Long-Term Prognostic Value of Dobutamine-Atropine Stress Echocardiography in 1737 Patients With Known or Suspected Coronary Artery Disease

A Single-Center Experience

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Background—The purpose of this study was to assess the long-term value of dobutamine-atropine stress echocardiography (DSE) for prediction of late cardiac events in patients with proven or suspected coronary artery disease.

Methods and Results—Clinical data and DSE results were analyzed in 1734 consecutive patients undergoing DSE between 1989 and 1997. Seventy-four patients who underwent revascularization within 3 months of DSE and 1 patient lost to follow-up were excluded; the remaining 1659 (median age, 62 years; range, 14 to 99 years) were followed up for 36 months (range, 6 to 96 months). Wall motion abnormalities at rest and the presence and extent of stress-induced wall motion abnormalities (ischemia) were scored for each patient. Cardiac events were related to clinical and ECG data and DSE results. Four hundred twenty-eight cardiac events occurred in 366, documented cardiac death in 108 (total death, 247), nonfatal infarction in 128, and late revascularization in 192 patients. In a multivariable Cox proportional-hazards model, the ratio of documented cardiac death or (re)infarction was increased in the presence of stress-induced ischemia (hazard ratio, 3.3; 95% CI, 2.4 to 4.4) and extensive rest wall motion abnormalities (hazard ratio, 1.9; 95% CI, 1.3 to 2.6). The number of ischemic segments was predictive for late cardiac events. A normal DSE carried a relatively good prognosis, with an annual event rate of cardiac death or infarction of 1.3% over a 5-year period.

Conclusions—In a large group of patients, DSE has an added value for predicting late cardiac events during long-term follow-up, improving the separation between high- risk and very-low-risk patients. **(*Circulation*. 1999;99:757-762.)**

Key Words: coronary disease ■ echocardiography ■ prognosis ■ risk factors

Dobutamine-atropine stress echocardiography (DSE) is commonly used to assess the extent, location, and severity of coronary artery disease (CAD).[1] DSE is widely available and particularly useful in patients who cannot exercise because of noncardiac disease such as stroke or peripheral vascular disease or when ECG abnormalities preclude the diagnosis of ischemia. Several studies have evaluated the prognostic value of DSE for cardiac events during vascular surgery,[2] after acute myocardial infarction,[3] and in patients with severe left ventricular dysfunction.[4] However, the long-term prognostic value of DSE in a large study group for late cardiac events remains ill defined. Assessment of the long-term prognosis of DSE is important because the test may not only identify high-risk patients in whom further interventions are necessary but also select low-risk patients in whom additional procedures and intensive medical follow-up are not required.

The principal purpose of this study was to assess the prognostic value and usual clinical parameters for late cardiac events of DSE in a large group of patients.

Methods

Patient Selection

Between 1989 and 1997, 1734 consecutive patients underwent DSE at the Thoraxcenter (Rotterdam, the Netherlands). The test was requested for diagnostic reasons in 707 patients, for preoperative cardiac risk assessment in 722, or for evaluation of viable myocardium in 305 with left ventricular dysfunction. Follow-up was successful in 1733 of the 1734 patients. Seventy-four patients who underwent coronary revascularization within 3 months of the DSE were excluded from analysis. In these patients, the decision to revascularize was already made on clinical grounds and coronary angiography results. DSE was performed as part of a protocol to evaluate the efficacy of new coronary artery intervention procedures. Data from the remaining 1659 patients are reported.

Clinical cardiac risk factors, including hypertension, smoking, hypercholesterolemia, diabetes mellitus, the presence congestive heart failure, angina pectoris, and a previous myocardial infarction (history and/or ECG), were recorded at the time of the DSE. Hypertension was indicated if blood pressure ≥140/90 mm Hg or if the patient was treated with antihypertensive medication. Diabetes mellitus was recorded in patients with a fasting glucose level of ≥7.8 mmol/L or in those who required treatment, and hypercholes-

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terolemia was indicated if total cholesterol was ≥6.4 mmol/L or the patient was receiving lipid-lowering therapy.

