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The Role of Myocardial Perfusion Imaging in Special Populations: Women, Diabetics, and Heart Failure

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Cardiovascular disease and its manifestations remain a major worldwide public health problem. Despite significant advances in diagnosis and treatment, coronary artery disease remains the leading cause of death of men and women in the developed world. Early and accurate diagnosis of coronary artery disease is crucial if men and women are to have improved outcomes. The continuous and dramatic growth in the field of nuclear cardiology during the past 2 decades has accounted for its central role in the clinical evaluation of patients with known or suspected coronary heart disease. The development of electrocardiogram-gated single photon emission tomography has facilitated the expansion of nuclear cardiology studies from the evaluation of myocardial perfusion alone to the evaluation of both perfusion and ventricular function data in a single study. Myocardial perfusion imaging with electrocardiogram-gated single photon emission tomography, with its ability to provide information about the physiologic significance of coronary stenosis, left ventricular function, and risk assessment of patients with coronary artery disease, is ideally suited for the diagnostic and prognostic evaluation of the patient who is at high to intermediate risk for ischemic heart disease.
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Cardiovascular disease is the number one killer of women and men in the world[1] and in the United States, with more than 1.4 million people succumbing to the disease each year. In the United States, coronary heart disease accounts for more than 900,000 deaths annually[2]; therefore, the use of a highly accurate diagnostic test such as electrocardiogram (ECG)-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is integral to improving outcome and significantly reducing mortality and morbidity from ischemic heart disease. In the past 2 decades there has been tremendous growth and evolution in the field of nuclear cardiology, specifically technological and radiopharmaceutical advances. Consequently, the accuracy of contemporary MPI with ECG-gated SPECT to assess the diagnosis and prognosis of coronary artery disease has improved.

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The Role of MPI in the Evaluation of Women With Suspected Coronary Artery Disease (CAD)

Gender Challenges With Noninvasive Testing

The female population is a special area of interest when it comes to cardiovascular disease because cardiovascular disease kills more women annually than all forms of cancer combined. CAD is the single largest killer of women in the United States and claims the lives of more than 250,000 women each year.[2] The historical underrepresentation of women in studies has led to the common misconception that heart disease is a "man's disease."[3-13] It also has resulted in a paucity of gender-specific data regarding the performance and characteristics, as well as the diagnostic accuracy of commonly used noninvasive tests. However, since 1990, when Congress mandated the inclusion of women in all federally funded trials, data affirming the different diagnostic accuracy of noninvasive cardiac tests for women have been collected. A number of early studies revealed that women are less frequently referred for noninvasive procedures despite the presence of multiple clinical variables or abnormal noninvasive

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tests.[3,6,7] Lower pre- and posttest noninvasive estimates of CAD may, in part, explain the reduced use of cardiac catheterization. In women with CAD, increased mortality has been repeatedly noted after myocardial infarction, where 38% of women as compared with 25% of men will die within 1 year of hospitalization.[2] These data support a worse prognosis for women with CAD compared with men. Therefore, the early diagnosis of CAD is crucial if women are to have improved outcomes.

The primary challenge with diagnostic testing for women is to determine who to screen and by what method. Exercise stress testing is the most common screening test used to detect CAD; however, this test is problematic because women have a higher rate of false-positives. Women, as evidenced by numerous reports, demonstrate a lower diagnostic accuracy with exercise electrocardiography, with an average sensitivity and specificity of 61% and 69%, respectively.[13,14] Additionally, women are typically older when they present and have greater functional impairment, resulting in a lower exercise capacity and an inability to attain maximal stress. ST-T wave changes in hypertensive women, lower electrocardiographic voltage, and hormonal factors also have been shown to affect test accuracy.[15-20] Because the accuracy of the exercise electrocardiogram (ECG) in women is highly variable and can be influenced by multiple factors, the American College of Cardiology/American Heart Association Guidelines recommend it as a first-line test only for those women with a normal baseline electrocardiogram and for those capable of performing maximal stress.[18] However, women with an intermediate-high pretest likelihood of CAD would benefit from the combined use of stress ECG-gated SPECT myocardial perfusion imaging which has added diagnostic and prognostic value.[14,21]

MPI for the Diagnosis of CAD in Women

The diagnostic value of stress MPI using contemporary techniques for detecting CAD in women has been supported by a growing body of evidence.[13,22-27] It is well known that the diagnostic accuracy of MPI in women is adversely affected by several gender-specific factors, including breast attenuation, small left ventricular (LV) chamber size, and the high prevalence of single-vessel coronary artery disease.[23,28] In a 1997 publication, Iskandrian and colleagues demonstrated a lower sensitivity for single vessel disease in women who had MPI with Thallium-201.[29] The lower sensitivity in women may be related to a small left ventricle chamber compared with their male counterparts.[28]

