CHAPTER 2

Known Coronary Artery Disease

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INTRODUCTION: THE CONCEPT OF RISK

Ischemic heart disease and its manifestations remains a major health problem. Despite remarkable achievements in diagnosis and treatment, heart disease remains the single leading cause of death in the United States.[1] Appropriate management of known coronary disease includes assessment of the individual risk of future cardiac events, including death and myocardial infarction (MI). High-risk patients (e.g., those with left main disease and/or three-vessel disease) benefit from an aggressive approach with coronary angiography and revascularization. On the contrary, the vast majority of individuals with low annual risk for cardiac events can be managed conservatively.[2]

Results from stress myocardial perfusion imaging (MPI) (thallium 201 [Tl-201] or technetium 99m [Tc-99m] agents) has the ability to distinguish patients at high risk (> 5% annual incidence of cardiac events) from those at low risk (< 1% annual incidence of cardiac events) and currently plays an important role in the management of patients with known coronary disease.[3] A normal Tl-201 or Tc-99m 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 electrocardiograms (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 extensive ischemia (> 20% of the left ventricle, defects in > 1 coronary vascular supply region) or reversible ischemia in multiple segments, predict an increased rate of cardiac events.[11] Other parameters, such as transient or persistent left ventricular (LV) cavity dilatation[12] and increased Tl-201 lung uptake[13] play an important role in risk stratification (Table 2-1).[3] All the above variables in-

Table 2-1
Predictors of Stress-Induced Ischemic Extent and Severity with Myocardial Perfusion SPECT

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

[a] Best assessed by obtaining a 5-minute poststress and 4-hour redistribution or rest anterior planar scintigram before the initiation of SPECT imaging.
Adapted from Yao and Rozanski[3] with permission.

dependently place patients with known coronary disease at increased risk for future cardiac events.

The introduction of the newer Tc-99m agents and the high count density achieved with them leads to both a higher quality of myocardial perfusion images and stable myocardial distribution with time.[14] By use of electrocardiographic gating during acquisition of tomographic perfusion images, important functional information of the LV is obtained (wall motion, wall thickening, cavity volumes, and ejection fraction). There is growing literature that gated single-photon emission computed tomography (SPECT) gives important additional information beyond MPI alone, with major implications in optimal patient care.[15,16] Patients with an ejection fraction < 45% and mild, moderate, or severe perfusion abnormalities have a high mortality rate, whereas patients with an ejection fraction > 45% have a cardiac death rate of < 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 coronary artery disease (CAD). In this chapter the focus will be on patients already diagnosed with CAD and will include subsets such as prior and post revascularization and the role in monitor medical therapy.

MYOCARDIAL PERFUSION IMAGING AND CHRONIC ISCHEMIC HEART DISEASE

Indications for Stress Myocardial Perfusion Imaging

Exercise stress testing alone is an important tool in following patients with known coronary disease, especially whenever there is a change in the frequency or pattern of symptoms. However, several factors may preclude use of exercise stress testing alone as the diagnostic modality to make further decisions. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for exercise testing[18] strongly recommend an imaging study as part of the evaluation in patients unable to exercise and in those with baseline ECG abnormalities (preexcitation, paced ventricular rhythm, > 1 mm of resting ST depression, complete left bundle branch block [LBBB]). The use of digoxin, presence of left ventricular hypertrophy (LVH), or any resting ST-segment depression decreases the specificity of exercise testing while sensitivity may remain unaffected.[18] Several other subsets of patients benefit incrementally with the use of radionuclide imaging. Those groups involve patients with previous MI and/or revascularization procedures (coronary artery bypass graft [CABG] or percutaneous transluminal coronary angioplasty [PTCA]), patients with prior angiography demonstrating significant disease (where identification of lesion-causing myocardial ischemia is important), high-risk individuals for future events (e.g., diabetics), and patients with a previous positive nuclear scan.[18–22] A summary of the conditions in which radionuclide perfusion imaging is preferred over conventional exercise stress testing is presented in Table 2-2.[23]