DSE Procedure

DSE was performed as previously described.[2] β-Blocker medication was not discontinued for the study. Off-line assessment of echocardiographic images was performed by 2 independent investigators. From 1989 to 1993, a 14-segment 4-point score was used;[5] after 1993, a 16-segment 5-point score was used.[6] Ischemic myocardium was considered to be present in segments exhibiting worsening of movement during stress, except for akinesia becoming dyskinesia, which was considered a mechanical phenomenon.[7] For each patient, the number of abnormal segments at rest was scored, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress on the basis of the standard 14- or 16-segment model, and the extent and location of stress-induced ischemia were noted. The location of ischemia was noted as either anterior (anterior, lateral, apical, and septal) or posterior (posterior and inferior). The intraobserver and interobserver agreements of the interpretation of the echocardiographic images were 92% and 90%, respectively. Extensive rest wall motion abnormalities (RWMAs) were considered if the wall motion score at rest was ≥1.70, which represents the optimal cutoff value for prediction of late cardiac death, (re) infarction, and revascularization assessed by receiver-operating characteristic analysis.

Follow-Up

Follow-up data were obtained in 1997, ranging from 6 to 96 months after DSE. Events were assessed by physicians who were unaware of the patients' former stress test results. The present status was determined by contacting the patient's general physician and/or through review of hospital records. The date of the last interview or review was used to calculate follow-up time. Evaluated end points included death, myocardial infarction, and coronary revascularization. Deaths were classified as either documented cardiac or other. Cardiac death was defined by clinical data of acute myocardial infarction and/or significant cardiac arrhythmias and/or refractory congestive heart failure, together with ECG and autopsy studies when available; nonfatal myocardial infarction was defined by cardiac isoenzyme levels and development of new ECG changes. Revascularization by coronary angioplasty or bypass surgery >3 months after the original DSE was considered to reflect new or progressive symptoms. In the case of 2 simultaneous cardiac events, the worse event was chosen: documented cardiac death was considered less severe than nonfatal infarction, which was less severe than coronary revascularization.

Statistical Analysis

Univariable and multivariable Cox proportional-hazards regression models were used to identify independent predictors of late cardiac events. The risk of a given variable was expressed by a hazard ratio (HR) with corresponding 95% CIs. Variables were considered significant if the null hypothesis of no contribution could be rejected at $P=0.05$. The probability of the absence of cardiac events was calculated by the Kaplan-Meier method and compared between groups by use of the log-rank test. Receiver-operating characteristic analysis was used to determine the "optimal" cutoff point for prediction of late events with respect the wall motion score at rest and the number of ischemic segments. The best cutoff point was defined as the point with the highest sum of sensitivity and specificity.[8]

Results

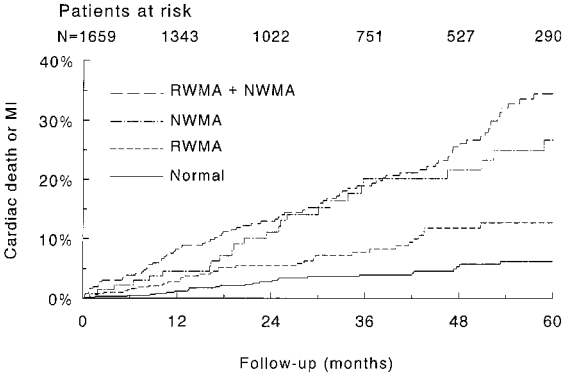
Demographics

Of 1659 patients, 1172 (71%) were male; the median age was 62 years (range, 15 to 99 years). Other characteristics were previous myocardial infarction, 705 (42%); typical angina pectoris, 358 (22%); diabetes mellitus, 137 (8%); hypercholesterolemia, 212 (13%); and hypertension, 485 (29%). Three hundred fifty-nine (20%) were taking β-blockers.

