The impact of diabetes mellitus on the prognostic value of a normal dobutamine stress echocardiogram in patients with intermediate to high cardiovascular risk

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ABSTRACT

Introduction: There is currently limited data on the prognostic value of a normal dobutamine stress echocardiogram (DSE) in patients with intermediate to high cardiovascular risk. The impact of diabetes mellitus, recently recognised as a cardiovascular risk-equivalent, has not been previously evaluated. This study aims to determine the prognostic value of a normal DSE in these patients.

Methods: The study population includes all patients with two cardiovascular risk factors or diabetes mellitus and a normal DSE (baseline and peak stress) with three months follow-up. A total of 122 patients (47 females, 75 males; mean age 59.6 years) were recruited. Impact of diabetes mellitus on subsequent cardiovascular events was determined.

Results: Diabetes mellitus was present in 32.8 percent, hypertension in 72.1 percent, smoking in 27.0 percent, family history of premature coronary artery disease in 15.6 percent, and hypercholesterolemia in 66.4 percent. On follow-up until 6.4 years (mean 4.1 years), there were four myocardial infarctions (0.8 percent per patient/year) and five revascularisation procedures (1.0 percent per patient/year). The majority of adverse events occurred among patients with diabetes mellitus (three out of four myocardial infarctions; four out of five revascularisations). Diabetes mellitus independently predicted subsequent cardiac events on both univariate and multivariate analyses (p value is equal to 0.015 and 0.011, respectively). Presence of diabetes mellitus also conferred a worse outcome on survival analysis (p value is equivalent to 0.0046).

Conclusion: The presence of diabetes mellitus adversely affects clinical outcome despite a normal DSE. Patients without diabetes mellitus, but with intermediate to high cardiovascular risk, and a normal DSE have a better medium term outcome.

INTRODUCTION

Dobutamine stress echocardiography (DSE) is used in the diagnosis of coronary artery disease, evaluation of myocardial viability, risk-stratification following a myocardial infarction, and in assessing preoperative risk before cardiac and non-cardiac surgeries. While a number of studies have demonstrated favourable outcomes following a normal DSE[1-4], data on its prognostic value specifically in patients with intermediate or high cardiovascular risk is limited. Recent data also suggest that diabetes mellitus is a coronary artery disease (CAD) risk-equivalent and its presence could therefore affect the predictive value of a normal DSE[5]. This study was undertaken to assess the role of a normal DSE in predicting cardiac events in patients with normal baseline findings and intermediate or high cardiovascular risk. We also wanted to determine if the presence of diabetes mellitus could impact negatively on patient outcome in spite of a normal DSE. This is important because the American Diabetes Association and the American College of Cardiology have recently concluded that there are currently insufficient outcome data to define the prognostic utility of DSE in patients with diabetes mellitus[6].

METHODS

Patients with a normal DSE and intermediate to high cardiovascular risk (defined as the presence of two or more traditional cardiovascular risk factors or diabetes mellitus) with at least three months follow-up were recruited over a two-year period from January 1996 to December 1997. The cardiovascular risk factors considered were gender and age (men older than 45 years, women older than 55 years), a significant family history of premature coronary artery disease (defined as a male relative younger

than 55 years or female relative younger than 65 years with documented coronary artery disease), history of cigarette smoking history, dyslipidaemia (defined as the use of lipid lowering therapy or LDL-cholesterol greater than 3.4 mmol/dL), and hypertension. With the release of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III), presence of diabetes mellitus is now considered a cardiovascular risk equivalent[5]. Patients with diabetes mellitus were therefore at high risk for subsequent cardio vascular events. Subjects with previous documented myocardial infarction, ischaemic heart disease, or electrocardiography (ECG) suggesting previous myocardial infarction were excluded from the study. Non-resident foreigners were also not included because they were unavailable for subsequent follow-up. Patients with abnormal baseline echocardiographic findings were also excluded.

DSE was performed with a VingMed machine (VingMed CFM800C. VingMed Sound A/S, Horten, Norway. A progressively-graded dobutamine infusion was given using the following protocol: 5, 10, 20, 30 and 40 μg/kg/min, with each stage lasting three minutes[1,7]. If necessary, intravenous atropine was administered after 40 μg/kg/min of dobutamine to increase the patient's heart rate to target heart rate (85% predicted maximum heart rate). Continuous three-lead electrocardiographical recording was maintained and 12-lead ECG was performed every three minutes during the test or when necessary. Echocardiographical images were obtained continuously during the test and recorded on sVHS videotape. Digitised images were obtained at baseline, low-dose (10 μg/kg/min), pre-peak, peak heart rate and during recovery. Images were obtained from the parasternal long and short axis, apical two and four chamber, and apical long axis views. The test was stopped if the patient achieved 85% of the predicted maximal heart rate, if new wall motion abnormalities occurred, if significant side effects developed, if ECG showed new or significant ST segment depression, or if the patient developed angina or hypotension. All studies were supervised and reviewed by an experienced echocardiographer. A normal test was defined as a normal resting echo with no stress-induced wall motion abnormality.

