Prognostic Value of Dobutamine Stress Echocardiography in Patients With Diabetes

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OBJECTIVE — The aim of this study was to assess the incremental value of dobutamine stress echocardiography (DSE) for the risk stratification of diabetic patients who are unable to perform an adequate exercise stress test. Exercise capacity is frequently impaired in patients with diabetes. The role of pharmacologic stress echocardiography in the risk stratification of diabetic patients has not been well defined.

RESEARCH DESIGN AND METHODS — We studied 396 diabetic patients (mean age 61 ± 11 years, 252 men [64%]) with limited exercise capacity who underwent DSE for evaluation of known or suspected coronary artery disease (CAD). End points were hard cardiac events (cardiac death and nonfatal myocardial infarction) and all causes of mortality.

RESULTS — During a median follow-up of 3 years, 97 patients (24%) died (55 cardiac deaths), and 27 patients had nonfatal myocardial infarction. In an incremental multivariate analysis model, clinical predictors of hard cardiac events were history of congestive heart failure, previous myocardial infarction, hypercholesterolemia, and ejection fraction at rest. The percentage of ischemic segments was incremental to the clinical model in the prediction of hard cardiac events (χ^2 = 37 vs. 18, $P < 0.05$). Clinical predictors of all causes of mortality were history of congestive heart failure, age, hypercholesterolemia, and ejection fraction at rest. Wall motion score index at peak stress was incremental to the clinical model in the prediction of mortality (χ^2 = 52 vs. 43, $P < 0.05$).

CONCLUSIONS — DSE provides incremental data for the prediction of mortality and hard cardiac events in patients with diabetes who are unable to perform an adequate exercise stress test.

Diabetes Care 26:1074–1078, 2003

Diabetes is a major risk factor for coronary artery disease (CAD) and its complications (1–7). Identification of diabetic patients at a high risk of death and myocardial infarction is an essential step for planning the appropriate management strategy. Exercise stress testing is the most widely used method for evaluation of CAD (8–10). However, exercise capacity is frequently impaired in diabetic patients, particularly because of the higher prevalence of peripheral neuropathy and vascular disease in this population (11–14). Dobutamine stress echocardiography (DSE) has been reported as a safe and feasible method for evaluation of CAD in diabetic patients with limited exercise capacity (15,16). However, data regarding the incremental value of the technique in the risk stratification of diabetic patients are scarce (2). Additionally, currently there is no outcome data to support the role of stress echocardiography in the prediction of all causes of mortality in diabetic patients.

The aim of this study was to assess the incremental value of DSE in the prediction of death and hard cardiac events in diabetic patients after adjustment for clinical data.

RESEARCH DESIGN AND METHODS

Patients

The study included 408 patients with diabetes who were unable to perform an adequate exercise test, who underwent DSE at the Thoraxcenter (Rotterdam, the Netherlands) between January 1994 and January 2001. Diabetes was defined in the presence of a fasting blood glucose ≥140 mg/dl or requirement for insulin or oral hypoglycemic agents. Seven patients were excluded because of inadequate echocardiographic images and five patients were lost to follow-up. The final population of the study consisted of 396 patients. Hypercholesterolemia was defined as total cholesterol >200 mg/dl or use of a cholesterol-lowering agent. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Heart failure was defined according to the New York Heart Association classification. Patients' clinical characteristics are presented in Table 1. The local medical ethics committee approved the study protocol. Patients gave an informed consent to undergo the study.

DSE protocol

Left ventricular (LV) ejection fraction at rest was assessed using the modified biplane Simpson rule (17). After baseline echocardiography, dobutamine was in-

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Received for publication 4 December 2001 and accepted in revised form 9 September 2002.
Abbreviations: CAD, coronary artery disease; DSE, dobutamine stress echocardiography; LV, left ventricular.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics of the study population*

Characteristics (N = 396)	*n*	%
Sex (male)	252	64
Age (years)	61 ± 11	
Previous myocardial infarction	205	52
Previous myocardial revascularization	191	48
History of typical angina pectoris	140	35
History of heart failure (class I–II)	40	10
History of heart failure (class III–IV)	44	11
Hypertension	183	46
Hypercholesterolemia	145	37
Smoking	123	31
β-blockers	144	36
Calcium channels blockers	151	38
ACE inhibitors	192	48
Aspirin	277	70
Statins	138	35
Diabetic nephropaty	32	8
Diabetes type 2	344	87
Diabetes type 1	52	13
Reason for referral		
Evaluation of chest pain	234	59
Preoperative assessment	4	1
Evaluation of risk factors	141	36
Functional assessment after myocardial infarction	17	4

ACE, angiotensin-converting enzyme.

fused at a starting dose of 5 μg/kg per minute for 3 min, followed by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min (low-dose stage). The dobutamine dose was increased by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 3 min, up to a maximum dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were an achievement of the target heart rate (85% of the maximal heart rate predicted for age), the maximal dose of dobutamine and atropine, >2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, hypertension (blood pressure >240/120 mmHg), a decrease in systolic blood pressure of >40 mmHg, and significant arrhythmias.