DSE Results

Heart rate during DSE increased from 73±14 to 124±21 bpm ($P=0.0001$) and systolic blood pressure from 136±24 to 138±30 mm Hg ($P=0.004$), whereas diastolic blood pressure decreased from 77±13 to 72±16 mm Hg ($P=0.0001$). The highest dobutamine dose used was 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 3% of the patients, 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 12%, 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 35%, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 50%. Atropine was administered in 354 patients (29%). Patients taking β-blocker therapy before the test required atropine more frequently (167 of 359, 47%) than those who were not (187 of 1300, 14%; $P<0.05$). Side effects requiring termination of the test were cardiac arrhythmias in 22 patients (1.3%) (ventricular fibrillation in 3, sustained ventricular tachycardia in 13, and atrial fibrillation in 6), symptomatic and severe hypotension (decrease in systolic blood pressure >40 mm Hg) in 6 (0.4%), hypertension (>240/130 mm Hg) in 3 (0.2%), and chills in 4 (0.2%). In addition, a number of side effects occurred in patients who were able to continue the test: short ventricular tachycardia (<10 complexes) in 44, atrial fibrillation in 21, and severe asymptomatic hypotension in 61 (4%). Thus, the total incidence of severe hypotension was 67 (4.4%). There were no myocardial infarctions or fatal complications of the stress test.

New wall motion abnormalities (NWMAs) were observed in 508 patients (31%), and ECG signs of ischemia were seen in 558 (34%). There was no relation between stress-induced ischemia (NWMA) and the occurrence of hypotension or arrhythmias, yet arrhythmias occurred more frequently in patients with extensive RWMA (wall motion score at rest >1.70) ($P=0.001$). The test was inconclusive, without achievement of target heart rate or ischemia, in 6.3% because of maximum dose of dobutamine and atropine (6%), cardiac arrhythmias (0.05%), symptomatic hypotension (0.15%), and nausea or chills (0.1%). Most patients with insufficient heart rate increase (69 of 95, 73%) were taking β-blockers. The



Kaplan-Meier curves for cardiac death or infarction during follow-up by results of DSE (with or without NWMA and/or RWMA). Each plot represents cumulative percentage of patients remaining event free. A significant difference exists in event-free survival between patients with NWMAs and RWMAs and those with normal DSE. MI indicates myocardial infarction.

TABLE 1. Univariable Predictive Value of Clinical Risk Factors for CAD and Stress Results for Late Cardiac Events

	HR (95% CI)			
	Cardiac Death	Cardiac Death/MI	Revascularization	Cardiac Death/MI/Revascularization
NWMA	3.6 (2.4–5.3)	3.6 (2.7–4.9)	4.1 (3.0–5.4)	3.4 (2.8–4.1)
Extensive RWMA	4.5 (3.0–6.6)	2.5 (1.9–3.5)	1.9 (1.5–2.5)	2.3 (1.9–2.7)
ST-segment changes during DSE	2.2 (1.5–3.2)	2.2 (1.6–2.9)	2.0 (1.5–2.7)	2.1 (1.7–2.6)
ECG-detected LBBB	3.6 (2.0–6.6)	3.1 (1.9–5.0)	1.0 (0.5–2.1)	2.3 (1.5–3.2)
Previous MI	2.9 (1.4–3.1)	1.9 (1.4–2.5)	2.5 (1.9–3.4)	2.5 (2.0–3.0)
Diabetes mellitus	1.4 (0.7–2.8)	1.9 (1.2–3.1)	1.2 (0.7–2.0)	1.6 (1.2–2.3)
Angina	1.2 (0.8–1.9)	1.5 (1.1–2.1)	3.6 (2.7–4.8)	2.4 (2.0–2.9)
Age (per year)	1.02 (1.00–1.04)	1.00 (0.99–1.01)	0.99 (0.98–1.00)	0.99 (0.99–1.00)
Age >70 y	1.3 (0.9–2.0)	1.0 (0.7–1.4)	0.5 (0.3–0.8)	0.7 (0.5–0.9)
Hypertension	0.9 (0.6–1.4)	1.0 (0.7–1.4)	1.5 (1.1–2.0)	1.3 (1.0–1.7)
Hypercholesterolemia	0.7 (0.3–1.9)	2.0 (1.1–3.5)	3.8 (2.6–5.6)	4.7 (3.4–6.6)

MI indicates myocardial infarction; Extensive RWMA, wall motion score at rest >1.70. See Methods for definition of hypertension and hypercholesterolemia.

cardiac event rate in these patients was not different from the event rate in patients with a complete DSE.