Follow-up information was obtained in two ways: (1) By review of the medical records, and (2) by telephone interviews. Pre-specified endpoint was a composite of myocardial infarction, cardiac death or need for revascularisation. The presence of myocardial

infarction or cardiac death was identified as a "hard event" while a "soft event" was defined as the need for revascularisation by either coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG). Myocardial infarction was defined by the presence of at least two of the following: typical chest pain, characteristic electrocardiographical changes, and elevation of the serum CKMB levels to at least three times of the normal level. Death was attributed to a cardiac cause if it occurred within 24 hours of a known cardiac event for which no other obvious cause was found.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 11.0 (SPSS Inc, Chicago, Illinois 60606, USA). Categorical data were reported as percentages and continuous data as mean with standard deviation. Survival curves were generated with the Kaplan-Meier estimator. Predictors of cardiac events were assessed univariately and then multivariately using the Cox proportional hazards model. A p-value of less than 0.05 was considered significant.

RESULTS

A total of 122 patients with intermediate or high cardiac risk were enrolled in the study, all of whom had normal echocardiography findings at baseline and peak stress. DSE served as the primary stress test in 58 patients (47.5%) and was performed for a positive or inconclusive treadmill stress test in the remaining 64 patients (52.5%). None of these patients were previously documented to have coronary artery disease. There were 47 (38.5%) females and 75 (61.5%) males, with a mean age of 59.6 ± 11 years. Diabetes mellitus was present in 40 patients (32.8%), hypertension in 88 patients (72.1%), a history of cigarette smoking in 33 patients (27.0%), significant family history of premature coronary artery disease in 19 patients (15.6%), and dyslipidaemia in 81 patients (66.4%).

During follow-up of up to 6.4 years (mean 4.1 ± 1.6 years), a total of nine events were documented. This translated to an event rate of 1.8% per patient/year. Four were hard events as previously defined (three myocardial infarctions and one cardiac death), giving a hard event rate of 0.8% per patient/year. Five patients necessitated revascularisation with three patients undergoing PTCA and another two proceeding to CABG for triple vessel coronary artery disease (soft event rate = 1.0% per patient/year). Among patients with events, diabetes mellitus was co-morbid in seven (three patients sustained myocardial infarction or death and four necessitated revascularisation). Total event rate in patients with

Table 1. Independent predictors of all events in univariate and multivariate analyses.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Increasing age	1.00 (0.94-1.07)	0.946	0.97 (0.89-1.05)	0.432
Hypertension	0.85 (0.21-3.43)	0.819	1.12 (0.23-5.54)	0.890
Diabetes mellitus	7.02 (1.46-33.79)	0.015	10.16 (1.71-60.31)	0.011
Dyslipidaemia	0.91 (0.23-3.65)	0.897	0.74 (0.18-3.07)	0.678
Significant family history	0.82 (0.10-6.70)	0.855	0.96 (0.11-8.25)	0.967
Significant smoking history	1.02 (0.21-4.95)	0.984	1.68 (0.242-11.592)	0.083

Fig. 1 Kaplan-Meier cumulative event-free survival of the cohort.
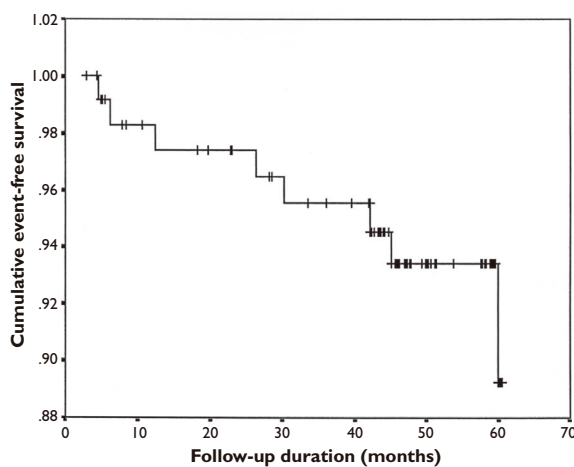
Fig. 2 Cumulative event-free survival in relation to presence of diabetes mellitus.

P=0.0046 by Log-Rank test.
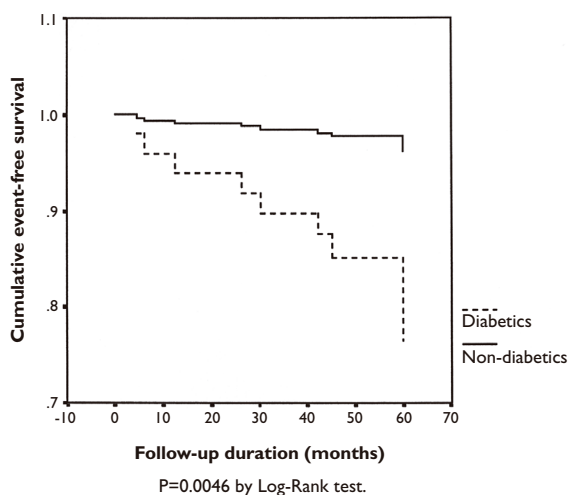
diabetes mellitus was calculated to be 4.3% annually. This contrasted with an event rate of 0.6% per patient/year among patients without diabetes mellitus.