Echocardiographic imaging and interpretation

Imaging was acquired at rest and continuously during the test and recovery. Images were recorded on videotapes and, in addition, the baseline, low-dose, peak-stress, and recovery images were recorded in a quad-screen format.

The interpretation of images was performed by two independent observers blinded to the patients' clinical data. In case of disagreement, a majority decision was achieved by a third observer. In our laboratory, the inter- and intraobserver agreement for DSE assessment are 92 and 94%, respectively (18). A 16-segment model was used for segmental analysis of LV function (17). Wall motion score index was determined at rest and peak stress as the sum of the segmental scores of the 16 segments divided by 16. Each segment was scored using a 5-point scale as follows: 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis. Ischemia was defined as new or worsened wall motion abnormalities during stress, which was indicated by an increase of wall motion score ≥1 grade in ≥1 segment (19). Ischemia was not considered to be present when akinetic segments at rest became dyskinetic during stress (20). DSE results were defined as abnormal if there was ischemia during stress or fixed wall motion abnormalities (19).

Follow-up

Follow-up was obtained by mailed questionnaires and scripted telephone interviews. Events were verified by contacting the patients' primary physician and reviewing medical records and death certificates. The end points considered were all causes of mortality and hard cardiac events (defined as nonfatal myocardial infarction and cardiac death). Sudden unexpected death occurring without another explanation was included as cardiac death. Myocardial infarction was defined according to usual clinical, electrocardiographic, and enzymatic criteria.

Statistical analysis

Continuous variables were presented as mean ± SD. Comparisons between groups were based on the Wilcoxon's rank-sum test. Categorical variables were summarized as percentages and group comparisons were based on the χ^2 test. Survival free of the end point of interest was estimated by the Kaplan-Meier method. Univariable and multivariable association of clinical and stress echocardiographic parameters with the end points of interest were assessed in the Cox proportional hazards framework. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The results of these analyses were summarized as hazard ratios with corresponding 95% CIs. The incremental value of DSE information over clinical data was assessed in two modeling steps. The first step consisted of fitting a multivariable model of only clinical data. Variables selected from the first step were then used as baseline risk factors, and dobutamine echocardiographic variables were added in a stepwise forward selection manner.

RESULTS — Clinical features are presented in Table 1. Dobutamine-atropine induced a significant increase of heart rate (77 ± 13 at rest to 132 ± 16 beats/min at peak dose, $P < 0.0001$), whereas systolic blood pressure did not increase (137 ± 27 mmHg at rest and 136 ± 32 mmHg at peak stress). Atropine was administered in 179 patients (45%). Angina occurred in 89 patients (22%), and ST-segment depression occurred in 61 patients (15%). Reasons for termination of the test were achievement of target heart rate in 320 patients (81%), angina in 42 patients (11%), ST-segment depression in 22 patients (5%), hypotension in 7 patients (2%), and ventricular arrhythmia in 5 patients (1%).

Resting wall motion abnormalities were detected in 309 patients (78%). Ischemia was detected in 144 patients (36%), and 129 of these patients had resting wall motion abnormalities as well. Among the 129 patients with resting and dobutamine-induced wall motion abnormalities, ischemia occurred in the vascular territory with resting wall motion abnormalities in 116 patients, whereas the remaining 13 patients had ischemia in vascular regions with normal resting wall motion in the related myocardial segments. DSE was considered abnormal (rest- and/or stress-induced wall motion abnormalities) in 324 patients (82%).

Outcome

During a median follow-up of 3 years (maximum 7 years), 97 patients (24%) died (55 cardiac deaths), 27 patients had nonfatal myocardial infarction (82 hard cardiac events), and 59 patients (15%) underwent myocardial revascularization.

Table 2—*Univariate association of clinical and stress echocardiographic variables with risk of hard cardiac events and death*

	Hard cardiac events				Death			
Variables	HR	95% CI	*P*	χ^2	HR	95% CI	*P*	χ^2
Age	—	—	—	—	1.03	1.01–1.05	0.003	9
Previous MI	2.1	1.2–3.4	0.004	8	—	—	—	—
History heart failure	2.3	1.4–3.7	0.0004	13	2.7	1.7–4.1	0.0001	21
WMSI rest	2.5	1.6–4.0	0.0001	18	2.3	1.5–3.4	0.0001	15
Ejection fraction rest (%)	0.02	0.01–0.09	0.0001	25	0.05	0.01–0.2	0.0001	20
Rest WMA	0.91	0.88–0.95	0.0001	21	0.89	0.84–0.94	0.0001	16
WMSI peak	—	—	—	—	2.4	1.6–3.7	0.0001	18
Ischemic segments (%)*	1.1	1.02–1.22	0.02	4	1.1	1.01–1.2	0.03	4

*Per increase of 10%. HR, hazard ratio; MI, myocardial infarction; WMA, wall motion abnormalities; WMSI, wall motion score index.

