Noninvasive Assessment of the Diabetic Patient for Coronary Artery Disease

Type 2 diabetes has been referred to as “a cardiovascular disease associated with hyperglycemia” (1). Such inversion of traditional terminology stems, in part, from the extraordinary frequency with which heart disease occurs in this condition. Cardiovascular diseases are indeed responsible for 65% of deaths in diabetic patients, the great majority of whom have type 2 diabetes (2). The Framingham Study (3) long ago demonstrated that diabetic individuals had a two- to fivefold increased risk of developing angina, myocardial infarction, and congestive heart failure. When individuals <45 years of age are examined separately, the risk of cardiovascular disease swells to >11-fold that of the general population (4). We recognize the link between diabetes and ischemic heart disease (IHD) on a daily basis in clinical practice, and it has been repeatedly demonstrated in a number of other epidemiological analyses (5–7). Even when the diabetic patient comes under appropriate medical care for vascular disease, outcomes are poorer than those of nondiabetic individuals. Specifically, mortality statistics after myocardial infarction (8) or even after revascularization procedures (9) are increased in the setting of preexisting diabetes. In addition to the obvious human costs, health care expenditures related to premature atherosclerosis are considerable, particularly when the additional costs of disability and lost productivity are calculated (4).

The cause of the macrovasculopathy of diabetes becomes apparent when one considers the deleterious effects of the hyperglycemic milieu, such as protein glycosylation, increased oxidative stress, endothelial dysfunction, and an underlying procoagulant state. In type 2 diabetes, these processes conspire with additional cardiovascular risk factors associated with the metabolic syndrome: obesity, hypertension, dyslipidemia, hyperinsulinemia, decreased fibrinolysis, and further endothelial abnormalities.

Offsetting this otherwise sobering picture are recent advances in cardiovascular risk reduction in patients with diabetes. A broad range of clinical trials, for instance, have unequivocally demonstrated the benefits of lipid-lowering therapy on cardiovascular event rates, often exceeding those in nondiabetic patients (10). Equally important is the aggressive control of hypertension (11), and certain antihypertensive drug classes, such as ACE inhibitors, may provide risk reduction even in patients with normal blood pressure (12). On the other hand, the cardiovascular benefits of traditional therapy for hyperglycemia (insulin or insulin secretagogues) has not been convincingly demonstrated (13). However, such a benefit appears to follow the use of metformin, an antihyperglycemic agent that decreases insulin resistance (14). The more recent advent of the thiazolidinedi-one class of medications holds additional promise, with early studies showing advantage in at least intermediate vascular end points (15).

Lastly, antiplatelet agents are a simple, often underutilized, but frequently effective (16) therapy for the prevention of vascular events in diabetes. Therefore, we have a substantial and growing armamentarium to prevent cardiovascular disease in our patients.

Simultaneous with advances in the treatment of diabetes, particularly regarding cardiovascular risk, there has been an extraordinary growth in the available modalities for diagnosing and treating coronary artery disease (CAD) over the past two decades. This has resulted in significant declines in the mortality from CAD during this period of time (17). Unfortunately, for reasons that are not completely understood, this decline has not been enjoyed to the same degree by diabetic patients (18). Despite our efforts to prevent cardiovascular disease, even the most aggressive programs will attenuate but not eliminate risk. Additionally, many patients with type 2 diabetes have preexisting IHD at the time of diagnosis. Compounding these problems are diagnostic concerns, such as the well-recognized atypical, often silent, manifestations of IHD in diabetic patients (19).

Because of the frequency of CAD in patients with diabetes and the potential complexities involved in its evaluation, the development of accurate and cost-effective diagnostic tests is of obvious importance. Several questions arise whenever noninvasive testing for CAD is being considered. First, what is the sensitivity of the test? That is, in the patient with significant underlying CAD, how reliable will the test be in detecting it? Second, what is the specificity of the test? That is, what is the likelihood that an abnormal test actually indicates the presence of a significant coronary stenosis? Third, will the information garnered from the study lead to additional testing and/or a meaningful change in the patient’s therapy (or outcome)? For instance, will an abnormal test lead to further and likely invasive investigations, such as coronary angiography, with an eye toward an interventional procedure, such as angioplasty, coronary stenting, or even coronary artery bypass grafting? Moreover, what is the likelihood that the CAD either predicts a future clinical event, such as myocardial infarction, or appears to be significant enough to compel revascularization?

Options available to evaluate patients noninvasively for CAD have gradually expanded over the years. Previously, exercise tolerance testing using conventional electrocardiogram (ECG) monitoring (ETT-ECG) was the only available method. By increasing heart rate, blood pressure, cardiac contractility, and ventricular wall tension, exercise raises myocardial oxygen demand. Because of decreased coronary reserve, stenotic arteries are unable to adequately respond to the requirements for increased blood flow. As a result, myocardial territories fed by these vessels are rendered ischemic, and this ischemia is detected on the surface ECG due to alterations in electrical repolarization currents. Although useful in many patients, this modality has proven suboptimal in certain situations.
for several reasons. ETT-ECG lacks the specificity to be cost-effective when screening low-risk populations while lacking the sensitivity to be consistently predictive in high-risk groups. As a result, the ETT-ECG is most useful in patients of moderate CAD risk (20). In addition to the inherent issues of diagnostic accuracy, ETT-ECG is particularly problematic in certain patient types. For instance, some may not be able to exercise on standard treadmills because of underlying peripheral vascular disease (PVD), or pulmonary, neurological, or orthopedic conditions. Others may be unable to reach the target workload required to validate the tests’ outcome. Still others may have preexisting abnormalities in the resting ECG that obscure any changes induced by exercise (20). Many of these concerns apply to the diabetic patient, who is inherently at high risk for developing CAD and whose exercise potential is often limited by obesity, deconditioning, PVD, or sensory or motor neuropathy.

