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Cardiovascular risk stratification of diabetic patients

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Diabetes mellitus is a complex clinical entity that will grow in importance in the future. The complications of diabetes have a significant impact on patient survival and quality of life, particularly with respect to coronary artery disease (CAD). Appropriate screening and aggressive intervention can significantly benefit many patients with diabetes. In addition, it is important to consider strategies useful not only in the diagnosis of CAD but also in the prognostic evaluation of diabetic patients with coronary disease. Prognostic data are essential in defining risk categories and to apply appropriate treatment for the degree of risk. Therefore, accurate cardiovascular risk stratification of patients with type 2 diabetes is required. However, this can be a problematic issue because the clinical presentation and progression of CAD differs between diabetic and nondiabetic subjects. In addition to a higher prevalence of CAD, patients with diabetes experience more diffuse and extensive coronary artery involvement, more often have left ventricular dysfunction, a more advanced coronary disease at the time of diagnosis, and more often experience silent ischemia. Furthermore, diabetic patients have frequently a less favorable response to revascularization procedures and a poorer long-term outcome. The purpose of this review is to discuss the relative role of various procedures for diagnosis of CAD and for cardiac risk stratification in patients with diabetes.

Key words: **Diabetes mellitus - Prognosis - Cardiac-gated imaging techniques.**

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Diabetes mellitus is a complex clinical entity that will grow in importance in the near future.[1, 2] Currently, more than 200 million subjects are affected by diabetes and it is expected that its prevalence will be over 350 million in twenty years.[3] The rise in the number of cases of diabetes has reflected the changes in the incidence of obesity. In addition, the incidence of diabetes increases with age and, therefore, the aging of the population will importantly contribute to a greater number of cases.[2] The complications of diabetes have a significant impact on patient survival and quality of life, particularly with respect to cardiovascular disease. Coronary artery disease (CAD), stroke, peripheral vascular disease, cardiomyopathy, and congestive heart failure are all forms of cardiovascular disease that are increased in diabetic patients.[4] Type 2 diabetes is considered as cardiovascular disease equivalent and diabetic patients have a higher risk of cardiovascular events than nondiabetic patients.[5] Cardiovascular diseases are the most common cause of mortality in diabetic patients.[6, 7] The overall prevalence of CAD, as derived from a range of diagnostic methods, is reported to be as high as 55% in diabetic patients compared with 2-4% in the general population.[8] In addition to the usual risk factors for CAD, diabetes adds another dimension to the risk. Approximately 20-25% of patients presenting with acute coronary syndromes or for percutaneous coronary intervention have diabetes.[9] Because CAD risk can be modified by intervention, it is important to be aware of the effect of diabetes in the development of coronary disease in diabetic patients. Appropriate screening and aggressive intervention can significantly benefit many patients with diabetes. In addition, it is important to consider strategies useful not only in the diagnosis of CAD but also in the prognostic evaluation of diabetic patients with coronary disease. Prognostic data are essential in defining risk categories; once the risk is assessed, appropriate treatment for the degree of risk can be applied. Therefore, accurate cardiovascular risk stratification of patients with type 2 diabetes is required. However, this can be a problematic issue because the clinical presentation and progression of CAD differs between diabetic and nondiabetic subjects. In addition to a higher prevalence of CAD,[8] patients with diabetes experience more diffuse and extensive coronary artery involvement, more often have left ventricular dysfunction, a more advanced coronary disease at the time of diagnosis, and more often experience silent ischemia. Furthermore, diabetic patients have frequently a less favorable response to revascularization procedures and a poorer long-term outcome. The purpose of this review is to discuss the relative role of various procedures for diagnosis of CAD and for cardiac risk stratification in patients with diabetes.

Diabetes and cardiovascular disease

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes mellitus.[7, 10] Compared with CAD in nondiabetic patients, coronary disease in diabetic patients is more advanced at diagnosis and is generally characterized by more extensive atherosclerosis and higher rates of left ventricular dysfunction and cardiac events.[11, 12] In diabetic patients, myocardial ischemia is more extensive, frequent, and silent than in nondiabetic patients.[7] The pain response to ischemia is often absent or blunted in individuals with diabetes, resulting in a lack of symptoms or in an atypical presentation.[7] The first sign of CAD in diabetics may be acute myocardial infarction or cardiac death; the myocardial infarction also may be silent.[11] At the time of diagnosis of CAD or first myocardial infarction, multivessel involvement is more frequently seen in diabetic patients as compared to nondiabetic patients.[10] The prognosis of CAD is less favorable in diabetic patients than in nondiabetic patients and post- myocardial infarction mortality is higher for the diabetic group. After a first event, the 1-year mortality rate is 44% for diabetic men and 37% for diabetic women compared to 33% for nondiabetic men and 20% for nondiabetic women.[12]

Cardiovascular risk in patients with diabetes

With diabetes, there is a two- to four-fold increase in the risk of cardiovascular events.[11] Both type 1 and type 2 diabetes are independent risk factors for CAD,[7] and diabetic patients have a greater morbidity and mortality after myocardial infarction than do nondiabetic patients.[11] The presence of type 2diabetes confers the same risk of cardiac events as the presence of pre-existing cardiovascular disease.[13] Giri *et al.*[14] evaluated 4755 patients symptomatic for CAD by with the use of stress myocardial perfusion imaging, followed for 3 years. The rates of cardiac events and procedures in the 929 diabetic patients were compared with the rates in the 3826 nondiabetic patients. Diabetic patients had higher event (death and myocardial infarction) rates than nondiabetic patients. Rates of percutaneous transluminal coronary angioplasty were slightly higher, while rates of coronary artery bypass graft surgery were

TABLE I.—*Risk factors for coronary artery disease.*

Traditional risk factors	Diabetes-specific risk factors
Diabetes	Albumin level
Hypertension	Fibrinogen level
Dyslipidemia	von Willebrand factor level
Obesity	Factor VIII activity
Smoking	Leukocyte count
Sedentary life-style	C-reactive protein
Interleukin-6	Lipoprotein-associated phospholipase A2

significantly (P<0.0001) higher in diabetic compared to nondiabetic patients. These results clearly demonstrate the increased risk of events in diabetic patients.[14]