The most recent meta analysis with a total of 4113 women[14] comparing exercise ECG to stress MPI and stress echocardiography revealed a reduced specificity for MPI as compared with stress echocardiography. The reduced specificity of MPI in that analysis is most likely attributable to the fact substantial data from older literature were used and more recent MPI data with advanced techniques were not included. Newer studies of MPI that incorporate contemporary techniques such as ECG-gated SPECT reveal its ability to assist in differentiating attenuation artifact from infarct. ECG-gated SPECT imaging using technetium99 m (^{99m}Tc)-based agents greatly enhances the diagnostic accuracy of MPI studies in women, suggesting that the specificity for ruling out disease equals or possibly even exceeds other techniques. Two studies that included 170 women with suspected CAD demonstrated that ECG-gated SPECT imaging improved the previously reported specificity for detection of CAD from 67% to 91% and 92%, respectively.[27,30]

Despite the recognized limitations, overall, stress MPI using contemporary techniques is integral to diagnosing CAD in women and is superior to exercise testing alone.[22,23,31-34] Pharmacologic stress testing with MPI has assumed an increasing and vital role in the evaluation of women with suspected ischemic heart disease because women who present with CAD are usually older and, consequently, have a higher incidence of decreased exercise capacity, in which case they become candidates for pharmacologic testing. It is estimated that approximately 40% of women that are referred for MPI studies for the evaluation of CAD are candidates for pharmacologic stress. Currently, there are limited data comparing pharmacologic stress to exercise electrocardiography; however, these data support its higher diagnostic accuracy.[13] Although studies support the similar diagnostic accuracy of exercise stress MPI and pharmacologic stress MPI, few are specific for pharmacologic stress with adenosine, dipyridamole, or dobutamine in women.[24,26,35,36] Although one study demonstrated a lower sensitivity of pharmacologic stress MPI for the detection of single-vessel disease in women compared with men,[29] pharmacologic stress with adenosine using a dual isotope protocol was shown to have a sensitivity of 93% and diagnostic accuracy of 88% in a cohort of women with suspected CAD who also had cardiac catheterization.[24]

In summary, SPECT MPI with exercise or pharmacologic stress plays an important role in the diagnosis of ischemic heart disease in women, is superior to exercise testing alone, and is an effective noninvasive method of assessing women with an intermediate to high pretest likelihood of CAD.

MPI in the Risk Assessment of Women With Suspected CAD

In addition to the diagnostic superiority of MPI in women, the technique also has been proven to have good prognostic value for the development of subsequent cardiac events and the need for revascularization. In fact, pooled data from more than 7500 women revealed an annual cardiac event rate of <1% for women with a normal myocardial perfusion study.[37-47] Conversely, data from more than 5000 women demonstrate a substantially increased risk of cardiac events in the presence of an abnormal perfusion study.[35,36] Even when a high pretest likelihood of coronary disease is present, a very low cardiac event rate and low performance of revascularization have been documented after a normal stress perfusion study.[36,40] As the extent of the perfusion defect increases, so do the rates of both myocardial infarction and cardiac death