Timing and Follow-Up in Stable Coronary Artery Disease

Millions of patients with CAD undergo stress MPI annually. Stress MPI is indicated in some as part of their initial risk assessment and/or prior

Table 2-2
Indications for the Use of Radionuclide Perfusion Imaging Rather than Exercise Electrocardiography[a]

- Complete left bundle-branch block
- Electronically paced ventricular rhythm
- Preexcitation (Wolff–Parkinson–White) syndrome or other, similar ECG abnormalities
- > 1 mm of ST-segment depression at rest
- Inability to exercise to a level high enough to give meaningful results on routine stress ECG[b]
- Angina and history of revascularization[c]

[a] The Guidelines were developed by the American College of Cardiology, the American Heart Association, the American College of Physicians, and the American Society of Internal Medicine.[1]
[b] Patients with this factor should be considered for pharmacologic stress tests.
[c] In patients with angina and a history of revascularization, characterizing the ischemia, establishing the functional effect of lesions, and determining myocardial viability are important considerations.
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to planning PTCA or CABG, but in the majority as part of their follow-up after an intervention (PTCA or CABG) or medical modification.

The role of stress MPI in stable CAD addresses the concept of risk and is linked to an effort of identifying individuals at higher risk for future cardiac events. Unless cardiac catheterization is indicated, patients with known CAD who present with changing symptoms suggestive of ischemia should first undergo stress testing, with or without MPI, to assess the risk of future events.[1] Furthermore, localization of ischemia, identification of extent and severity of ischemic zones, and assessment of LV performance is desirable for most patients who are being evaluated for intervention or titration of medical therapy[24] (Table 2-3). Routine testing in patients with stable symptoms, and in patients with severe comorbidity that is likely to limit life expectancy or prevent revascularization, is not supported by any evidence.[1]

Although the field of nuclear cardiology has substantial data regarding prognosis and risk stratification, there is a paucity of published evidence regarding the widespread practice of follow-up testing using MPI. Clinical cardiologists and internists must use their best judgment to answer important questions: What constitutes a "definite" change that is outside the limit of reproducibility of the test? What constitutes a "clinically significant" improvement or worsening? What degree of improvement should be expected after medical management or intervention? If the patient does improve on medical therapy, does this mean a favorable prognosis?[25] In the absence of randomized trials, some observational studies try to address this deficiency in the literature. Berman et al.[26] followed a cohort

Table 2-3
Uses of Radionuclide Testing in Assessment of Severity/Prognosis/Risk Stratification of Chronic Ischemic Heart Disease

Indication	*Test*	*Class*
1. Assessment of LV performance	Rest or exercise RNA	I
	Gated sestamibi perfusion imaging	IIb
2. Identification of extent and severity of ischemia and localization of ischemia	Exercise or pharmacologic myocardial perfusion imaging	I

LV, left ventricular; RNA, radionuclide angiography.
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of 421 patients with abnormal baseline nuclear scans who underwent revascularization or conservative management. Patients had serial MPI with at least a 1-year interval between the two studies. The finding of this study showed that remarkable improvement in reversible ischemia occurred in patients with intermediate and extensive stress defects at baseline. The improvement was greater in those who underwent revascularization. However, it is clear that much more needs to be done. Several randomized trials are already under way that test the hypothesis that the suppression of ischemia with medical therapy is a favorable prognostic indicator that can be used to properly select patients for medical therapy or revascularization. Until results are available, the current literature supports the concept that a low-risk scan has a period of "warranty" of 12 to 18 months and a high-risk scan requires further investigation.[11,27]

MYOCARDIAL PERFUSION IMAGING AND REVASCULARIZATION PROCEDURES

Prior to Revascularization Procedures

Over the years, myocardial perfusion scintigraphy has evolved as an essential tool in the evaluation and assessment of patients prior to coronary revascularization. It has a dual role. Prior to 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, and despite some limitations in the setting of multivessel disease,[28] MPI remains the test of choice for identifying the lesion responsible for the ischemic symptoms, or so-called "culprit lesion."[24]