The traditional risk factors for CAD are well documented (Table I). Diabetic patients have a higher prevalence of traditional CAD risk factors compared to those without diabetes.[11] The traditional risk factors accounts for less than half of the excess mortality seen in diabetes, making diabetes itself an independent risk factor for CAD.[11] Some risk factors are modifiable, and intervention is effective in reducing risk.[1] However, more recent investigations have indicated the role of other risk factors in the development of CAD in diabetic patients (Table I). In particular, levels of albumin, fibrinogen, and von Willebrand factor; factor VIII activity; and leukocyte count were predictors of coronary heart disease among persons with diabetes.[15] These associations may reflect 1) the underlying inflammatory reaction or microvascular injury related to atherosclerosis and a tendency toward thrombosis or 2) common antecedents for both diabetes and CAD. If any of these factors are modifiable, intervention may further reduce the risk of CAD in diabetic patients. However, their actual role and potential treatment require further investigation.

CAD in diabetic patients

Factors that differentiate CAD in diabetic patients may provide evidences to the differences in prognosis for this population as well as indicate CAD testing limitations. In diabetic patients, CAD may be associated with generalized endothelial dysfunction and small-vessel abnormalities in addition to the larger-vessel abnormalities seen in nondiabetic patients with CAD.[11, 16, 17] In a recent study, Storto *et al.*[17] assessed coronary flow reserve by sestamibi imaging in patients with type 2 diabetes without CAD and with normal coronary vessels at angiography. Myocardial blood flow under resting conditions was not different in control subjects versus patients. Conversely, stress myocardial blood flow was higher in control subjects than in patients (P<0.01). Thus coronary flow reserve was higher in control subjects than in diabetic patients (2.40±0.3 vs 1.36±0.8, P<0.0001). These results demonstrate that type 2 diabetic patients without a history of CAD and with normal coronary arteries have impaired coronary vascular function in response to dipyridamole-induced hyperemia.[17] Pathologic studies have demonstrated that the coronary arteries in diabetic patients with CAD show diffuse disease in contrast to the more localized involvement often seen in nondiabetic patients.[11] Diabetic patients with CAD demonstrate increased morbidity and mortality rates from myocardial infarction as well as increased risks for recurrent infarction, congestive heart failure, cerebrovascular disease, and peripheral vascular disease, leading to the poor prognosis associated with CAD in diabetic patients.[7, 8, 11] Silent or asymptomatic myocardial ischemia has a prevalence of 10-20% in the diabetic population.[18] The prevalence of asymptomatic CAD in patients with type 2 diabetes is significant and has been reported to range from 10-12%.[18-20] Differences in the prevalence of asymptomatic CAD in diabetics may relate to the populations studied, evaluation methods used, or number of years that a patient has had diabetes.

American Diabetes Association Indications for cardiac testing of the diabetic patients

The American Diabetes Association (ADA) has developed a list of indications (Table II)

TABLE II.—*American Diabetes Association indications for cardiac testing in diabetic patients.*

Patients with signs or symptoms of CAD
Patients with peripheral or carotid vascular occlusive disease
Patients ≥35 years of age with a sedentary life-style before beginning a exercise program
Patients with 2 or more of the following risk factors in addition to diabetes — Elevated cholesterol and LDL, or low HDL —Elevated blood pressure — Smoking — Family history of premature CAD — Positive microalbuminuria/macroalbuminuria test result

CAD: coronary artery disease; LDL: low-density lipoproteins; HDL: high-density lipoproteins.

TABLE III.—*American Diabetes Association recommendations for evaluation of diabetic patients.*

Patients with symptoms
Asymptomatic patients at increased risk of CAD
Reevaluation at least annually if symptoms or risk changes

CAD: coronary artery disease.

for cardiac testing in diabetic patients to aid in identification of patients who would be considered at higher than average risk of cardiac events.[11] Symptomatic patients and those with findings suggestive of ischemia and infarction at electrocardiogram (ECG) should be evaluated. Patients with peripheral or carotid vascular disease, including those with claudication and transient ischemic attacks, are likely to have generalized occlusive disease with a high incidence of coexisting CAD that justifies cardiac testing. Sedentary diabetic patients ≥35 years of age should be tested prior to initiating an exercise program. Indeed, exercise has beneficial effects but could also trigger symptoms. Risk factors for CAD are additive; the presence of multiple risk factors in a patient substantially increases risk, particularly in diabetic patients who already have a great risk for CAD. At present, data indicate that the presence of two risk factors such as elevated cholesterol and low-density lipoprotein levels or a low high-density lipoprotein level, elevated blood pressure, smoking, family history of premature CAD, or microalbuminuria and/or macroalbuminuria, in addition to diabetes, is an indication for testing.

The ADA has reviewed the problem of diagnosing CAD in diabetic patients and issued a consensus document with recommendations (Table III) that are based on the great body of knowledge on CAD and its prevention and treatment in mixed populations in whom diabetes is prevalent.[11] Patients with symptomatic disease require evaluation upon presentation. With asymptomatic diabetic patients, evaluation should occur when an increased risk is recognized. Recommendations on screening asymptomatic patients are made on the basis of current information on CAD and diabetes, since data from controlled studies are currently lacking. The ADA consensus panel assumed that asymptomatic diabetic patients identified as having CAD by noninvasive testing were at substantial risk. Framingham Study data suggest that even asymptomatic diabetic patients with multiple risk factors have an ~3% per year incidence of cardiac events,[11] as would be expected from the high incidence of silent ischemia. Annual reevaluation is suggested to monitor the development or progression of risk factors that would indicate the need for cardiac testing.[1] In addition, if risk increases or symptoms change, reevaluation should be considered. At a minimum, evaluations should be performed every 2-3 years, depending on the actual annual risk of events.

