Use of Stress Echocardiography to Predict Mortality in Patients With Diabetes and Known or Suspected Coronary Artery Disease

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OBJECTIVE — This study sought to determine whether stress echocardiography using exercise (when feasible) or dobutamine echo could be used to predict mortality in patients with diabetes.

RESEARCH DESIGN AND METHODS — Stress echo was performed in 937 patients with diabetes (aged 59 ± 13 years, 529 men) for symptom evaluation (42%) and follow-up of known coronary artery disease (CAD) (58%). Stress echocardiography using exercise was performed in 333 patients able to exercise maximally, and dobutamine echo using a standard dobutamine stress was used in 604 patients. Patients were followed for ≤9 years (mean 3.9 ± 2.3) for all-cause mortality.

RESULTS — Normal studies were obtained in 567 (60%) patients; 29% had resting left ventricular (LV) dysfunction, and 25% had ischemia. Abnormalities were confined to one territory in 183 (20%) patients and to multiple territories in 187 (20%) patients. Death (in 275 [29%] patients) was predicted by referral for pharmacologic stress (hazard ratio [HR] 3.94, P < 0.0001), ischemia (1.77, 2.3) for all-cause mortality. The risk of death in patients with a normal scan was 4% per year, and this was associated with age and selection for pharmacologic stress testing. In stepwise models replicating the sequence of clinical evaluation, the predictive power of independent clinical predictors (age, selection for pharmacologic stress, previous infarction, and heart failure; model $\chi^2 = 104.8$) was significantly enhanced by addition of stress echo data (model $\chi^2 = 122.9$).

CONCLUSIONS — The results of stress echo are independent predictors of death in diabetic patients with known or suspected CAD. Ischemia adds risk that is incremental to clinical risks and LV dysfunction.

Approximately 50% of mortality in diabetic patients is related to coronary disease (1), and diabetes has a significant impact on outcome in patients with established coronary disease (2). This increased risk in the diabetic population is equivalent to the risk of nondiabetic patients after infarction (3), a finding that has engendered calls for more aggressive risk factor intervention in this group. A further strategy would be to screen patients for existing evidence of coronary disease, with the intent of myocardial revascularization in those at greatest risk. In nondiabetic patients, a number of factors may be used to stratify the level of risk of coronary disease, including clinical history, resting ventricular function, exercise capacity, the presence and extent of ischemia at single-photon emission–computed tomography (SPECT), or stress echo. The detection of a spectrum of risk within the diabetic group is more difficult; sex and lipids levels are less predictive in diabetic than nondiabetic patients (4), and silent ischemia is more common (5). However, resting ST segment changes may be false positive responses for epicardial coronary disease (5), and false positive ST segment changes and poor exercise capacity may reduce the utility of standard exercise electrocardiogram testing. In this context, an imaging strategy may have some merit for the identification of risk among those with known or suspected coronary disease. Because stress echo is accurate but relatively expensive, we sought to evaluate a testing strategy based on this approach.

RESEARCH DESIGN AND METHODS

Patient population. This was a cohort study involving 937 predominantly non–insulin-dependent diabetic patients with known or suspected coronary disease who undertook stress echo at three large expert laboratories (Cleveland Clinic Foundation, Indiana University, and Asheville Cardiology Associates) between 1988 and 1994. Clinical, exercise, and echocardiographic data of these patients were obtained prospectively, and follow-up was obtained up to 9 years later (1998–1999). Consent was obtained before testing, and the study was approved by the Institutional Review Board.

The mean age of the group was 59 ± 13 years, and 43% of patients were women. Cardiovascular risk factors were highly prevalent, 57% were current or
previous smokers, and 64% had hypertension either diagnosed (blood pressure >140/90 mmHg) or treated. Either hypertension or heart disease were the indication for calcium channel blockers in 35%, ß-adrenoceptor blockers in 17%, digoxin in 13%, ACE inhibitors in 20%, and diuretics in 25% of patients.

The primary objective of the test was for prognostic reasons after myocardial infarction in 26% of patients for follow-up of known coronary disease in 32%. Stress echo was performed for diagnostic purposes in patients with chest pain or similar symptoms in 27% of patients, and the remaining 15% had the test performed for the evaluation of other symptoms, particularly exertional dyspnea or palpitations. On the basis of age, sex, and symptom status (6), 11% of patients were considered to have a low probability of coronary disease (<20%), 47% had an intermediate probability (20–80%), and 42% had a high probability (>80%) of disease.

Stress testing. Exercise echo was performed using standard techniques and end points (7) if the referring physician considered it likely that the patient would exercise maximally at treadmill testing (n = 333, average workload 8 ± 3 METs). The presence of angina, ST segment changes, and exercise capacity were combined into the Duke treadmill score, a prognostic tool that has been well validated in nondiabetic patients (8). Dobutamine-atropine stress was performed using a standard protocol (9) in patients who were unable to exercise (n = 604).