Fifteen patients (4%) underwent early revascularization (within 3 months after DSE), and 44 patients (11%) underwent late revascularization (>3 months). Thirty-seven (9%) and 22 patients (6%), respectively, underwent coronary artery bypass procedures and percutaneous transluminal coronary angioplasty during follow-up. Among the 144 patients who had ischemia by DSE, 54 underwent subsequent revascularization (91% of the total population revascularized). The remaining 90 patients with ischemia were treated medically during follow-up.

Clinical and DSE variables associated with an increased risk of hard cardiac events and all causes of mortality in the univariate analysis are demonstrated in Table 2.

Predictors of hard cardiac events and total mortality in the multivariate analysis model are presented in Table 3. Event-free survival curves according to the results of DSE are presented in Fig. 1 for hard cardiac events. Both fixed and transient wall motion abnormalities (ischemia) were associated with higher event rate. The cumulative hard cardiac event rate was higher in patients with abnormal, as compared with patients with normal, DSE results (7 vs. 5% at 1 year, 18 vs. 8% at 3 years, and 23 vs. 10% at 5 years; overall $P = 0.01$). Survival curves according to the presence of wall motion abnormalities at rest or induced during dobutamine stress are shown in Fig. 2. The cumulative death rate in patients with abnormal, as compared with patients with normal, DSE results was 9 vs. 3% at 1 year, 29 vs. 11% at 3 years, and 31 vs. 24% at 5 years (overall $P = 0.04$).

CONCLUSIONS — In this study, we assessed the predictors of death and nonfatal myocardial infarction in 396 diabetic patients with limited exercise capacity and known or suspected CAD who underwent DSE. During a median follow-up period of 3 years, 97 patients died (55 cardiac deaths). Nonfatal myocardial infarction occurred in 27 patients. Clinical predictors of hard cardiac events were a history of congestive heart failure, previous myocardial infarction, hypercholesterolemia, and ejection fraction at rest. Clinical predictors of all causes of mortality were age, hypercholesterolemia, ejection fraction at rest, and history of congestive heart failure. DSE provided incremental prognostic information for the prediction of both end points. Hard cardiac events were independently predicted by ejection fraction at rest as well as by the percentage of ischemic segments at stress. These findings demonstrate the importance of resting LV function and the severity of myocardial ischemia in determining the outcome of diabetic patients.

Peak dobutamine wall motion score index, which measures the sum of resting and stress-induced wall motion abnormalities, was incremental to clinical data in the prediction of all causes of mortality. The cumulative death rate in patients with abnormal, as compared with patients with normal, DSE results was 9 vs. 3% at 1 year, 29 vs. 11% at 3 years, and 31 vs.

Table 3—*Independent predictors of hard cardiac events and death using a two-step model*

		Hard cardiac events				Death			
Model	Variables	χ^2	*P*	HR (95% CI)	Model χ^2	χ^2	*P*	HR (95% CI)	Model χ^2
Clinical	Age	—	—	—		10	0.001	1.04 (1.01–1.06)	
	Heart failure	8	0.004	2.1 (1.3–3.3)		20	0.0001	2.8 (1.8–4.4)	
	Previous MI	6	0.01	1.9 (1.1–3.1)	18	—	—	—	43
	Hypercholesterolemia	10	0.0009	2.7 (2.0–6.0)		4	0.04	1.6 (1.0–2.5)	
	Ejection fraction	8	0.004	0.017 (0.01–0.1)		8	0.004	0.1 (0.02–0.5)	
Clinical + DSE	Sex	5	0.03	0.5 (0.3–0.9)		—	—	—	
	Heart failure	11	0.001	1.8 (1.1–2.9)		—	—	—	
	Ejection fraction	19	0.0001	0.21 (0.01–0.12)		—	—	—	52
	Ischemic segments (%)*	3	0.07	1.1 (1.00–1.22)	37	—	—	—	
	WMSI peak	—	—	—		13	0.0004	1.9 (1.36–2.65)	

*Per increase of 10%. HR, hazard ratio; MI, myocardial infarction; WMSI, wall motion score index.