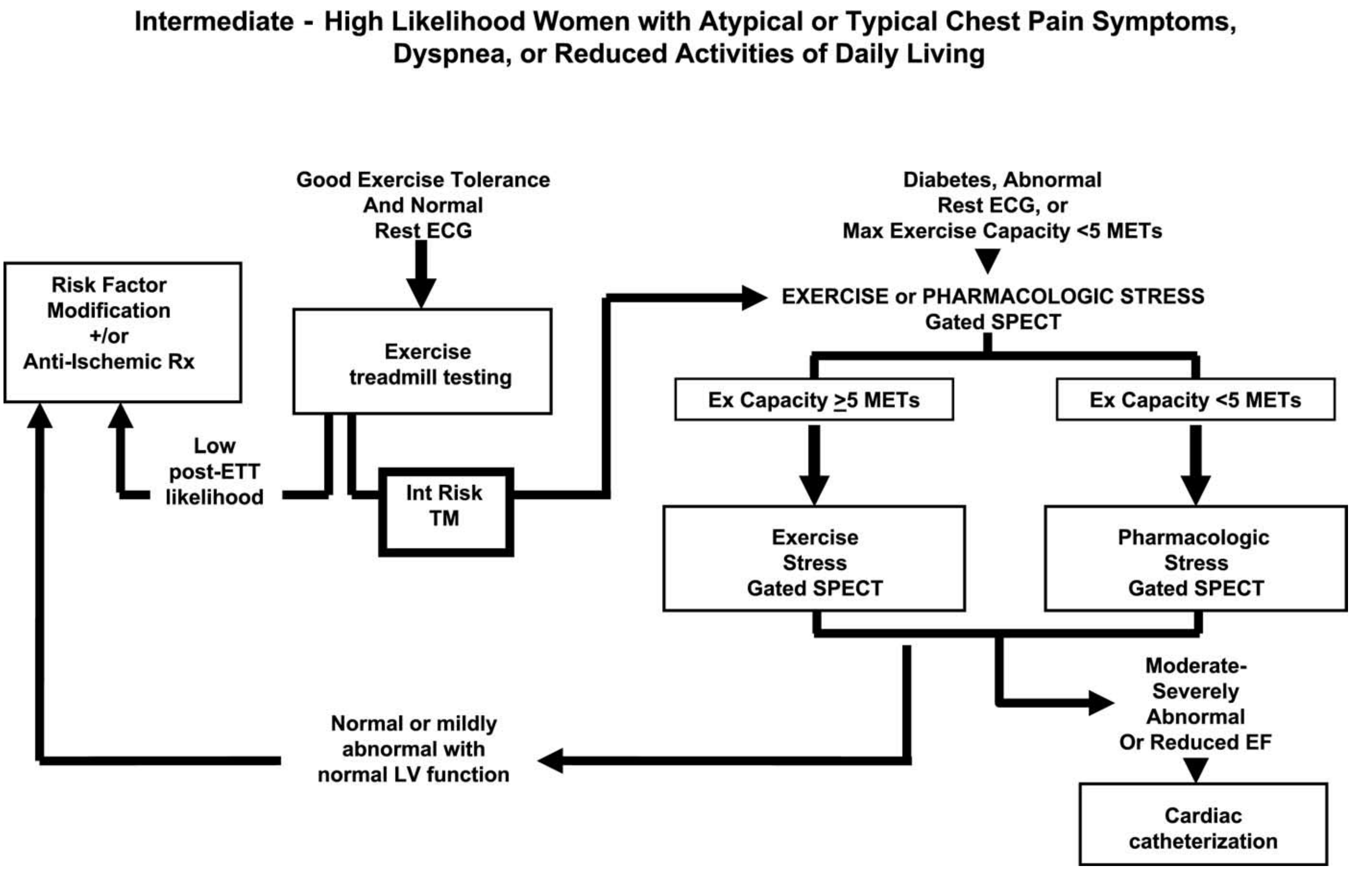

Figure 1 Algorithm for women with suspected CAD. (Reprinted from Mieres JH, Shaw LJ, Hendel RC, et al: American Society of Nuclear Cardiology consensus statement: Task Force on Women and Coronary Artery Disease—The role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women. J Nucl Cardiol 10:95-101, 2003, with permission from the American Society of Nuclear Cardiology.)

(4-6 fold increase).[35,36] The odds ratio for an event with an abnormal scan has been found to be substantially higher for women than for men.[36]

Even when other clinical risk factors are present, the perfusion defect severity and extent independently predict future cardiovascular events.[35,36,41,42] Therefore, an abnormal SPECT study is independently valuable beyond any clinical or stress test parameter.[35,36,41,42] Myocardial perfusion imaging also has demonstrated prognostic value for women with regards to specific applications, such as in the assessment of perioperative risk before major noncardiac surgery.[48]

Recommendations for MPI in Women

The early and accurate detection of flow-limiting coronary artery disease in women is crucial to select patients for referral for invasive procedures, coronary artery revascularization with percutaneous coronary intervention, or coronary artery bypass graft surgery. The diagnostic and prognostic value of stress MPI using contemporary techniques for the detection of coronary artery disease in women is firmly established.[49,50] The use of ECG-gated SPECT imaging adds significantly to the diagnostic accuracy of imaging in women by improving specificity to >90%. Although MPI with attenuation correction techniques is in evolution, limited data support improved specificity in women with suspected CAD.[51] MPI in women adds incremental value to the use of clinical variables or exercise stress testing alone in the risk assessment of women with known or suspected coronary artery disease. Therefore, based on the clinical evidence, SPECT MPI with ECG gating continues to be the cornerstone of the noninvasive evaluation of women with an intermediate pretest likelihood of coronary artery disease.[49]

The current evidence supports the use of ECG-gated SPECT MPI for symptomatic women who have an intermediate pretest likelihood of coronary artery disease. Although the data are not as strong for women with a high pretest likelihood of CAD, MPI adds incremental prognostic value over resting ECG and clinical variables in this group.[36,40] Despite a high pretest likelihood of disease in women, a normal scan is associated with <1% cardiac event year during a 20-month period.[36] Additional candidates for imaging include diabetic women[38] and those who, because they are incapable of maximal exercise, should undergo pharmacologic stress.

Women should be referred for stress testing according to their likelihood of CAD. Although low-risk women should not be referred, those at intermediate-to-high risk are appropriate for