Potential benefits of CAD screening in diabetic patients

Identification of diabetic patients early in the course of CAD allows risk stratification when the disease process is more likely to be modifiable. Patients at low risk of events can be managed medically without further unnecessary testing, while patients with advanced disease can undergo revascularization procedures that could prolong life. Diagnosis of CAD provides an incentive that improves compliance with risk factor intervention and treatment regimens.[21] Aggressive use of “secondary” interventions to address risk factors for CAD has been proven to reduce associated morbidity and mortality.[10] Since the presence of diabetes confers a risk similar to that of established CAD, it has been suggested that all diabetic patients be treated as if they have coronary disease.[10] Because of the known potential benefits of early diagnosis and treatment in diabetic patients, there is a growing interest in appropriate evaluation of asymptomatic patients, many of whom have silent disease.[22] However, the clinical role is not precisely defined due to lack of outcome studies in diabetic patients. As reported above, the ADA guidelines [11] recommend to testing patients with symptoms suspicious of CAD and patients with no symptoms and ≥2 risk factors.[11] However, it has been recently demonstrated by the DIAD study that the rate of high-risk SPECT scans is similar in patients with ≥2 versus <2 risk factors.[23] Therefore, in DIAD study selecting only patients who met ADA guidelines would have failed to identify 41% of patients with silent ischemia.[23] DIAD study assessed the prevalence and clinical predictors of silent myocardial ischemia in asymptomatic patients with type 2 diabetes mellitus.[23]

Studies currently under way will further define the role of screening and determine the clinical and economic benefit. To date, several well-powered studies have demonstrated that stress myocardial perfusion single-photon emission computed (SPECT) yields incremental prognostic value over pre-SPECT data, enhances risk stratification, and, when, applied to appropriate patient populations, reduces costs, in part by decreasing the need for additional invasive evaluation.[24-29] It can be hypothesized that a Bayesian approach could be more effective for identify which diabetic patients should undergo myocardial perfusion imaging. Thus, in patients with diabetes the use of an aggregate score incorporating and weighting multiple risk factors could be superior to an approach based on the number of risk factors to define the patient's risk.[29, 30] To classify patients in different risk subsets, the likelihood of CAD can be calculated by CADENZA.[31] The pre-scan likelihood of CAD can be analyzed as aggregate descriptors of proven prognostic importance based on Bayesian analysis of the patient data listed in Table IV. In addition, evaluating how the risk changes over time as a function of patients' characteristics and test results, might help to guide therapeutic decision and to determine the timing to retest the patients during the follow-up.[32, 33] It is within this context that the Impact of inDucible Ischemia by Stress SPECT (IDIS) trial was conceived.[34] IDIS is a prospective, multi-center trial designed: 1) to evaluate the prevalence of inducible ischemia by SPECT in symptomatic and asymptomatic diabetic patients with different pre-scan likelihood of ischemia; 2) to determine the number of patients who were reclassified with respect to their risk of adverse outcomes by the addition of SPECT data to pre-SPECT information; and 3) to prospectively evaluate subsequent patient outcome during long-term follow-up.[34] In particular, the temporal characteristics of cardiac risk in diabetic patients undergoing stress SPECT will be assessed by parametric survival model, estimating time to pre-defined risk and the level of risk at specific time intervals during the follow-up. These times might represent the warranty period before re-testing diabetic patients. To date, a total of 1006 patients have been enrolled in the IDIS trial, and the preliminary results indicate that the majority of patients (N.=577,

TABLE IV.—*Patient data used for the analysis of the pre-scan likelihood of coronary artery disease.*

Patients with signs or symptoms of CAD
Age
Gender
Presenting symptom
Blood pressure
Smoking history
Serum cholesterol
Glucose intolerance
Family history of coronary artery disease
Rest ECG characteristics
Results of ECG stress testing
— Heart rate
— Blood pressure
— Duration
— Magnitude and slope of ST segment changes
— Exertional hypotension

57% of the total) have abnormal SPECT findings.

The rate of major cardiovascular events for diabetic patients with myocardial infarction is significant. The Finnish Monitoring International Cardiovascular Disease (FINMONICA) study [12] reported a case fatality rate of 45% in diabetic men and 39% in diabetic women, which was significantly higher than the rate of 38% in nondiabetic men and 25% in nondiabetic women. Of the patients who died, 50% of men and 25% of women died prior to hospitalization. This population would not largely benefit from secondary prevention. Thus, this situation stresses the importance of early detection of CAD and aggressive management of cardiovascular risk factors in reducing fatality rates.[10]

Test options in diabetic patients

Diabetic patients are at risk of underlying CAD even in the presence of normal resting ECG and, therefore, further evaluation is required. Additional procedures are needed for diagnostic purposes to document the presence or absence of CAD and to determine the severity of the disease and the location of ischemic vessels.[35] Prognostic information is also necessary to estimate the risk of future cardiovascular events. Treatment planning is based on the presence or absence of CAD and the risk of future cardiac events. Various invasive and noninvasive procedures can be used for the cardiac evaluation of diabetic patients with known or suspected CAD (Table V). Nuclear cardiology is the most widely used noninvasive approach, with positron emission tomography (PET) and SPECT imaging, for the assessment of myocardial perfusion and inducible ischemia. The recent introduction of atherosclerosis imaging modalities, such as computed tomography (CT) for coronary artery calcium, may enhance risk stratification, particularly in uncomplicated and asymptomatic diabetic patients.[36, 37] CT based techniques also allow noninvasive imaging of coronary arteries. Although the accuracy of available methods for evaluating coronary anatomy is excellent, current debates focus on their role in clinical practice. With CT based techniques the assessment of diffuse atherosclerosis without ischemia may target preclinical disease. Recently, extensive research is currently being performed in the development of noninvasive coronary angiography using cardiac magnetic resonance (MR). Finally, techniques combining the evaluation of coronary anatomy and myocardial perfusion are quickly developing and it is possible to have a complete assessment of CAD with a single exam. The clinical challenge is to determine the most appropriate and cost-effective tests for the diabetic patients.