Echocardiography. A standard two-dimensional echo was performed at rest in all patients. The extent of resting left ventricular (LV) dysfunction was evaluated subjectively by an experienced observer on the basis of the extent of myocardium showing abnormal wall motion, and LV function was classified as normal (ejection fraction [EF] >55%) or mildly (EF 40–55%), moderately (EF 30–39%), or severely impaired (EF <30%). Stress echos were interpreted independent of clinical, exercise, or angiographic data using standard criteria by experienced observers, who had been
trained in the performance of the technique (10). Myocardial segments were combined into vascular territories for the purpose of expressing the extent of ischemia as one-, two-, or three-vessel coronary artery disease (CAD). Because previous studies in the nuclear literature (11) showed that total extent of malperfused myocardium at peak stress is predictive of outcome, we produced an analogous “summed stress score” by counting the number of territories showing either rest or stress-induced changes.

Follow-up. Follow-up data were gathered after 3.9 ± 2.3 years (range 1 month to 9.3 years) by clinic review or telephone contact with the patient or the patient’s physician. The primary end point was total mortality. Patients were censored at the time of coronary bypass surgery or coronary angioplasty.

Statistical analysis. Descriptive statistics of continuous variables were expressed as mean and SD and, for categorical variables, as frequency and percent. Differences between survival curves based on individual variables were compared with the log rank test. The effects of ischemia on outcome, independent of clinical, exercise, and resting echocardiographic variables, was investigated using a Cox proportional hazards model and expressed as hazard ratio (HR). A series of models were used to investigate the prognostic value of ischemia incremental to clinical data and resting LV function. Analyses were performed using SPSS statistical software (SPSS, Chicago), and P values <0.05 were considered to be statistically significant, except for multiple comparisons, where significant P values were defined by the Bonferroni method.

RESULTS

Outcomes. Patients were followed for ≤9 years, during which time revascularization was performed in 103 (11%) patients, and 275 (29%) died. In the first 5 years of follow-up, 226 died before revascularization.

Resting and stress echocardiography. The presence and severity of resting LV dysfunction and ischemia are summarized in Fig. 1. Overall, 567 (60%) patients had a completely normal study (no abnormality at rest or stress).

Significance of a negative test in diabetic patients. Of the 567 patients with a completely normal test, 100 (18%) died during follow-up. The mortality in these patients averaged 4% per year in the first 5 years of follow-up, but this was very different in patients undergoing exercise and dobutamine stress (Fig. 2). The independent predictors of adverse outcome were diuretic use, a surrogate of heart failure (HR 2.04, 95% CI 1.15–3.61, P = 0.01),
and referral for dobutamine echo (22.54, 7.13–71.31, \( P < 0.0001 \)), probably reflecting inability to exercise. Ignoring the nature of the test markedly reduced the predictive power of this model (\( \chi^2 = 63.6–32.5 \)), and the predictors of death became age (HR 1.01, 95% CI 1.01–1.03, \( P = 0.04 \)) and probability of CAD (2.53, 1.24–3.89, \( P = 0.03 \)).

**Prediction of mortality.** Of the 370 patients with either rest or stress-induced wall motion abnormalities, 165 (45%) died during follow-up. Both ischemia and resting LV dysfunction were associated with mortality; 115 of 232 (50%) patients with ischemia died during follow-up, as well as 123 of 275 (45%) with LV dysfunction. These associations were the same in patients with and without known CAD (Fig. 3).

The univariate and multivariate predictors of mortality are listed in Table 1. Both the presence and the extent of resting LV dysfunction (Fig. 4A) and ischemia (Fig. 4B) were predictive of death, as was the total extent of abnormal wall motion (Fig. 4C). Again, the strongest predictor of outcome was referral for pharmacologic rather than exercise testing. The other major determinants of outcome were the presence of ischemia, increasing age, and heart failure (evidenced by associated medical therapy with digoxin or diuretics). As the use of pharmacologic stress is based on the clinical assessment of the patient and may be a reflection of informal clinical assessment of risk level, a separate model was developed without noting the type of stress protocol. If the nature of the test was ignored, resting LV dysfunction became an independent predictor of outcome; otherwise, the same variables remained predictive of mortality, although the power of the model was reduced.