These issues and others faced by the ETT-ECG led to the development of adjunctive myocardial imaging, which increases both the sensitivity and specificity of routine exercise testing. First, stress nuclear (SN) testing was developed. SN uses radiopharmaceuticals, such as TI-201 and Tc-99m-sestamibi, to perform myocardial perfusion imaging. The visualization of regions of underperfused myocardium not only increase the diagnostic accuracy over conventional ETT-ECG, but also allow for a more precise assessment of the amount and specific location of myocardium at risk (21), even in single-vessel disease, which can be associated with a false negative ETT-ECG. Single photon emission computed tomography (SPECT) adds enhanced cross-sectional detail to these images. Myocardial scar can also be visualized on SN rest images, and, with certain isotopes, such as Tc-99m-sestamibi, ejection fraction can additionally be measured. More recently, stress echocardiography (SE) was developed. During SE, the patient undergoes an ultrasonographic examination of the heart both pre- and immediately postexercise. By comparing the two sets of digitally acquired 2-D images, myocardial territories that are ischemic will appear to be hypococontractile when compared with normally perfused segments (22). As in SN, patients undergoing SE can also be assessed for previous infarction as well as for left ventricular performance. Whereas both of these imaging technologies enhance the positive and negative predictive value of routine ETT, they have certain unique characteristics, including limitations that are beyond the scope of these editorial comments (21–23). Of great importance, both SN and SE have expanded the potential of exercise testing to those patients in whom baseline ECG abnormalities (e.g., left bundle branch block) prevent adequate evaluation through conventional ECG analysis.

However, even SN and SE per se remain suboptimal techniques for those patients who are unable to exercise sufficiently or safely because of other underlying medical conditions. In these situations, pharmacological agents are used that behave as coronary vasodilators (e.g., dipyridamole or adenosine) or that mimic the effects of exercise by increasing contractility and myocardial oxygen demand (e.g., dobutamine). The former accentuate the differences in coronary flow reserve between normal and diseased vessels, ideal for SN, whereas the latter mimics the effects of exercise on myocardial contractility, most appropriate for SE (23). Either pharmacological “stress” agent can be used successfully with both imaging techniques. It should be noted, however, that when pharmacological stress is used, two potentially important pieces of information are lost: the exercise capacity of the patient and the precise workload threshold for the development of symptoms, such as angina.

In this issue, Bigi et al. (24) add to the body of knowledge regarding the evaluation of patients with diabetes for IHD. The authors evaluated the prognostic value of pharmacological SE in 259 patients with diabetes being studied for known or suspected CAD. During a mean follow-up of 24 months, there were 13 cardiac deaths and 13 nonfatal myocardial infarctions. Univariate predictors of poor outcome included known CAD, a positive SE, and abnormal wall motion scores, both at rest and after stress, as well as the variation between these two indexes. Multivariate analysis demonstrated that the poststress wall motion score was the sole independent prognostic indicator. When compared with ETT-ECG, which was additionally performed in more than half of the study participants, SE provided 43% additional prognostic information, and an abnormal SE was associated with a significantly decreased event-free survival. These data reaffirm the previous findings of Marwick et al. (25) in a group of general CAD patients that included some participants with diabetes.

The value of SE in the risk stratification of diabetic patients with known or suspected CAD is thus demonstrated. Similar data exists for SN (26), but these techniques have not been adequately compared in diabetic patients. Comparative studies of SN and SE in CAD patients in general have been conflicting, with most investigations marred by variable quality in the techniques at individual centers. One study involving two investigators from well-regarded laboratories in echocardiography and nuclear cardiology suggested that the two modalities have equal sensitivity for detecting CAD, but that SE may be slightly more specific (27). A recent meta-analysis (28) appeared to confirm this impression, but the methodology used has been fairly criticized, and a reanalysis suggested no major differences overall (29). At this juncture, the best noninvasive test for diabetic patients being evaluated for CAD remains unclear. Until further information is available, the choice of test should be based on local availability and expertise, cost considerations, as well as certain clinical concerns, such as the precise purpose for the test and unique patient-specific characteristics (22). The exact roles for emerging technologies in this field, such as electron beam computed tomography, magnetic resonance imaging, and positron emission tomography, are unknown.

Recently, the Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes (30) provided us with a comprehensive set of guidelines for the evaluation of IHD in our patients. For those questions where clinical trial evidence was insufficient, recommendations of the panel were based essentially on expert opinion. One important area in which the panel deemed current evidence inadequate was in screening the asymptomatic diabetic patient for CAD. The ongoing Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial (31) will soon provide data in this regard. Clearly, further investigations into the diagnosis as well as the management of CAD in patients with diabetes are needed. Past experience teaches us that what may be true for the population with CAD at large may not
necessarily apply to the person with both diabetes and CAD (8,9). Continued interchange and collaboration between the cardiology and diabetology communities will be critical to improve outcomes in these patients.

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