, Kafka HP, Leach AJ, et al: Coronary artery by-pass fate and patient outcome: angiographic follow-up of 5,056 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28:616–626.
31. Greenberg BH, Hart R, Botvinick EH, et al: Thallium-201 myocardial perfusion scintigraphy to evaluate patients after coronary artery bypass surgery. Am J Cardiol 1978; 42:167–176.
32. Gibson RS, Watson DD, Taylor GJ, et al: Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. J Am Coll Cardiol 1983;1:804–815.
33. Nallamothu N, Johnson JH, Bagheri B, et al: Utility of stress single-photon emission computed tomography (SPECT) perfusion imaging in predicting outcome after coronary artery bypass grafting. Am J Cardiol 1997;80: 1517–1521.
34. Lakkis NM, Mahmarian JJ, Verani MS, et al: Exercise thallium-201 single photon emission computed tomography for evaluation of coronary artery bypass graft patency. Am J Cardiol 1995;76:107–111.
35. Pfisterer M, Emmenegger H, Schmitt HE, et al: Accuracy of serial myocardial perfusion scintigraphy with thallium-201 for prediction of graft patency early and late after coronary artery bypass surgery: a controlled prospective study. Circulation 1982;66:1017–1024.
36. Palmas W, Bingham S, Diamond GA, et al: Incremental prognostic value of exercise thallium-201 myocardial single photon emission computed tomography late after coronary artery bypass surgery. J Am Coll Cardiol 1995;25: 403–409.
37. Zellweger M, Lewin H, Shenghan L, et al: When to stress patients after coronary artery bypass surgery? risk stratification in patients early and late post-CABG using stress myocardial perfusion SPECT: implications of appropriate clinical strategies. J Am Coll Cardiol 2001;37:144–152.
38. Hecht HS, Shaw RE, Bruce RT, et al: Usefulness of tomographic thallium-201 imaging for detection of restenosis after percutaneous transluminal angioplasty. Am J Cardiol 1990;66:1314–1318.
39. DePuey EG: Myocardial perfusion imaging with thallium-201 to evaluate patients before and after percutaneous transluminal coronary angioplasty. Circulation 1991;84: I59–I65.
40. Jain A, Mahmarian JJ, Borges-Neto S, et al: Clinical significance of perfusion defects by thallium-201 single photon emission tomography following oral dipyridamole early after coronary angioplasty. J Am Coll Cardiol 1988;11: 970–976.
41. Wijns W, Serruys PW, Reiber JH, et al: Early detection of restenosis after successful percutaneous transluminal coronary angioplasty by exercise-redistribution thallium scintigraphy. Am J Cardiol 1985;55:357–361.
42. Manyari DE, Knudtson M, Kloiber R, et al: Sequential thallium-210 myocardial perfusion studies after successful percutaneous transluminal coronary angioplasty: delayed resolution of exercise-induced scintigraphic abnormalities. Circulation 1988;77:86–95.
43. Hardoff R, Shefer A, Gips S, et al: Predicting late restenosis after coronary angioplasty by very early (12 to 24 H) thallium-201 scintigraphy: implications with regard to mechanisms of late coronary restenosis. J Am Coll Cardiol 1990;15:1486–1492.
44. Iskandrian AS, Lemlek J, Ogilby JD, et al: Early thallium imaging after percutaneous transluminal coronary angio-

plasty: tomographic evaluation during adenosine-induced coronary hyperemia. J Nucl Med 1992;33:2086–2089.
45. Mak KH, Belli G, Ellis SG, et al: Subacute stent thrombosis: evolving issues and current concepts. J Am Coll Cardiol 1996;27:494–503.
46. Baim D, Levine MJ, Leon MB, et al: Management of restenosis within the Palmaz-Schatz coronary stent (the US multicenter experience: the US Palmaz-Schatz stent investigators). Am J Cardiol 1993;71:364–366.
47. Gibbons RJ, Balady GJ, Beasley JW, et al: ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30:260–315.
48. Blumenthal R, Gregory C, Schulman S, et al: Medical therapy versus coronary angioplasty in stable coronary artery disease: a critical review of the literature. J Am Coll Cardiol 2000;36:668–673.