TABLE V.—*Test options for cardiac evaluation of diabetic patients.*

Cardiac catheterization
Exercise stress testing
Functional imaging
— Stress echocardiography
— Stress myocardial perfusion imaging (SPECT and PET)
— Magnetic resonance imaging
Anatomical imaging
— Multislice CT
— Electron beam CT
— Magnetic resonance imaging
Hybrid imaging
— SPECT/CT
— PET/CT

SPECT: single-photon emission computed tomography; PET: positron emission tomography; CT: computed tomography.

Cardiac catheterization

Invasive angiography is currently considered the "gold standard" for detection of CAD. Both spatial (0.2 mm) and temporal (5 ms) resolutions of the technique are high, and the degree of luminal narrowing can be quantified accurately. However, this test is invasive and associated with a measurable risk. Catheterization provides primarily anatomic information and information on the degree of stenosis, but it does not provide information on perfusion to the same extent as myocardial perfusion imaging. Information on cardiac function can be obtained, but less invasive methods of obtaining the same information are available. Catheterization does not provide detailed validated information on risk stratification and physiology. Current practice is to reserve catheterization for patients with unstable disease or patients with known CAD who are candidates for revascularization. Thus, catheterization cannot be used as a first-line test in diabetic patients.

Exercise stress test

ECG exercise stress testing alone is not indicated because it is unlikely to provide information related to abnormalities of perfusion and function present in the early stages of disease. An ECG stress test may not answer the clinical questions relevant to patients at intermediate risk of CAD, i.e. presence and severity of disease and risk of future myocardial infarction. The ECG exercise stress test has a lower incremental value than SPECT for risk stratification, especially if gated SPECT is used.[38] In addition, in patients not able to exercise to maximal capacity there is a decrease of test sensitivity. ECG changes and angina symptoms occur at the end of the ischemic cascade and a negative result with exercise stress test does not exclude CAD. Finally, the diagnostic accuracy of this test has been demonstrated to be low in patients with diabetes.[39]

Stress echocardiography

Stress echocardiography is a noninvasive test that expands the use of echocardiographic techniques. This procedure is used to assess systolic wall motion. Both physical exercise and pharmacological stress can be used. Resting wall motion abnormalities mainly represent infarcted myocardium, while those induced by stress reflect ischemia.

DIAGNOSTIC ACCURACY

In the general population, the sensitivity and specificity of exercise echocardiography for the detection of CAD, as compared with invasive angiography, are 84 and 82%, respectively.[40] The sensitivity and specificity of dobutamine stress echocardiography are 80% and 84%, respectively.[40] The sensitivity and specificity for dipyridamole stress echocardiography (71% and 93%, respectively) appear comparable.[41] Therefore, under ideal conditions, the diagnostic accuracy of stress echocardiography is similar to that of stress SPECT in the general population. However, this procedure is operator dependent, necessitating a skilled technical staff. In addition, exercise stress is technically difficult. Unless imaging is performed immediately post-stress, the sensitivity of the test may be compromised. For this reason, pharmacologic stress is generally preferred. In a recent study, Ferro *et al*.[42] directly compared the interpretive reproducibility of stress echocardiography and SPECT in the same patients undergoing simultaneous pharmacologic stress imaging after uncomplicated acute myocardial infarction (Figure 1). Intraobserver agreement percentages in the identification of patients with ischemia were 98% for SPECT and 91% for stress echocardiography (P=NS) and κ values were excellent (>0.80) for both techniques. Interobserver agreement was higher (P<0.01) for SPECT (96%) than for stress echocardiography (79%). Similarly, κ value was excellent for SPECT (0.92) and only moderate for stress echocardiography (0.56). The intraclass coefficients of correlation for intra- and interobserver reproducibility were higher for SPECT (0.98 and 0.97, respectively) than for stress echocardiography (0.80 and 0.71, respectively; P<0.001 for both). These results demonstrate that stress SPECT imaging has a better interpretive reproducibility than stress echocardiography.[42]

DIAGNOSTIC ACCURACY IN DIABETIC PATIENTS

Stress echocardiography has not been fully validated in diabetic patients. Studies that addressed the issue of CAD detection with this procedure in patients with diabetes are very limited. Hennessy *et al*.[43] evaluated 52 diabetic patients with dobutamine stress echocardiography and reported a sensitivity of 82% and a specificity of 54%. It is conceivable that the underlying cardiomyopathy associated with diabetes may complicate the interpretation of stress echocardiography studies in the presence of resting wall motion abnormalities.