It is now well established that even though the presence of angiographically detected coronary disease increases with age,[29] the prognosis of intermediate lesions in such a population is determined by the extent and severity of reversible ischemia.[27] 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 prior to CABG, where typically all lesions with ≥ 50% stenosis are bypassed, this is extremely useful for further management decisions with respect to percutaneous interventions.[30] The absence of reversible ischemia in patients with known CAD is an excellent prognostic marker and predicts a low annual event rate.[31] Still in these patients, who represent a considerable proportion of the PTCA population, the decision to perform PTCA is often based on the information obtained by coronary angiography alone, and its benefit is unproven.[32,33]

After Coronary Artery Bypass Surgery (CABG)

Recent figures estimate that 598,000 CABG procedures are performed annually in the United States.[34] The long term effectiveness of this now common procedure is limited by graft stenosis and progression of native disease. 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 ACC/AHA Guidelines argue against routine testing of asymptomatic patients but do allow the "assessment of selected symptom-free patients,"[34] such as patients with an abnormal ECG response to exercise or those with resting ECG changes precluding identification of ischemia during exercise. Current literature supports the notion that a cutoff point of 5 years can be applied to patients post-CABG. In patients late post-CABG (> 5 years), irrespective of symptoms, myocardial perfusion single-photon emission computed tomography (SPECT) has been an effective method for risk stratification. Palmas et al.[35] studied 294 patients ≥ 5 years post-CABG. The Tl-201 reversibility score (a global measure of ischemic index) and the presence of increased lung uptake added significant prognostic information to a clinical model. Simi-

larly Zellweger et al.[36] identified 1,765 patients who underwent myocardial perfusion SPECT 7.1 ± 5.0 years post-CABG. Patients > 5 years post-CABG irrespective of symptoms, and symptomatic patients ≤ 5 years post-CABG, benefited from nuclear testing because the assessment of ischemia provided a guide to appropriate therapy. Asymptomatic patients ≤ 5 years post-CABG have 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 Tc-99m sestamibi images) predicted a significantly higher annual mortality rate (2.1% and 3.1%, respectively; Figure 2-1).

After Percutaneous Coronary Intervention (PCI)

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 and/or stent placement.[37,38] One point of controversy is the optimal time of performing SPECT imaging after PTCA. Initial studies[39] reported a high frequency of false-positive transient myocardial perfusion defects when SPECT imaging was performed in the first few weeks after angioplasty. Iskandrian et al.[38] proposed a pharmacologic SPECT strategy early after angioplasty without an increased false-positive rate. Although current consensus is to obtain an exercise myocardial perfusion study 4 to 6 weeks postintervention,[3,24] whenever indicated, the proper timing for use of myocardial perfusion SPECT remains to be determined. Based on existing knowledge about the timing interval of subacute thrombosis[40] (< 4 weeks) and in-stent restenosis[41] (3–6 months), we propose an algorithm (Figure 2-2) as a guide for the management of patients with known CAD after percutaneous coronary intervention (PCI). Asymptomatic patients may be considered for stress MPI 4 to 6 weeks postintervention in order to assess the functional results of PTCA and establish a "new baseline."[24] Subsets of patients that benefit from this approach