49. Mahmarian J, Moye L, Verani M, et al: High reproducibility of myocardial perfusion defects in patients undergoing serial exercise thallium-201 tomography. Am J Cardiol 1995;75:1116–1119.
50. Rainwater J, Steele P, Kirch D, et al: Effect of propranolol on myocardial perfusion images and exercise ejection fraction in men with coronary artery disease. Circulation 1982;65:77–81.
51. Steele P, Sklar J, Kirch D, et al: Thallium-201 myocardial imaging during maximal and submaximal exercise: comparison of submaximal exercise with propranolol. Am Heart J 1983;106:1353–1357.
52. Hockings B, Saltissi S, Croft DN, et al: Effect of beta adrenergic blockade on thallium-201 myocardial perfusion imaging. Br Heart J 1983;49:83–89.
53. Shehata A, Gillam L, Mascitelli V, et al: Impact of acute propranolol administration on dobutamine-induced myocardial ischemia as evaluated by myocardial perfusion imaging and echocardiography. Am J Cardiol 1997;80: 268–272.
54. Marie P, Danchin N, Branly F, et al: Effects of medical therapy on outcome assessment using exercise thallium-201 SPECT imaging. J Am Coll Cardiol 1999;34:113–121.
55. Stegaru B, Loose R, Keller H, et al: Effects of long-term treatment with 120 mg of sustained-release isosorbide dinitrate and 60 mg of sustained-release nifedipine on myocardial perfusion. Am J Cardiol 1988;61:74E–77E.
56. Mahmarian J, Fenimore N, Marks G, et al: Transdermal nitroglycerin patch therapy reduces the extent of exercise-induced myocardial ischemia: results of a double-blind, placebo-controlled trial using quantitative thallium-201 tomography. J Am Coll Cardiol 1994;24:25–32.
57. Billinger M, Seiler C, Fleisch M, et al: Do beta-adrenergic blocking agents increase coronary flow reserve? J Am Coll Cardiol 2001;38:1866–1871.
58. Flaker G, Warnica W, Sack F, et al: Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. J Am Coll Cardiol 1999;34: 106–112.
59. Scandinavian Simvastatin Survival Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. Lancet 1994;344:1383–1389.
60. Rubins HB, Robins SJ, Collins D, et al: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. N Engl J Med 1999;341:410–418.
61. Gould L, Martucci J, Goldberg D, et al: Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. Circulation 1994;89:1530–1538.
62. Schwartz RG, Kalaria V, Mackin M, et al: Serial quantitative single photon emission computed tomography monitors improved myocardial perfusion accompanying cholesterol reduction therapy. (Absract) Circulation 1998; 98(Suppl):I-95.
63. Schwartz RG, Pearson T, Williford M, et al: Pravastatin improves stress induced radionuclide myocardial perfusion abnormalities by six months: Coronary Artery Disease Regression SPECT Monitoring Trial. J Am Coll Cardiol 2001;37(Suppl A):424A.
64. Schwartz RG, Pearson T: Can single photon emission tomography myocardial perfusion imaging monitor the potential benefit of aggressive treatment of hyperlipidemia? J Nucl Cardiol 1997;6:555–568.
65. Prasad A, Husain S, Quyyumi A, et al: Abnormal flow-mediated epicardial vasomotion in human coronary arteries is improved by angiotensin-converting enzyme inhibition. J Am Coll Cardiol 1999;33:796–804.
66. Schlaifer J, Wargovich T, O'Neil B, et al: Effects of quinapril on coronary blood flow in coronary artery disease patients with endothelial dysfunction. Am J Cardiol 1997;80:1594–1597.
67. Van Den Heuvel A, Dunselman P, Kingma T, et al: Reduction of exercise-induced myocardial ischemia during add on treatment with the angiotensin-converting enzyme inhibitor enalapril in patients with normal left ventricular function and optimal beta blockade. J Am Coll Cardiol 2001;37:470–474.
68. Gould L, Ornish D, Scherwitz L, et al: Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. JAMA 1995;274:894–901.
69. Parisi AF, Hartigan PM, Folland ED, for the ACME Investigators: Evaluation of exercise thallium-201 scintigraphy versus exercise electrocardiography in predicting survival outcomes and morbid cardiac events in patients with single- and double-vessel disease: findings from the Angioplasty Compared to Medicine Study. J Am Coll Cardiol 1997;30:1256–1263.