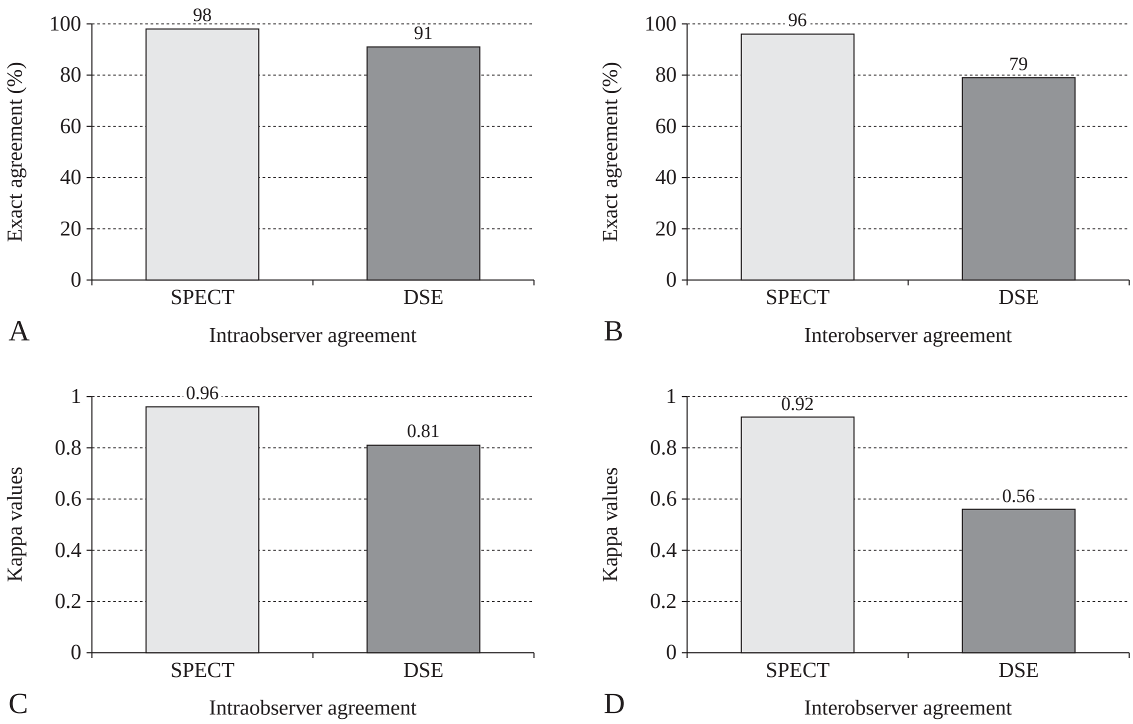

Figure 1.—Intra-observer and inter-observer agreement in the identification of patients with ischemia at stress single-photon emission computed tomography (SPECT) and dobutamine stress echocardiography (DSE) expressed as exact agreement rates (A, B) and k values (C, D).

Prognostic value

Previous studies have demonstrated the prognostic value of stress echocardiography in patients with suspected or known CAD.[44-48] Despite the extensive use of both stress echocardiography and SPECT in the evaluation of myocardial ischemia and viability, the comparative prognostic value of these noninvasive techniques has not been fully defined. Few data have directly compared the value of exercise echocardiography and SPECT for risk stratification in the same patients with suspected or known CAD (49,50). Recently, Acampa *et al.*[51] directly compared the prognostic value of predischarge dobutamine stress echocardiography and dobutamine myocardial SPECT perfusion imaging in 146 patients with prior myocardial infarction. In that study, myocardial ischemia was detectable in 55 (58%) patients at SPECT and in 63 (67%) patients at stress echocardiography. Concordance between SPECT and stress echocardiography in detecting ischemia was observed in 72% of the patients (Figure 2). Ischemia at SPECT was a significant predictor of cardiac events (hazards ratio = 4.8; 95% confidence interval, 1.4-16.3; $P<0.01$). However, ischemia at stress echocardiography (biphasic or worsening patterns) was not associated with events, whereas biphasic pattern alone was associated with a poor outcome compared with direct worsening ($P<0.05$). At Cox multivariate analysis, ischemia at SPECT but not biphasic pattern at stress echocardiography was a significant independent predictor of events ($P<0.01$). These results indicate that, after myocardial infarction, ischemia at SPECT is associated with an increased risk of cardiac events at long-term follow-up, while ischemia at stress echocardiography was unable to stratify patients after myocardial infarction.[51] In another study, Acampa *et al.*[52] enrolled 196 patients who had myocardial infarction and no ischemia on dobutamine stress echocardiography and/or SPECT.

		DSE Positive	DSE Negative
SPECT	Positive	23%	10%
	Negative	18%	49%

Concordance: 72%; κ=0.41

Figure 2.—Concordance between myocardial perfusion single-photon emission computed tomography (SPECT) and dobutamine stress echocardiography (DSE) for the classification of patients as nonischemic (negative) or ischemic (positive).

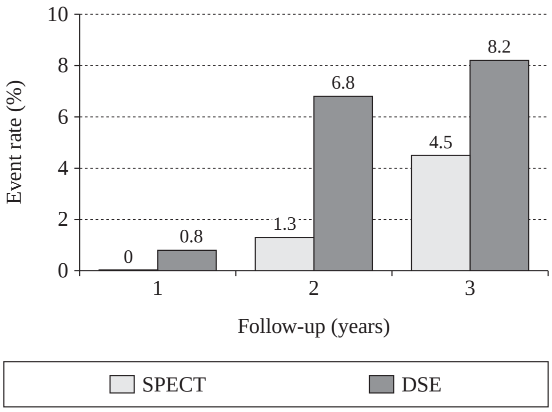

Figure 3.—Annual cardiac event rate in patients without evidence of ischemia at single-photon emission computed tomography (SPECT) or dobutamine stress echocardiography (DSE).

Negative studies were observed in 125 patients on stress echocardiography and in 159 on SPECT. Cardiac events occurred in 14% of patients who did not have ischemia on stress echocardiography and in 9% of patients who did not have ischemia on SPECT. Event-free survival rate was higher in the presence of negative findings on SPECT compared with stress echocardiography ($P<0.05$). The distribution of cardiac events rate over time is depicted in Figure 3. As shown, for the first year of the study follow-up, patients with negative DSE and stress SPECT had the same event rate. Beyond 1 year, patients with negative DSE demonstrated a sharp increase in the incidence of cardiac events. Thus, the lack of residual ischemia on SPECT identifies patients at low risk of events, and a negative finding on stress SPECT is superior to a negative finding on stress echocardiography.

Prognostic value in diabetic patients

The prognostic value of stress echocardiography in diabetic patients has not been fully studied. Hung *et al.*[53] reported that the predictive value of dobutamine stress echocardiography was lower in diabetic patients than nondiabetic patients after acute myocardial infarction. Other studies with evaluated the prognostic value of stress echocardiography in diabetic patients with cardiac symptoms using exercise or pharmacological stress.[54-58] The results of these investigations confirm the higher event rate in the presence of an abnormal study compared with a normal study, similar to nondiabetic patients. Marwick *et al.*[54] evaluated the prognostic value of stress echocardiography in 937 diabetic patients. Survival was related to whether the patients were able to exercise, with those not able having a worse survival. However, in diabetic patients a higher event rate may be observed even in the presence of a normal stress echocardiograhic study. Kamalesh *et al.*[59] performed a follow-up study (mean 25 months) in 233 patients (144 nondiabetic and 89 diabetic) with a negative stress echocardiogram. The diabetic patients had a significantly higher incidence of nonfatal infarctions (6.7% *vs* 1.4%), with a higher annual hard event rate (6.0% *vs* 2.7%). Elhendy *et al.*[55] evaluated 563 patients with diabetes with exercise echocardiography with follow-up of up to 5 years. Although the 1-year event rate was 0%, there was a gradual increase up to 7.6% at the 5-year follow-up. Considering an event rate <1% indicative for a low-risk group, the warranty period of a normal stress echo is 2 years.