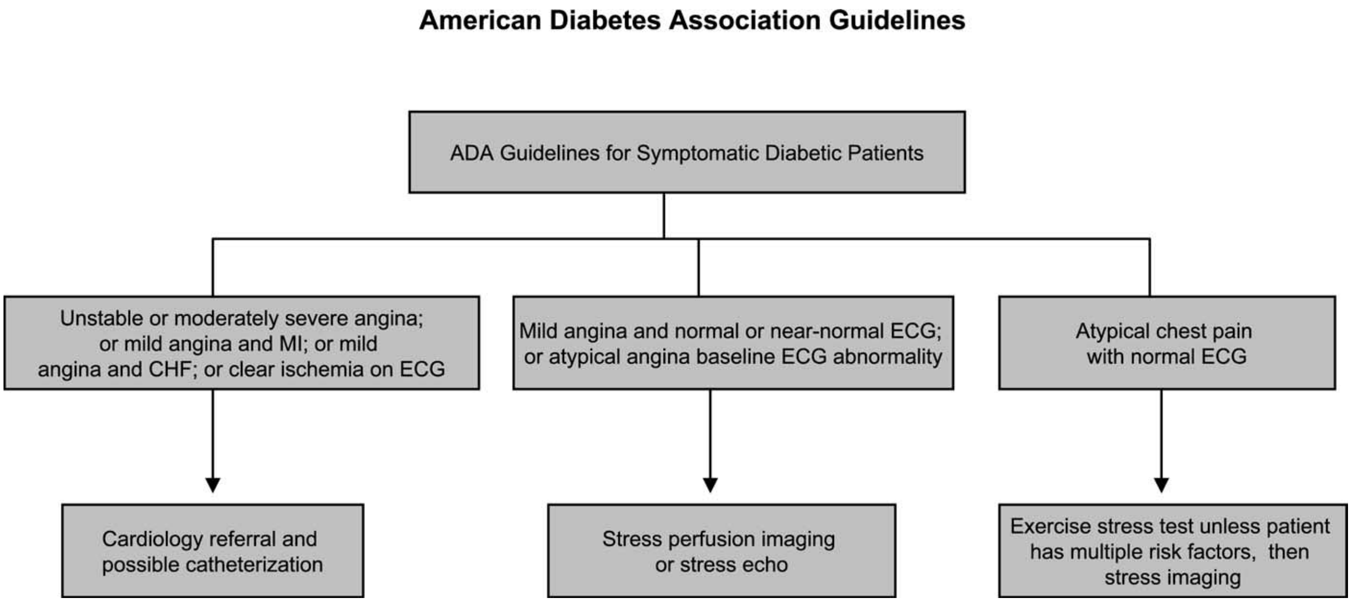

Figure 2 American Diabetes Association guidelines for noninvasive evaluation with stress testing. (Source: ADA consensus. Diabetes Care 1998).

both diagnostic and prognostic evaluations. A strategy incorporating stress ECG-gated SPECT MPI as the initial test for detecting coronary artery disease and assessing prognosis in women who have an intermediate to high pretest likelihood of coronary artery disease (Fig. 1) can be instrumental in the accurate diagnosis and risk assessment of women with suspected CAD.

The Role of MPI in the Clinical Management of Diabetes Mellitus

Background

Diabetes mellitus is a metabolic disorder that affects millions of Americans every year, and its prevalence has been increasing during the past decade. Since 1990, the prevalence of those diagnosed with diabetes increased by 61%. In just 2 years, from 2000 to 2001, the prevalence of the disease increased by 8.2%.[2] In terms of morbidity and mortality, the impact of diabetes is significant and, by all indications, the number of people affected will continue to increase. Cardiovascular disease is the leading cause of diabetes-related death. People with diabetes are 2 to 4 times more likely to develop cardiovascular disease resulting from a variety of risk factors. The overall prevalence of CAD among diabetic patients has been estimated to be as high as 55%, which is significantly higher than the 4% that is estimated among the general population.[52]

The increased risk for diabetic patients, when compared with nondiabetic patients, include a higher prevalence of CAD, a less favorable response to intervention, and short long-term survival.[53] An additional challenge in this population is that myocardial ischemia tends to be silent or asymptomatic.[54] All of these factors make it especially important to be able to identify subclinical CAD in diabetic patients, and stress MPI has been shown to contribute considerable diagnostic and prognostic information in the diabetic population.[38,55]

Several studies have provided data to support the use stress SPECT MPI in diabetic populations.[55-58] Each of the studies reveals the considerable value in the addition of cardiac imaging with stress SPECT imaging because exercise ECG alone as a means of evaluating diabetic patients is not adequate due to a low specificity and sensitivity.

MPI in the Diagnosis of CAD in Patients With Diabetes

Patients with diabetes who develop symptoms suggestive of ischemic heart disease usually are referred for noninvasive evaluation with stress testing[52,59,60] (Fig. 2). Although the mode of stress testing is not specific for the symptomatic patient with diabetes, exercise tolerance testing alone (low sensitivity and specificity) as a means of assessing the diabetic patient with suspected CAD may not be adequate.[52] Thus, stress ECG-gated SPECT MPI having a high diagnostic and prognostic accuracy for CAD can be very beneficial in the clinical evaluation of diabetics with suspected CAD.[52]

A growing number of studies demonstrate a similar diagnostic accuracy between diabetic and nondiabetic patients. In a 1995 publication, Paillole[56] and colleagues reported a sensitivity and specificity of 80% and 87%, respectively, for ^{201}Tl MPI with dipyridamole. In a retrospective review, Bell and colleagues reported a sensitivity of 97% and a positive predictive value of 88% in a cohort of diabetic patients that were referred for myocardial perfusion imaging, followed by cardiac catheterization.[58] Kang and colleagues reported a sensitivity of 86% and a modest specificity of 56% in a cohort of diabetics with suspected CAD who had both MPI and