70. Dakik HA, Verani MS, He ZX, et al: Adenosine SPECT to assess anti-ischemic drug therapy versus coronary revascularization following myocardial infarction: a prospective randomized trial. (Abstract) J Nucl Cardiol 1997;4: S44.
71. National Center for Health Statistics: Advanced Data for Vital and Health Statistics, United States, 1988. DHHS Publication No. PHS 89-1232. Washington, DC, US Government Printing Office, 10–17, 66–7, 100–1, 1989.
72. Gibbons R, Antman M, Alpert J, et al: ACC/AHA Guideline update for perioperative cardiovascular evaluation for non-cardiac surgery: executive summary (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Non-Cardiac Surgery). J Am Coll Cardiol 2002;39:542–553.
73. Jeffrey CC, Kunsman J, Cullen DJ, et al: A prospective evaluation of cardiac risk index. Anesthesiology 1983;58: 462–464.
74. Brown KA: Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. Circulation 1991;83:363–381.
75. Lette J, Waters D, Cerino M, et al: Preoperative coronary artery disease risk stratification based on dipyridamole imaging and a simple three step, three segment model for patients undergoing non-cardiac vascular surgery or major general surgery. Am J Cardiol 1992;69:1553–1558.

76. Brown KA, Rowen M: Extent of jeopardized viable myocardium determined by myocardial perfusion imaging best predicts perioperative cardiac events in patients undergoing non-cardiac surgery. J Am Coll Cardiol 1993;21:325–330.
77. Eagle KA, Coley CM, Newell JB, et al: Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Int Med 1989;110:859–866.
78. Bonow RO: Assessment of myocardial viability with thallium-201. In: Zaret BL, Beller GA, eds. *Nuclear Cardiology: State of the Art and Future Directions*. 2nd Edition. St. Louis, MO: Mosby; 1999:503–512.
79. Dilsizian V, Rocco TP, Freedman NMT, et al: Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. N Engl J Med 1990;323:141–146.
80. Leppo JA: Preoperative cardiac risk assessment for noncardiac surgery. J Nucl Cardiol 1995;2:461–465.
81. Stratmann HG, Younis LT, Wittry MD, et al: Dipyridamole technesium-99m sestamibi myocardial tomography in patients evaluated for elective vascular surgery: prognostic value for perioperative and late cardiac events. Am Heart J 1996;131:923–929.
82. Stratmann HG, Younis LT, Wittry MD, et al: Dipyridamole technesium-99m sestamibi myocardial tomography for preoperative cardiac risk stratification prior to major or minor nonvascular surgery. Am Heart J 1996;132:536–541.
83. Maunoury C, Stone DA, Chen CC, et al: Preoperative cardiac risk assessment with adenosine stress dual-isotope myocardial single photon emission computed tomography. Clin Cardiol 1996;19:488–490.
84. Van Damme H, Pierald L, Gillain D, et al: Cardiac risk assessment before vascular surgery: a prospective study comparing clinical evaluation, dobutamine stress echocardiography, and dobutamine Tc-99m-sestamibi tomoscintigraphy. Cardiovasc Surg 1997;5:54–64.
85. Hendel RC, Whitfield SS, Billegas BJ, et al: Prediction of late cardiac events by dipyridamole thallium imaging in patients undergoing elective vascular surgery. Am J Cardiol 1992;70:1243–1249.
86. Younis LT, Aguirre F, Byers S, et al: Perioperative and long-term prognostic value of intravenous dipyridamole thallium scintigraphy in patients with peripheral vascular disease. Am Heart J 1990;119:1287–1292.
87. Golden MA, Whittemore AD, Donaldson MC, et al: Selective evaluation and management of coronary artery disease in patients undergoing repair of abdominal aortic aneurysms. Ann Surg 1990;212:415–420.
88. Younis L, Stratmann H, Takase B, et al: Preoperative clinical assessment and dipyridamole thallium-201 scintigraphy for prediction and prevention of cardiac events in patients having major noncardiovascular surgery and known or suspected coronary artery disease. Am J Cardiol 1994;74:311–317.