Follow-Up Results

Of the 74 patients who were referred for coronary revascularization within 3 months of DSE, 49 had stress-induced myocardial ischemia. None of these patients sustained a myocardial infarction before revascularization. Death was assessed in 247 of 1659 patients. Cardiac events occurred in 366 patients: documented cardiac death in 108, nonfatal myocardial infarction in 128, and late coronary revascularization in 192. Nonfatal stroke occurred in 28 patients.

Predictive Value of Clinical Data and DSE Results

Death occurred in 14% during the 5-year follow-up in patients with a normal test versus 30% in patients with both NWMAs and RWMAs ($P=0.0001$) (the Figure). A univariable Cox model was used to identify the predictive value for cardiac events for all clinical data and stress test results. The significant results for cardiac death, cardiac death or (re)infarction, coronary revascularization, and all cardiac event are presented in Table 1. The strongest univariable predictor was NWMA. In patients with "limited" ischemia (1 segment), the HR was 2.9 (range, 1.3 to 3.0), which increased to 4.0 (range, 2.6 to 5.2) ($P=0.001$) if ≥2 ischemic segments were present. There was no further increase in HR if >2 segments showed ischemia. No relation was observed between the location of ischemic segments (anterior versus inferior) and subsequent cardiac death or infarction.

In a stepwise logistic regression model, NWMA was the strongest predictor of cardiac death, infarction, and late coronary revascularization (Table 2).

To evaluate the additional prognostic value of specific clinical characteristics and extensive RWMA in patients with NWMA for the predictive value of cardiac death or infarction, an interaction analysis was performed (Table 3). In all patients, induction of NWMA increased the risk for cardiac death and (re)infarction 2.4-fold. In patients with extensive RWMA or a left bundle-branch block (LBBB), the incremen-

TABLE 2. Multivariable Predictive Value of Clinical Risk Factors for CAD and Stress Results for Late Cardiac Events

	HR (95% CI)			
	Cardiac Death	Cardiac Death/MI	Revascularization	Cardiac Death/MI/Revascularization
NWMA	3.1 (2.0–4.6)	3.3 (2.4–4.4)	3.3 (2.4–4.5)	3.5 (2.8–4.3)
Extensive RWMA	3.9 (2.6–5.8)	1.9 (1.3–2.6)	NS	1.7 (1.4–1.8)
ECG-detected LBBB	NS	2.2 (1.4–3.5)	NS	1.7 (1.2–2.6)
Diabetes mellitus	NS	1.7 (1.0–2.7)	NS	NS
Angina	NS	NS	2.4 (1.7–3.2)	1.7 (1.4–2.0)
Age (per year)	1.04 (1.02–1.06)	NS	NS	NS
Hypercholesterolemia	NS	NS	4.0 (2.7–5.8)	3.0 (2.2–4.1)

Abbreviations and explanations as in Table 1.

TABLE 3. Study Results

	No. of Patients			Cardiac Death or MI, n (%)			Likelihood Ratio	
Presenting Feature	All	No NWMA	NWMA	All	No NWMA	NWMA	No NWMA	NWMA
β-Blocker use								
No	1300	901	399	163 (12.5)	62 (6.9)	101 (25.3)	0.52	2.4
Yes	359	250	109	34 (9.5)	12 (4.8)	22 (20.2)	0.48	2.4
LBBB on ECG								
No	1583	1107	476	176 (11.1)	67 (6.1)	109 (22.9)	0.52	2.4
Yes	76	44	32	21 (27.6)	7 (15.9)	14 (43.8)	0.50	2.0
Previous MI								
No	954	741	213	79 (8.3)	33 (4.5)	46 (21.6)	0.52	3.1
Yes	705	410	295	118 (16.7)	41 (10.0)	77 (26.1)	0.55	1.8
Rest wall motion score								
<1.7	1350	976	374	135 (10.0)	53 (5.4)	82 (21.9)	0.51	2.5
≥1.7	309	175	134	62 (20.1)	21 (12.0)	41 (30.6)	0.54	1.8
Diabetes mellitus								
No	1522	1061	461	175 (11.5)	67 (6.3)	108 (23.4)	0.52	2.4
Yes	137	90	47	22 (16.1)	7 (7.8)	15 (31.9)	0.44	2.4
Sex								
Male	1172	773	399	156 (13.3)	54 (7.0)	102 (25.6)	0.49	2.2
Female	486	377	109	41 (8.4)	20 (5.3)	21 (19.3)	0.61	2.6
Age, y								
<70	1207	802	405	149 (12.3)	53 (6.6)	96 (23.7)	0.50	2.2
≥70	452	349	103	48 (10.6)	21 (6.0)	27 (26.2)	0.54	3.0
All patients	1659	1151	508	197 (11.9)	74 (6.4)	123 (24.2)	0.51	2.4