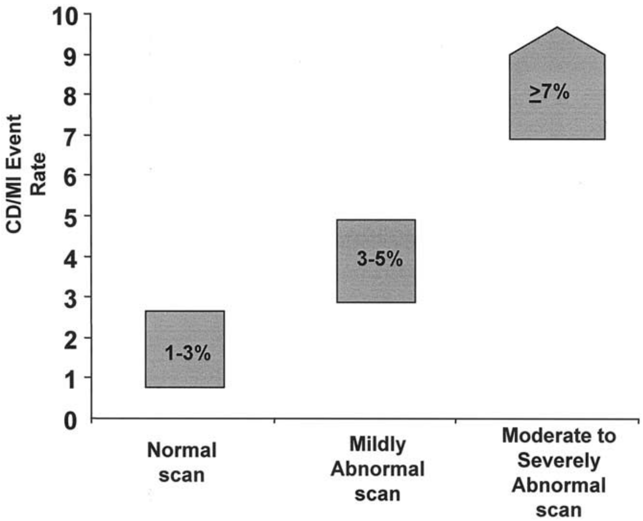

Figure 3 Cardiac event rates among patients with diabetes as a function of scan abnormality. (Reprinted with permission from Kang X, Berman DS, Lewin HC, et al: Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. Am Heart J 138:1025-1032, 1999.)

cardiac catheterization for the detection of ≥50% coronary stenosis.[55] A growing body of evidence demonstrates clinical value in using stress MPI in the evaluation of the diabetic patient with symptoms or other conditions suggested of CAD.

MPI in the Risk Assessment of Patients With Diabetes Mellitus

Using stress imaging to risk stratify diabetic patients has been shown to be especially beneficial. While it is known that abnormal stress thallium studies are associated with greater cardiac events than a normal scan, more recent data have shown the ability to successfully risk stratify diabetic patients according to defect size and extent, finding that as with the general population, the larger the defect size, the greater the risk for a coronary event.[38,55] In a cohort of 1271 diabetic patients and 5862 non diabetic patients, Kang and colleagues assessed prognosis based on defect extent and severity. Similar to studies in the general population, the coronary event risk was directly associated with the extent and severity of perfusion abnormality on myocardial perfusion imaging[55] (Fig. 3).

Recent data from Giri and colleagues demonstrated excellent utility of stress MPI in diabetic patients by showing the additional prognostic value of MPI in the risk assessment of the diabetic patient with suspected CAD. In a cohort of 2826 patients (589 with diabetes mellitus) who underwent adenosine SPECT MPI, Berman and colleagues found that adenosine MPI results provided incremental prognostic value over clinical variables. Patients with an abnormal perfusion scan who had insulin-dependent diabetes mellitus were at greater risk for cardiac death than noninsulin-dependent diabetics with an abnormal perfusion scan[61] (Fig. 4). For predicting either cardiac death alone or cardiac death combined with nonfatal myocardial infarction, data from MPI is a better predictor of cardiac events than the presence of diabetes in combination with clinical risk.[38,61] These studies demonstrate that in the diabetic patient with suspected CAD, stress MPI provides incremental prognostic value compared with clinical variables alone.

MPI in Women With Diabetes

Women with diabetes have an increased risk of cardiovascular death that is 7.5 times higher times that of a woman

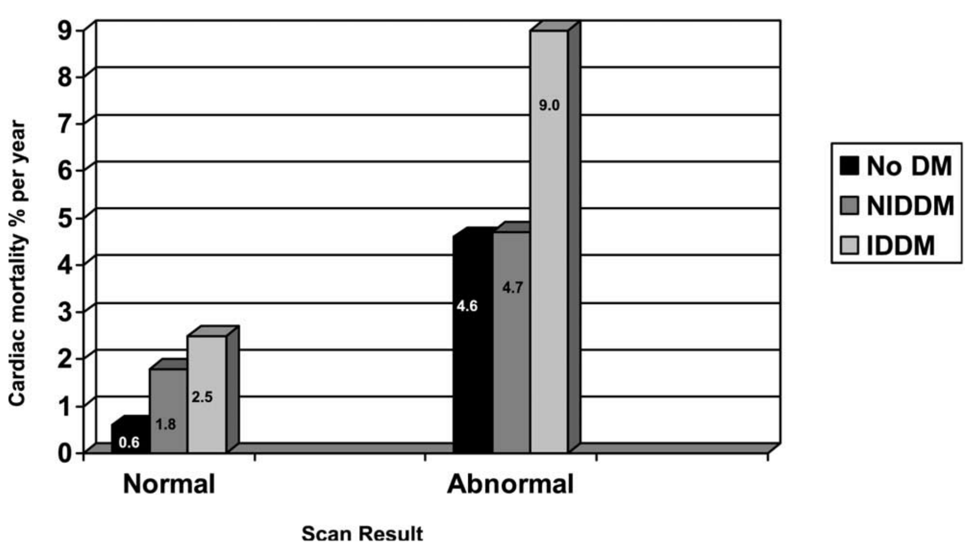

Figure 4 Cardiac mortality in patients without diabetes mellitus, noninsulin-dependent diabetes mellitus, and insulin diabetes mellitus. (Reprinted from Berman DS, Kang X, Hayes SW, et al: Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 41:1125-1133, 2003, with permission from the American College of Cardiology Foundation.)