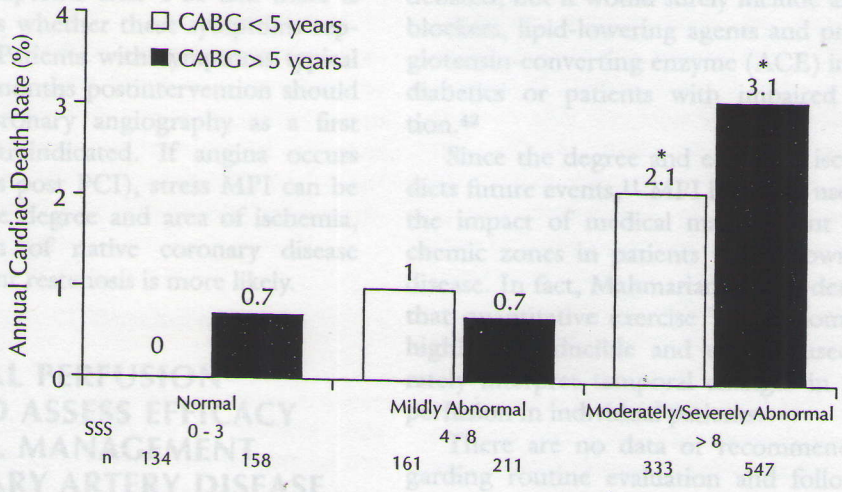

Figure 2-1. Annual cardiac death (CD) rates as a function of SSS in patients ≤ 5 and > 5 years post-CABG (n = 1,544). Statistically significant increase as a function of SSS (p = 0.049, 0.005 for ≤ 5 and > 5 years, respectively. CABG = coronary artery bypass graft surgery; SSS = summed stress score. (Reprinted from Zellweger et al.[36] with permission.)

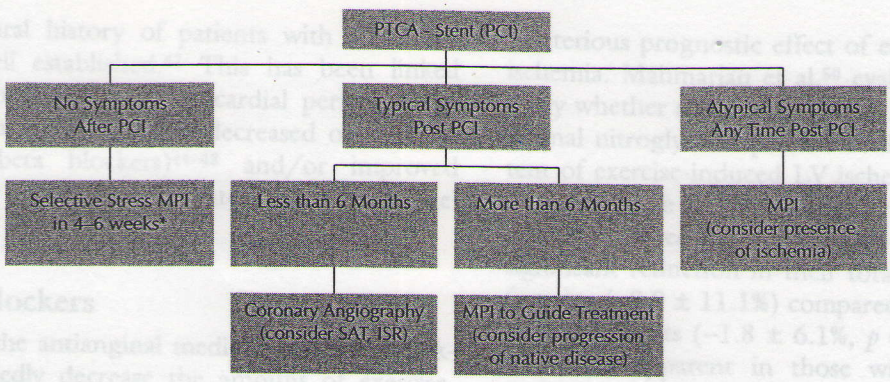

Figure 2-2. Proposed algorithm for management of patients after percutaneous intervention (PCI) with respect to nature and timing of symptoms. ACC/AHA practice guidelines favor selective evaluation in patients considered to be at particular high risk (e.g., patients with decreased LV function, multivessel CAD, proximal left anterior descending disease, previous sudden death, diabetes mellitus, hazardous occupations and suboptimal PCI results).[18] PTCA = percutaneous transluminal coronary angioplasty; PCI = percutaneous intervention; MPI = myocardial perfusion imaging; SAT = subacute thrombosis; ISR = in-stent restenosis.

include those at high risk post PCI (patients with decreased LV function, multivessel disease, proximal left anterior descending disease, previous sudden death, diabetes mellitus, hazardous occupations, and suboptimal PCI results).[18] Stress MPI is also recommended in patients who develop atypical symptoms after PCI and there is necessity to assess whether these symptoms represent ischemia. Patients with symptoms typical of ischemia < 6 months postintervention should proceed with coronary angiography as a first step, unless contraindicated. If angina occurs later (> 6 months post 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.

MYOCARDIAL PERFUSION IMAGING TO ASSESS EFFICACY OF MEDICAL MANAGEMENT OF CORONARY ARTERY DISEASE

Intensive medical therapy with risk factor modification is essential in the management of patients with coronary artery disease. While high-risk patients demonstrate a survival benefit from CABG, low 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 LV function.[42]

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.[43] demonstrated that quantitative exercise Tl-201 tomography is highly reproducible and can be used to accurately interpret temporal changes in myocardial perfusion in individual patients.