Myocardial perfusion imaging

The most widely available technique to assess myocardial perfusion is SPECT using diffusible radiotracers as thallium-201 (Tl-201) or technetium-99m (Tc-99m) labeled agents (sestamibi and tetrofosmin).[60] SPECT is performed at rest and during stress to produce images of regional myocardial blood flow. During maximal exercise or vasodilator stress, myocardial blood flow is typically increased three- to five-fold compared to rest. In the presence of a significant coronary stenosis, myocardial perfusion will not increase appropriately in the territory supplied by the artery with the stenosis, creating heterogeneous uptake. In patients who are unable to exercise, coronary vasodilator agents, such as dipyridamole or adenosine, may be used to increase blood flow.[61] The capabilities of radionuclide techniques to assess myocardial perfusion in the presence of coronary artery stenosis are related to the relationship between myocardial distribution of a perfusion tracer and corresponding regional blood flow. The available SPECT flow agents are characterized by a rapid myocardial extraction and by a cardiac uptake proportional to blood flow.[62-65] Despite Tl-201 has been the most used tracer to assess myocardial blood flow, its physical characteristics are suboptimal. The energy level (69 to 83 KeV) is marginally suitable for imaging with conventional gamma camera and makes some problems for attenuation within the body. The long physical half-life (73 hours) and biological half-life (10 days) lead to a radiation dose to the kidneys and only a small amount (74 to 111 MBq) of Tl-201 can be administered.[60] The energy level (140 KeV) of Tc-99m labeled tracers is ideal for imaging with conventional gamma camera, decreasing problems for tissue attenuation. Moreover, the half-life (6 hours) permits that larger dose can be administered to the patient as compared to Tl-201.[62] It has also been showed that both sestamibi and tetrofosmin tomography yield images of comparable quality and provided similar results in the identification of patients with CAD and in the detection of the individual stenosed coronary vessels.[66]

Diagnostic accuracy

The accuracy of stress myocardial perfusion imaging with SPECT has been validated in several clinical studies in a wide range of populations and with a range of stress protocols.[67] Based on pooled analysis, the mean values for sensitivity and specificity of SPECT for detection of CAD (defined typically as >50% stenosis on coronary angiography) are 88±8% and 82±11%, respectively, as compared with invasive angiography.[68] Although SPECT is very sensitive, specificity is relatively lower.[69] One of the causes of reduced specificity is the occurrence of artifacts due to soft tissue attenuation. Dedicated hardware and software programs have been developed to allow direct reconstruction of attenuation-corrected images based on measurements of the attenuation distribution profile.[70] The use of ECG-gated imaging, allowing simultaneous assessment of myocardial perfusion and ventricular function, has led to further improvement of the diagnostic accuracy of SPECT. In addition, gated SPECT may be useful to differentiate ischemic from nonischemic cardiomyopathy.[71] The most recent nuclear medicine computer systems allow complex procedures, such as image reconstruction, quantification and display, to be performed rapidly. Because the tomographic projections are easily–standardized from patient to patient, quantification of myocardial tomograms and comparison to normal limits, established in population of healthy subjects, can be accomplished. Quantification makes possible to document objectively specific patterns of abnormal perfusion or soft-tissue attenuation, suspected from subjective image interpretation. A further advantage of quantification approach is the standardization of image interpretation resulting in a reduction of intra- and interobserver variability.[68]

Diagnostic accuracy in diabetic patients

There are important differences in the appearance of CAD in diabetic patients that may have an effect on the diagnostic accuracy of tests when used specifically in this group. Because the manifestations of CAD in diabetic patients could have a potential effect on the specificity and accuracy of myocardial perfusion imaging in this population, Kang *et al*.[72] compared the diagnostic value of myocardial perfusion imaging in diabetic patients with that found in nondiabetic patients. In this retrospective study, 203 consecutive registered patients with diabetes and 260 patients without diabetes with known or suspected CAD underwent rest/stress myocardial perfusion imaging with exercise or adenosine. A total of 138 diabetic and 188 nondiabetic patients had coronary angiography within 6 months; the remaining patients in each group had a low likelihood of CAD and were not referred for coronary angiography. The overall sensitivity, specificity, and normalcy rates in diabetic patients were not significantly different from those seen in nondiabetic patients, and were slightly but not statistically better for stenoses ≥70% than for stenoses ≥50%. These data confirm the accuracy of stress myocardial perfusion imaging for the evaluation of CAD in diabetic patients.

Prognostic value

In addition to documenting the presence of ischemia, myocardial perfusion imaging provides information on the potential risk of future cardiac events to allow development of a prognosis. A meta-analysis of 14 studies of risk assessment using myocardial perfusion imaging in patients with stable symptoms included data from more than 12,000 patients.[73] In this evaluation, the annual risk of nonfatal myocardial infarction or death was 0.6% in patients with a normal finding. In contrast, the annual event rate associated with an abnormal finding was 7.4% rate. This prognostic information has great clinical utility in determining which patients are at low risk for cardiac events and for selecting treatment appropriate to this risk. An abnormal image following myocardial perfusion imaging carries the association of a significantly higher cardiac event rate than a normal image. Several investigations also have demonstrated further value of myocardial perfusion imaging by showing that a relationship exists between the extent of the abnormalities and the event rates. In a study by Ladenheim *et al.*[74] using myocardial perfusion imaging, 1689 patients with symptoms suggestive of CAD but without previous myocardial infarction or coronary artery bypass graft were followed for 1 year. Coronary events occurred in 74 patients in the year after testing. Both the extent and severity of hypoperfusion were exponentially correlated with the event rate. The greater the extent of hypoperfusion, the greater the event rate was. The event rate was threefold higher in patients unable to exercise to at least 85% of maximal heart rate for all extents and severities. Characterization of the degree of abnormality can be achieved by a number of visual and computerized quantitative methods to increase the information obtained from myocardial perfusion imaging. The extent of the defect also was found to correlate with risk of cardiac events over time. Machecourt *et al.*[75] studied a total of 1926 patients with stable angina but without previous myocardial infarction or revascularization, using stress thallium imaging and following these patients for an average of 33 months. In patients with a normal study finding, annual total and cardiovascular mortality rates were 0.42% per year and 0.10% per year, respectively. With an abnormal study finding, the total and cardiovascular mortality rates were 2.1% and 1.5%, respectively. The extent of the defect on images provided the best correlation with prognosis. Cardiovascular survival differed according to the number of abnormal segments on the stress myocardial perfusion imaging images, decreasing with an increasing number of affected segments.