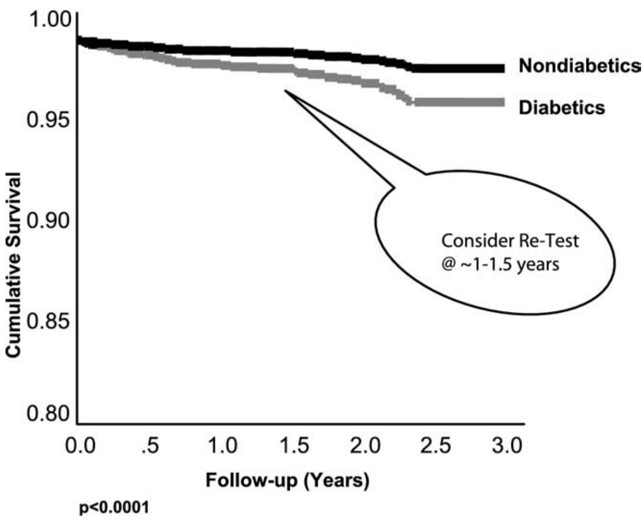

Figure 5 Kaplan–Meier survival curves comparing the subset of diabetic and nondiabetic patients with a normal stress. (Source: Giri S, Shaw LJ, Murthy DR, et al: Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 105:32-40, 2002.)

without diabetes as a result of losing the premenopausal protection seen in those women without diabetes. There are additional considerations for women with diabetes and the use of stress SPECT imaging. Giri and coworkers demonstrated that[38] the presence and extent of perfusion abnormalities were the strongest predictors of cardiac events among diabetic women, with a significantly higher number of events in diabetic versus nondiabetic women. Among the cohort of women in this study, the estimate of ischemic burden with stress myocardial perfusion imaging significantly improved risk stratification compared with the presence of diabetes and clinical risk.[61-64]

Recommendations for Stress MPI in the Clinical Management of Patients With Diabetes

As evidenced by a growing body of data, stress MPI has significant diagnostic and prognostic value in the diabetic patient with suspected CAD because the results of the perfusion study can be used in the day-to-day clinical management. In the diabetic patient with a normal MPI, aggressive risk factor modification and medical management can be implemented with an earlier time to retesting when compared with the nondiabetic population[38] (Fig. 5), whereas the diabetic patient with a moderate-to-high risk scan should be referred immediately for more aggressive, invasive management. SPECT myocardial perfusion imaging provides perfusion and function imaging that has incremental prognostic value in the clinical management of symptomatic diabetic patients (Fig. 5).

The Role of MPI in Patients with Congestive Heart Failure (CHF)

Background

The American Heart Association estimates that 4.7 million Americans have CHF and that 400,000 new cases will be diagnosed in the coming year. Heart failure is the leading cause of hospitalization in people older than the age of 65, and the risk of developing the disease increases with age. The risk of developing heart failure is slightly greater in men than in women. African Americans are twice as likely to acquire the disease as Caucasians, and mortality from the disease is also twice as great in this group. Since the 1970s, heart failure has been on the increase because the number of people 65 or older has increased. Approximately 20% of CHF patients will die within 1 year of diagnosis, and 50% will die within 5 years.[2]

CHF is in itself not a diagnosis. Rather it is the physiological result of damage to the heart caused by some underlying condition. Therefore, it is not enough to say that a person has CHF. CHF must be caused by some underlying process, and the diagnosis of that process is important in terms of treatment and prognosis. The most common etiology of heart failure is ischemic cardiomyopathy, which accounts for 60% to 70% of case and, of these, most patients have viable but dysfunctional myocardium. MPI offers 2 vital roles in these patients in that help one to detect the presence or absence of underlying CAD and to assess any possible hibernating and viable myocardium.[65]

There has been a considerable amount of evidence demonstrating the effectiveness of MPI using both thallium (^{201}Tl) and technetium (^{99m}Tc) as they provide insight into the etiology of heart failure. They effectively detect the presence of hibernating or chronically ischemic myocardium with a high specificity and sensitivity.[66-68] They also help identify the presence of nonischemic cardiomyopathy as the etiology of CHF.[69]

MPI in the Detection of CAD and Impact on Prognosis in CHF

The major parameters that influence prognosis and treatment strategies in the patient with heart failure include (1) LV function and remodeling, (2) the contribution of myocardial ischemia from CAD, and (3) the presence of viable myocardium.[70] This section will specifically address the role of MPI in the detection of CAD and the assessment of myocardial viability in the clinical evaluation of the patient with heart failure.