There are no data or recommendations regarding routine evaluation and follow-up with perfusion imaging of patients with CAD and known myocardial perfusion defects in the absence of symptoms. However, the beneficial impact of various pharmacologic interventions on

the natural history of patients with CAD has been well established.[42] This has been linked with improvement in myocardial perfusion defects as a result of either decreased oxygen demand (beta blockers)[44–48] and/or improved coronary blood flow (nitrates, calcium channel blockers, statins).[49,50,51]

Beta Blockers

Among the antianginal medications, beta blockers markedly decrease the amount of exercise-induced ischemia in multiple studies[44–46] and may normalize the test.[46] The impact of 1-week treatment with propranolol on improving myocardial blood flow distribution has been established in men with CAD.[44] 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.[47] 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 ± 4,248 vs. 19,894 ± 3,985, $p < 0.001$) despite a higher infusion dose. The SPECT myocardial ischemia score was also lower (6.9 ± 5.8 vs. 10.1 ± 7.1, $p = 0.047$).

Thus, existing data suggest that the antiischemic effect of beta blockers is primarily by decreasing the heart rate and myocardial oxygen demand. Improvement in myocardial ischemia was recorded as early as 1 week after oral treatment, and acutely with intravenous administration of beta blockers.

Calcium Channel Blockers and Nitrates

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[48] or alone,[49–50] 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.[50] evaluated prospectively whether short-term (6.1 ± 1.8 days) transdermal nitroglycerin patches could limit the extent of exercise-induced LV ischemia as assessed by quantitative Tl-201 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.

Lipid-Lowering Agents

The impact of lipid-lowering agents in the secondary prevention of coronary disease has been demonstrated in multiple large studies (CARE,[52] 4S,[53] VA-HIT[54]). The mechanism is multifactorial and not solely based on reducing ischemia. Gould et al.[51] 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[55] used SPECT imaging 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 % LV mass hypoperfused) was significantly im-

proved (pretreatment: 19 ± 16, posttreatment: 9 ± 13, $p = 0.022$). Furthermore, 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.[56] Despite a significant reduction of low-density lipoprotein (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[51–53] rather than LDL reduction. Whether stress MPI may identify effective clinical response to statin therapy and facilitate optimal medical and/or revascularization therapy needs to be determined by larger-scale trials in the fututre.[57]

Angiotensin-Converting Enzyme Inhibitors

There is growing evidence that ACE inhibitors exert a beneficial effect in patients with known coronary disease. Since the mechanism is complex (improved endothelial function, vasodilation and reduced afterload, antiplatelet effect, inhibition in neurohormonal activation), there is no large study to examine their direct anti-ischemic mechanism using MPI. In two studies, ACE inhibition was associated with improved epicardial[58] and microvascular blood flow,[59] 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 min in the enalapril group vs. 4.4 ± 1.3 min in the placebo group, $p < 0.05$) without affecting the double product.[60] Further studies are needed to elucidate a direct anti-ischemic mechanism and explore the role of MPI in monitoring such an effect.

Lifestyle Modifications

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 on patients with documented coronary disease. The impact of these changes on the extent of atherosclerosis, as determined by angiography, is modest. 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.[61]

CONCLUSIONS

The value of stress MPI has been well established in patients with CAD for both risk stratification and clinical decisions. A normal perfusion scan provides an excellent prognosis. Furthermore, identification and extent of ischemic zones provides information regarding the functional status of single or multiple lesions in patients who are being evaluated for intervention or titration of medical therapy. When coronary anatomy in known, MPI remains the test of choice for identifying the lesion responsible for the ischemic symptoms. After percutaneous coronary interventions, MPI can assist in the diagnosis of in-stent restenosis or establish a "new baseline" in certain high-risk individuals. Recent data suggest that SPECT imaging can be used to assess efficacy of medical treatment (particularly statins) of CAD. Whether this approach may identify individual clinical response to various pharmacologic interventions and facilitate optimal medical and/or revascularization therapy needs to be determined by larger-scale trials in the future.

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