Diabetes mellitus was the single predictor of subsequent cardiac events on univariate analysis. None of the usual traditional cardiovascular risk factors such as hypertension, smoking or dyslipidaemia

predicted the occurrence of subsequent cardiac events. In a multivariate model of traditional cardiovascular risk factors, diabetes mellitus remained independently predictive of clinical events (Table I). Kaplan-Meier cumulative survival function of the entire patient cohort is shown in Fig. 1. Cumulative event-free survival was 97.5% at 24 months and 94.3% at 48 months. When the survival function was compared among diabetics and non-diabetics, patients without diabetes mellitus experienced a greater cumulative event-free survival (p=0.0046 by Log-Rank test, Fig. 2).

DISCUSSION

This study shows that the prognosis among patients with diabetes mellitus is significantly worse in spite of a normal DSE. This supports current consensus that diabetes mellitus is a cardiovascular risk equivalent instead of a risk factor. The prognostic value of a normal DSE has been demonstrated in previous studies[1-4], and patients with negative DSE results experience low subsequent cardiac and mortality rates. These studies, however, included all-comers and did not specifically considered patients with intermediate or high cardiovascular risk. The negative predictive value of a normal DSE could therefore be accentuated by presence of patients with low cardiovascular risk. Studies in the general population have shown the annualised rates for subsequent infarction and cardiac death to range from 0% to 3.1%[1,8,9]. Subgroup analysis of diabetic patients in these studies has however revealed conflicting results, largely from the small proportion of patients with diabetes mellitus.

The current study, however, considered only patients with intermediate to high cardiovascular risk. Specifically, we considered the influence of diabetes mellitus on subsequent outcome. Although significant advances in the management of ischaemic heart disease has improved prognosis in the general population, patients with diabetes mellitus continue to have a high incidence of ischaemic heart disease and poor clinical

outcome[10]. Specifically, mortality from coronary artery disease has declined significantly in both non-diabetic men and women in the past decade but this improvement is minimal for diabetic men, and diabetic women actually experience an increase in mortality[11]. These data underscore the need for accurate risk stratification among diabetic patients. Two small studies of diabetic patients with normal DSE have suggested a low false-negative rate with good prognosis among patients with a negative scan[12,13].

A significant finding of our study is the adverse impact of diabetes mellitus on the otherwise excellent outcome after a normal DSE. The presence of diabetes mellitus independently predicted subsequent myocardial infarction, cardiovascular mortality and need for revascularisation. The other cardiovascular risk factors of hypertension, smoking, dyslipidaemia, a significant family history of coronary artery disease, and increasing age were not predictive of subsequent events. The reason for this reduced predictive value of a negative stress echocardiogram in patients with diabetes mellitus is uncertain. Previous studies have shown that the presence of diabetes mellitus is associated with an adverse cardiovascular outcome[14]. A recent study looking specifically at diabetic patients has also demonstrated an increased risk for cardiac events in spite of a negative stress echocardiogram[15]. The authors suggested that the absence of ischaemia on DSE is a less reliable indicator of event-free survival in diabetics compared with non-diabetics. One possibility is that diabetic patients are more likely to have diffuse coronary artery disease. This global rather than regional reduction of myocardial reserve may result in increased difficulty in the recognition of regional wall motion abnormalities.

Diabetes mellitus is known to result in a prothrombotic milieu[10]. Elevated coagulation factors, reduced fibrinolysis and increased platelet aggregation may result in increased risk of coronary occlusion. Because diabetic patients are also predisposed to autonomic dysfunction, the increased cardiac mortality may be consequent to ventricular arrhythmias. In fact, diabetes mellitus was recognised as a coronary artery disease risk-equivalent in the most recent NCEP guidelines[5], thus elevating its status beyond that of a simple cardiovascular risk factor. The previous account may explain the increased adverse outcome in patients with diabetes mellitus despite a normal DSE.

Our study has several limitations. These include a small population size and a relatively limited number of female patients. That none of the traditional cardiovascular risk factors such as hypertension, smoking and dyslipidaemia predicted the occurrence

of subsequent cardiac events suggests that the study may be underpowered. Nonetheless, diabetes mellitus was strongly predictive of subsequent events. Post-DSE management of patients was at the discretion of the attending physician and information on subsequent management was not available. Potential bias cannot therefore be discounted. Because these patients all have normal DSE findings, coronary angiography was not performed in the majority. We therefore do not have survival data correlating with angiographical findings.

In conclusion, this study demonstrates that a normal DSE does not accurately predict a favourable outcome among patients with diabetes mellitus. Despite a normal DSE and no previous documentation of ischaemic heart disease, diabetics continue to have a higher risk for subsequent cardiac events. These findings support the current recommendation of treating diabetes mellitus as a coronary artery disease risk-equivalent and underscore the need for aggressive risk factor control in diabetic patients, even when the DSE is normal. In patients without diabetes mellitus, however, DSE is likely to remain a useful test.

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