Determining whether LV dysfunction is caused by the consequences of CAD or to one of the many other etiologies included in the term “nonischemic cardiomyopathy” is a crucial step in determining the management strategy for the patient with heart failure.[70] Limited data, from the 6 published studies in the literature,[70,71] report that the sensitivity of MPI for detecting CAD in a patient with CHF and LV dysfunction is 100%. The ability of MPI to identify significant

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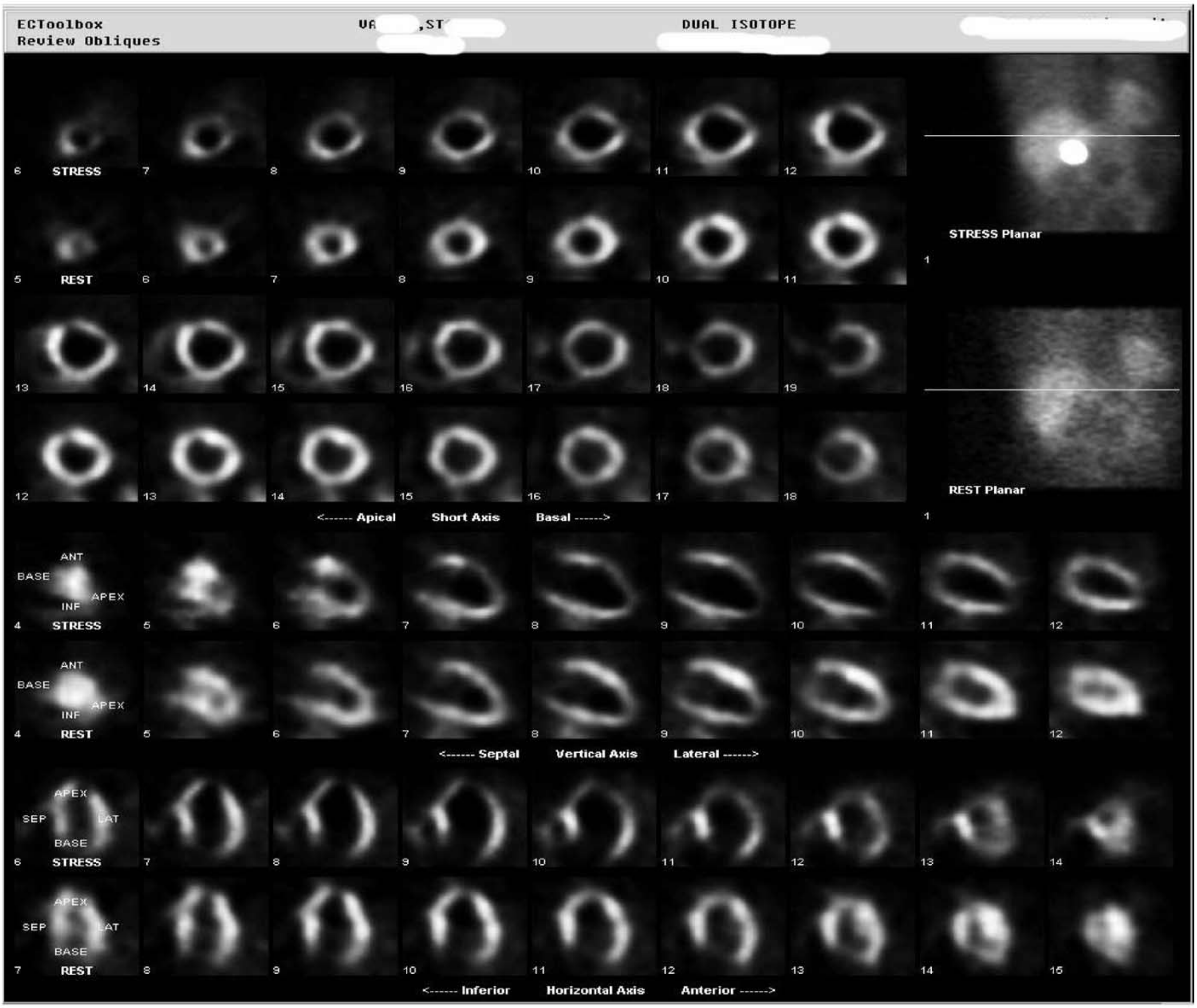