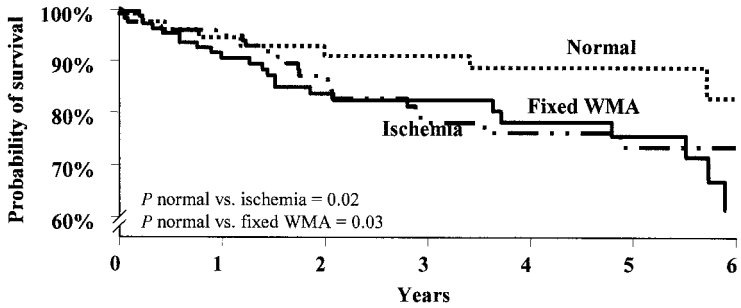

Figure 1—*Kaplan-Meier curves for survival, free of hard cardiac events in patients with normal DSE, ischemia, and fixed wall motion abnormalities (WMA).*

24% at 5 years (overall $P = 0.04$). From these data it appears that the maximal value of a normal DSE study in the prediction of a lower risk status is obtained at an intermediate term follow-up of 3 years, when survival curves showed the greatest diversion between patients with normal and abnormal study.

Previous studies

To date, this is the first study that evaluates the role of stress echocardiography in the prediction of all causes of mortality in diabetic patients. The prognostic value of DSE in diabetic patients has been a subject of controversy among previous studies. Hung et al. (21) studied 116 diabetic and 222 nondiabetic patients after acute myocardial infarction. They observed that shorter dobutamine time, as opposed to DSE positivity, has a higher value for the prediction of events in diabetic patients during a mean follow-up of 21 months. Conversely, Bates et al. (16) reported that DSE was a powerful test for the prognostic stratification of 53 patients with juvenile-onset insulin-dependent diabetes who were considered for kidney and/or pancreas transplantation. Recently, Bigi et al. (22) studied 108 diabetic patients who were followed-up for 20 ± 17 months after DSE and 151 diabetic patients who were followed-up for 33 ± 26 months after dipyridamole stress test. Cox's model selected peak wall motion score index as the only significant independent predictor of cardiac events. The study included patients who were able to perform exercise stress test and, as such, represent a lower risk population. This may explain the higher mortality rate in our study as compared with Bigi et al. (24 vs. 8%). Another explanation for the higher mortality in our study is the longer duration of the follow-up (3 vs. 2 years). Elhendy et al. (10) assessed the value of exercise echocardiography in the prediction of cardiac events in 563 diabetic patients. The extent of both resting LV dysfunction and myocardial ischemia was predictive of cardiac events incremental to clinical data. The event rate in that study was much lower than in our study (9 vs. 21%), reflecting the high-risk status of a population unable to perform exercise stress test in our study. Although exercise stress testing is the most physiological stress method for inducing myocardial ischemia and provides data on exercise capacity, our study showed that DSE is an alternative in patients with limited exercise capacity. Due to the high event rate in this group, stress testing is more likely to identify a larger proportion of patients at highest risk of adverse outcome.

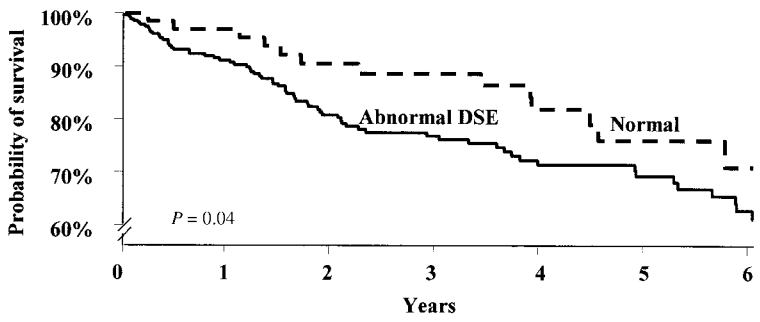

Figure 2—*Kaplan-Meier survival curves of patients with normal and abnormal DSE results.*

The American Heart Association recommended the use of exercise stress myocardial perfusion imaging for the evaluation of CAD in diabetic patients based on the published data on the utility of the technique in diabetic patients. It was concluded that there are currently no outcome data to define the role of stress echocardiography as a prognostic tool in diabetic patients (2). Our study supports recent evidence of the value of stress echocardiography as a prognostic tool in diabetic patients (23,24).

Limitations of the study

While the results in this study support the utility of DSE in patients with diabetes, they do not demonstrate superiority of DSE over exercise stress testing. The latter provides additional prognostic information by assessing exercise capacity, heart rate recovery, and other parameters measured during treadmill or bike testing.

In conclusion, DSE provides data incremental to clinical variables for the prediction of death and cardiac events in diabetic patients with suspected or known CAD who are unable to perform an adequate exercise stress test. Resting LV function and extent of myocardial ischemia during DSE are important predictors of outcome in these patients.

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