Ischemia as an incremental predictor of mortality. The incremental value of ischemia was assessed by developing a sequence of Cox models, starting with clinical variables, adding resting LV function, and finally including ischemia. When the nature of the stress was accounted for, the clinical model (age, heart failure, previous infarction, and dobutamine stress) was strongly predictive of death (\( \chi^2 = 104.8 \)) and was not strengthened by addition of resting LV function data, although ischemia strengthened the predictive power of the model (\( \chi^2 = 122.9 \)), showing this finding to be not only an independent but also an incremental predictor of death during follow-up. However, when the predictors of death were examined independent of the nature of the stress test, the predictive power of clinical assessment (age, heart failure, and previous infarction; \( \chi^2 = 50.4 \)) was strengthened by resting LV function data (\( \chi^2 = 70.6 \)), and evidence of ischemia also provided incremental prognostic data (\( \chi^2 = 91.3 \)).

**CONCLUSIONS** — The results of this study demonstrate that diabetic patients may be stratified on the basis of clinical variables, resting LV function, and ischemia. The presence of ischemia is an independent predictor of death, incremental to the other factors. These results support the findings of previous smaller studies of stress echo in patients with diabetes (12–14), which were not powered to examine a mortality end point.
Significance of a negative stress echocardiogram. Recent studies with exercise and dobutamine echo in unselected patients have shown the yearly event rate with a negative test to be of the order of 1% per year (15,16). The findings of the current study show that the total mortality of diabetic patients with a negative scan result (~4% per year) is higher than might be anticipated in an unselected group, and this is particularly a problem in the patients undergoing dobutamine stress, most of whom were unable to exercise. Poor exercise capacity is well known as a marker of mortality risk, even in older subjects (17). This effect is perhaps greater in diabetic patients because of the intensity of their comorbidities. The patients who died despite a negative test tended to be older and have evidence of heart failure. In a previous work examining composite end points, “false negative” exercise echocardiograms were predicted by low workload, anginal symptoms in the absence of identifiable wall motion abnormalities, and LV hypertrophy (11).

Stratification of risk in patients with positive tests. Previous studies in unselected patient groups have shown that the presence of ischemia confers risk of subsequent cardiac events, although without further differentiation of the group, these patients are not at very high risk (~5% per year). The risk of death after an abnormal test in a patient with diabetes (over 10% per year) is higher. This risk can be substratified according to the type and extent of abnormality (Fig. 4A and B). The effect of extent is best represented by the total extent of abnormal wall motion, which includes both resting LV dysfunction and induced by stress (Fig. 4C). This effect is analogous to the correlation of the extent and severity of perfusion defects with the outcomes of patients studied using SPECT (18). Multivariate analysis of our data showed ischemia to be an independent predictor of mortality in patients with diabetes.

A significant body of literature has been developed to predict death in unselected patients with known or suspected coronary disease. Important clinical vari-

Figure 4—Influence of extent of abnormal wall motion at rest (A), with stress (B), and in combination (C). The extent of abnormal wall motion is expressed as the number of abnormal coronary vascular territories.
ables include age, the presence of heart failure or previous infarction, and diabetes. Previous studies using both exercise (15) and dobutamine echo (16) have shown that knowledge of resting LV dysfunction, exercise capacity (during exercise testing), and the presence and extent of ischemia add incremental data to the prediction of death. The incremental benefit of stress echocardiographic findings have been confirmed and extended in this group of patients with diabetes, among whom the identification of a spectrum of risk may rationalize the selection of patients for intervention.

Limitations. This prospective study of stress echo was purely observational. It remains unclear whether the cause of this ischemia is due to disease of the conduit vessels, as some of these patients might be expected to have small vessel disease. However, it is unusual for the latter problem to induce motion abnormalities at stress echo (19), which usually reflects the presence of significant (>50%) stenoses in large (>1 mm) epicardial vessels (20). It is also undefined whether the risk shown in this study is amenable to procedural or intensive medical intervention. These questions warrant consideration of a subsequent interventional study.

The patients in this study were studied at three high-volume expert centers, and the ability to obtain the same level of prognostic value in other environments is undefined. However, expert accuracy may be attained by training. Given the extensive literature on prognosis and the accuracy of stress echo, it is likely that adequately trained readers would replicate these results.

Clinical implications. The results of this study suggest that in diabetic patients with known or suspected coronary disease, the presence of ischemia at stress echo permits the identification of a high-risk subgroup. The importance of ischemia as a predictor of death in this study suggests that revascularization should be considered as a prognostic measure in diabetic patients. Although diabetes increases the risk of peri-operative complications (21) and increases the long-term risks after both angioplasty (22) and coronary bypass surgery (21), the prognostic benefits of intervention compared with medical therapy are still preserved (23). Nonetheless, the coronary anatomy in diabetic patients identified as being at high risk may not be amenable to revascularization, and additional studies are needed to prove that revascularization alters outcome in patients identified as at risk based on the results of screening.

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References
Prediction of death in diabetic patients