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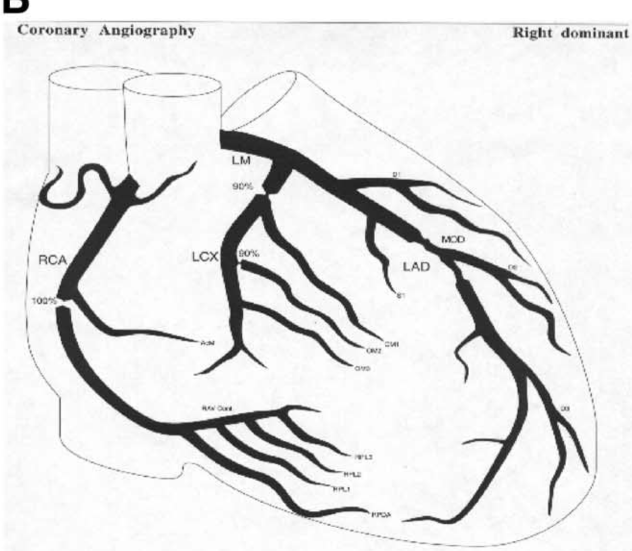

Figure 6 (A) Case of a 66-year-old diabetic man with a history of an enlarged heart and no history of myocardial infarction who was admitted to the hospital with a 3-month history of worsening, exertional dyspnea, and new onset CHF. MPI demonstrates a dilated left ventricle with a moderate amount of stress-induced ischemia of the apical, distal anterior, distal inferior, distal septal and anterolateral walls. (B) Schematic of cardiac catheterization after stress MPI confirmed significant CAD with an occluded right coronary artery, moderate complex lesions in the mid-left anterior descending artery, and 90% stenosis of both the proximal left circumflex and obtuse marginal 2. This patient was referred for coronary artery revascularization with bypass graft surgery.

CAD in the setting of LV dysfunction likely the result of there being a moderate-to-large amount of inducible ischemic or hibernating myocardium in these patients. The negative predictive value for predicting the absence of significant CAD was 100%.[70] The frequent false positive studies, caused by perfusion defects in patients with normal epicardial coronary arteries and nonischemic cardiomyopathy, has resulted in a modest specificity in the 40% to 50% range for myocardial perfusion imaging studies. The perfusion abnormalities, fixed and reversible defects, noted in patients with heart failure and nonischemic cardiomyopathy are most likely the result of the territories of myocardial fibrosis and/or abnormalities in coronary blood flow reserve in the absence of epicardial CAD.[72-74]

Although the presence of a perfusion abnormality in the patient with heart failure may not be highly specific for CAD, the pattern of perfusion abnormality can aid in differentiating between ischemic and nonischemic etiology of heart failure.[69,71,75] Data using gated SPECT MPI have shown that patients with heart failure and ischemic cardiomyopathy have more extensive and more severe defects than those with nonischemic cardiomyopathy.[69] In a recent retrospective analysis, Miller and colleagues demonstrated a high mortality rate at 5-year follow-up in patients with large perfusion defects (fixed or reversible) who had an ischemic etiology of heart failure. In this group, patients with heart failure and no perfusion defects had more favorable outcomes.[76]

The magnitude of perfusion defects in patients with heart failure due to nonischemic cardiomyopathy has been shown to affect outcome. A worse outcome has been observed in patients with nonischemic cardiomyopathy and extensive perfusion abnormalities, whereas patients with a normal perfusion pattern had a more benign outcome.[77] In summary, these data point to the fact that the use of gated SPECT MPI can be useful in the early assessment of patients with heart failure and LV systolic dysfunction and aid in determining if coronary artery disease is the etiology of heart failure, as illustrated in the following case.

Figure 6A is an example of a 66-year-old man who was admitted to the hospital with new onset heart failure and had a history of cardiomyopathy on chest x-ray. He had no documented history of CAD. The MPI study was instrumental in defining the etiology of heart failure.

Detection of Viable Myocardium in the Setting of CHF

The major question in the patient with heart failure caused by CAD and LV dysfunction is whether or not to proceed with coronary artery revascularization for improvement in symptoms and outcome. The identification of reversible myocardial dysfunction (ie, hibernating or stunned myocardium) is an important finding in the patient with coronary artery disease, LV systolic dysfunction, and CHF. The presence of viable myocardium can aid in the decision to proceed to coronary revascularization, as areas of hibernating or stunned myocardium contain preserved cell membrane integrity despite abnormal myocyte contractility, and the contractibility that can be restored after improvement in blood flow. There is now a large body of evidence to support the use of various protocols using MPI to detect viable myocardium and to predict improvements in regional function in patients with ischemic LV dysfunction.[78,79] A 1997 meta-analysis by Bax and colleagues found that all of the radionuclide techniques, which include, MPI with rest/redistribution ^{201}Tl, rest ^{99m}Tc sestamibi, ECG-gated SPECT sestamibi imaging, as well as stress/redistribution/reinjection ^{201}Tl imaging, predicted improvement in regional and global LV function after revascularization.[78] Using the quantitative analysis of regional tracer uptake as a correlation of the magnitude of viable myocardium, all myocardial perfusion techniques have similar negative and positive predictive value for predicting improvement in regional myocardial function.[78] SPECT perfusion imaging with ^{201}Tl and ^{99m}Tc sestamibi are slightly more sensitive than dobutamine echocardiography, but the latter has a higher specificity.[78]

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