The addition of left ventricular ejection fraction information from gated SPECT provides additional prognostic information. In a study by Sharir *et al.*[76] a total of 1680 patients underwent myocardial perfusion imaging and gated SPECT and were followed for an average of 569 days. Evaluation of data according to stress perfusion scores and ejection fraction (<45% and ≥45%) indicated that the ejection fraction provided incremental information in patients with abnormal images. Patients with normal ejection fraction had a significantly lower cardiac death rate than patients with abnormal ejection fraction. Similar findings were seen for end-systolic volume, indicating that both parameters have incremental prognostic value over prescan and perfusion information in predicting cardiac death and provide useful prognostic information in addition to that provided by myocardial perfusion imaging.[76]

The additional information provided by parameters used in CAD has been evaluated, and the contribution of each measured in both the short and long term.[38] The incremental prognostic value of the exercise stress test and thallium-201 SPECT were studied in 1137 patients referred for evaluation of chest pain or suspected silent ischemia. The patients were followed for an average of 72 months. The incremental prognostic value of commonly performed evaluations was evaluated. In the sequence usually available, information on age, gender, symptoms, exercise stress test, SPECT imaging, and determination of number of defects from the myocardial perfusion imaging images each provides additional data over that previously available. Myocardial perfusion imaging, particularly with evaluation of the degree of abnormality, provides important incremental value over that of other approaches.

Prognostic value in diabetic patients

In evaluating 4775 patients symptomatic for CAD with the use of stress myocardial perfusion imaging and following these patients for 3 years, Giri *et al.*[14] compared results of the incremental value of stress myocardial perfusion imaging in a group of 929 diabetic patients. The incremental value of nuclear imaging in diabetic patients was considerable for end points of cardiac death and the combination of cardiac death and/or myocardial infarction. Nuclear imaging provided the greatest incremental value compared with clinical risk and the presence of diabetes, and identified patients at high risk of cardiac events.[14] Thus, nuclear imaging results have important incremental value in diabetic patients similar to that seen in unselected populations. In the same patient populations the unadjusted 3-year survival was lower for diabetic than for nondiabetic patients; however, once adjusted for clinical risk and myocardial perfusion imaging results, survival was similar.[14] The overall 3-year survival by group was 91% for diabetic patients and 97% for nondiabetic patients. In patients with normal scans, the 3-year survival was 96.7% for the diabetic group and 98.5% for the nondiabetic group. In diabetic patients, the risk associated with a normal finding was similar but slightly higher than that for nondiabetic patients. Kang et al.[77] defined event rates and risk for diabetic patients on the basis of SPECT results. Over the follow-up period, patients with diabetes had significantly higher rates of hard events (cardiac death or nonfatal myocardial infarction) (4.3% per year versus 2.3% per year, $P<0.001$) and higher total event rates (hard events and late revascularization) (9.0% per year versus 5.3% per year, $P<0.001$) compared with rates among patients without diabetes. Cox proportional hazards analysis revealed that nuclear testing added incremental value over clinical and historical variables among patients with diabetes ($P<0.001$). The event rates rose significantly as a function of summed stress score and summed difference score among both patients with diabetes and patients without diabetes ($P<0.001$). The patients with diabetes with normal scans had relatively low hard event rates (1% to 2% per year), those with mildly abnormal scans had intermediate hard event rates (3% to 4% per year), and those with moderately to severely abnormal scans had relatively high hard event rates (>7% per year). The results of this study indicated that stress myocardial perfusion SPECT is valuable for risk stratification and management of patients with diabetes.[77]

Coronary calcium imaging

Given that atherosclerosis is the pathologic lesion underlying most clinical manifestations of cardiovascular disease, its direct quantification by imaging tests provide an integrated measure of the pathological effects of cardiovascular risk factors. Anatomical imaging assesses atherosclerosis by direct visualization of the coronary arteries. The modalities available include MR imaging, multislice CT, and electron beam CT. Histological, sonographic, and fluoroscopic studies have showed that the extent of coronary calcification is closely associated with total artery atherosclerotic plaque burden.[78] Coronary calcification is also closely associated with coronary artery plaque on a site-by-site basis.[78] Many studies have shown that coronary artery calcium (CAC) scores predict incident CAD in the general population.[79] No prior patients preparation or interruption of medication is generally required for coronary calcium imaging. A large observational study by Raggi *et al.*,[80] comprising 903 diabetic patients and 9474 nondiabetic low-to-intermediate risk subjects, demonstrated that diabetic patients with no detectable CAD had an excellent 5-year survival, which was not significantly different to nondiabetics (98.9% and 99.4%, respectively, corresponding to an annual mortality rate of 0.36% and 0.12%; P=0.05), implying that coronary calcium continues to be a robust prognostic marker even in the presence of type 2 diabetes. This study also showed that all-cause mortality in asymptomatic patients with diabetes increased in proportion to their baseline CAC scores. Consequently, a risk stratification approach using the combination of CAC scores and clinical variables was superior to each individually. Moreover, an alternative and more recently evolving strategy for enhancing the clinical- and cost-effectiveness of myocardial perfusion imaging in asymptomatic diabetic patients is to perform CAC imaging to identify those patients with subclinical CAD. Using this approach, Anand *et al.*[37] have prospectively evaluated 510 asymptomatic diabetic without known CAD. Stress myocardial perfusion imaging was performed in all patients with moderate-severe subclinical atherosclerosis (CAC>100 Agatston units). Significant CAC (>10 Agatston units) was found in 46.3% of the patients. No cardiac events or perfusion abnormalities occurred in subjects with CAC≤10 Agatston units up until 2 years follow-up. CAC and SPECT were synergistic for the prediction of short-term cardiovascular events. However, since the coronary arteries are small, tortuous, and move during the cardiac cycle, imaging remains technically difficult. Further studies evaluating the impact of CAC imaging on clinical outcomes and its cost-effectiveness are warranted. As a result, these new techniques have shortcomings and limitations, but with recent and ongoing technical advances, image quality and diagnostic accuracy are improving. Besides noninvasive angiography, these techniques may also allow assessment of plaque composition in the near future.

Hybrid imaging: SPECT/CT and PET/CT

PET and SPECT scanners have now been linked to CT scanners, which are digital radiological systems that acquire data in the axial plane, producing images of internal organs at high spatial and contrast resolution.[68] The combination of PET or SPECT and CT as a single unit provides spatial and pathological correlation of the abnormal functional and/or metabolic activities, allowing images from both systems to be obtained by a single instrument in one examination procedure with optimal co-registration of images. The resulting fusion images facilitate the most accurate interpretation of both PET or SPECT and CT studies. CT attenuation maps from these integrated systems are used for rapid and optimal attenuation correction of the PET or SPECT images. In addition, PET-CT and SPECT-CT images are used to guide intervention. This process of integration of imaging systems has progressed to MR.[81, 82] The major advantage of the integrated approach to the diagnosis of CAD is the added sensitivity of PET or SPECT and CT angiography. As not all coronary artery stenoses are flow limiting, PET or SPECT stress perfusion imaging complements the anatomical CT data by providing functional information on the hemodynamic significance of such stenoses, thus allowing more appropriate selection of patients who may benefit from revascularization procedures.[68, 81, 82] While the principle may be the same, each modality has its specific benefits. Earlier studies conducted with three-dimensional image fusion of CT and SPECT showed promising results.[83-86] One of the major uses of SPECT/CT is the production of better attenuation correction. Apparent perfusion defects occur most often in the anterior wall in women and in the inferior wall in men, and soft-tissue attenuation can also shift between resting and stress images. Interpreting these examinations requires clinicians to recognize any attenuation artifacts and allow for them in evaluating the underlying perfusion pattern.[87] In addition, to being intuitively convincing, these images provide a panoramic view of the myocardium, the regional myocardial perfusion and the coronary artery tree, thus eliminating uncertainties in the relationship of perfusion defects and stenotic coronary arteries in watershed regions. This may be particularly helpful in patients with multiple perfusion abnormalities and complex CAD.[88] Similarly, the integration of PET and CT scanners enables detection and quantification of the burden of calcified and non-calcified plaques, quantification of vascular reactivity and endothelial health, identification of flow limiting coronary stenosis. Integrated PET/CT offers an opportunity to assess the presence and magnitude of subclinical atherosclerotic disease burden and to measure myocardial blood flow as a marker of endothelial health and atherosclerotic disease activity. Because not all coronary stenoses detected by CT are flow limiting, the stress myocardial perfusion PET data complement the CT anatomic information by providing instant readings about the clinical significance of such stenosis.[89] Further studies are needed to refine these technologies, address the issue of cost-effectiveness, and validate a range of clinical applications in large-scale clinical trials including patients with diabetes.

Conclusions

Diabetic patients have a significantly increased risk of cardiovascular events. In this population, CAD is often silent and more advanced at diagnosis and associated with an unfavorable prognosis. Early intervention may prevent progression of disease and decrease risk. Myocardial perfusion imaging allows the risk stratification of diabetic patients, which can be used in determining management of patients with suspected CAD. In individuals without diabetes, patients with a low risk of events may be managed with risk factor modification. As the degree of risk increases, medical management may be added. Patients at the highest degree of risk require more aggressive management, which may include catheterization and revascularization. The same principles guiding the use of risk data in the management of nondiabetic patients also apply to diabetic patients with normal scan results; however, the degree of risk based on a given scan appearance tends to be slightly higher. Diabetic patients with moderately to severely abnormal scan results are an exception, as the differences in risk are significantly higher. Additional prognostic information is provided from the functional data that can be obtained simultaneously with a gated SPECT.

Riassunto

La stratificazione del rischio cardiaco dei pazienti diabetici

Il diabete mellito è un'entità clinica complessa che tenderà a crescere nel futuro. Le complicazioni del diabete hanno un impatto significativo sulla sopravvivenza del paziente e sulla qualità della vita, in particolare riguardo la malattia delle arterie coronariche (CAD). Uno screening appropriato ed un intervento aggressivo possono significativamente dare beneficio a molti pazienti affetti da diabete. Inoltre, è importante prendere in considerazione strategie utili non solo nella diagnosi di CAD, ma anche nella valutazione prognostica dei pazienti diabetici affetti da malattia coronarica. I dati prognostici sono essenziali per definire le categorie di rischio e nell'applicare trattamenti appropriati a seconda del grado di rischio. Perciò è richiesta un'accurata stratificazione del rischio cardiovascolare dei pazienti con diabete di tipo 2. In ogni caso, questo può essere un risultato difficile da ottenere in quanto la presentazione clinica e la progressione della CAD differisce tra soggetti diabetici e non diabetici. Oltre a una più alta diffusione di CAD, i pazienti affetti da diabete hanno un interessamento coronarico molto più diffuso ed esteso, presentano un maggior numero di episodi di disfunzione ventricolare sinistra, malattia coronarica in stadio più avanzato al momento della diagnosi e molti più episodi di ischemia silente. Per di più, i pazienti diabetici hanno frequentemente una risposta meno favorevole alle procedure di rivascolarizzazione ed un esito più sfavorevole a lungo termine. Lo scopo di questa rassegna è discutere il ruolo relativo di varie procedure per la diagnosi di CAD e per la stratificazione del rischio cardiaco in pazienti diabetici.

Parole chiave: Diabete mellito - Prognosi - Imaging cardiaco.

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