Abbreviations as in Table 1.

tal value of NWMA was less (1.8 and 2.0, respectively). The cardiac event rate in patients with hypotension or hypertension during DSE was not significantly different. The annual event rate of cardiac death or myocardial infarction was 1.2% over a 5-year period in 641 patients with a normal DSE (no RWMA and no NWMA): 5.4% in patients with NWMA and 6.8% in patients with both NWMA and RWMA (the Figure).

Discussion

As shown in previous studies,[4,9–11] parameters representing impaired left ventricular function (extensive RWMA) and parameters representing the presence or extent of CAD (NWMA, angina, and a previous infarction) or a high likelihood of CAD (diabetes mellitus and old age) were related to cardiac death, (re)infarction, and coronary revascularization at long-term follow-up. This is the first study using DSE to confirm these results in a large study population with nearly complete long-term follow-up. The rate of cardiac death or myocardial infarction in patients with NWMA or extensive RWMA increased 3.6- and 2.5-fold, respectively. In patients with extensive RWMA or an LBBB, induction of NWMA during DSE increased the frequency of cardiac death or (re)infarction during a 5-year period from 12% to 31% and from 16% to 44%, respectively (Table 3). The incremental value of NWMA in these subgroups of patients was less compared with the entire population. This may be related to the high pretest likelihood of underlying CAD in both groups or to the difficulty in assessing NWMA in these patients. The absence of NWMA, even in patients with β-blocker therapy and diabetes mellitus, carried a good prognosis, with an annual rate of any cardiac event of 1.3% (cardiac death, infraction, or revascularization). Hypotension or hypertension during DSE did not alter its prognostic value.

In contrast to previous post–myocardial infarction studies, the predictive value for cardiac death of impaired left ventricular function in this study was less than markers of ischemia,[12] although the difference was not significant. This may be related to patient selection and study procedures. In most postinfarction series, patients with signs of ischemia underwent PTCA or CABG to reduce myocardial ischemia. In contrast, many patients were enrolled for evaluation before vascular surgery (42%), whereas few of these patients did undergo PTCA or CABG. Furthermore, 74 patients (4%) who underwent early coronary revascularization were excluded from analysis.

Prognostic Value of Noninvasive Stress Testing: A Comparison Between Stress Echo and Myocardial Perfusion Imaging

In most comparative studies, stress echocardiography is less sensitive for the detection of myocardial ischemia but more specific than perfusion scintigraphy.[13] Therefore, DSE may have an advantage for short-term risk assessment, such as

preoperative cardiac risk stratification, because more severe CAD, which is related to perioperative cardiac events, will be detected and treated with a reduced rate of false-positive results compared with myocardial perfusion scintigraphy.[2] However, mild CAD missed by DSE may have a negative impact on the long-term prognostic value of a normal DSE. Previous studies by Krivokapich et al[14] with exercise stress echo and Sciari et al[3] and Poldermans et al[15] with DSE reported an average high annual incidence of cardiac death or infarction of 6.6% to 8.5% in patients with proven or suspected CAD without stress-induced ischemia. The recent study of Steinberg et al[16] showed a similar frequency of nonfatal infarction in patients with and without ischemia during DSE (4.8% versus 3.8%) during a 5-year follow-up in a group of 120 patients. This seems to be in contrast to the results with perfusion scintigraphy; the annual event rate of cardiac death or infarction in patients with a "normal" perfusion scintigraphy was <1% (range, 0% to 2.2%) in 3573 patients with a mean follow-up of 28 months,[10] and a positive perfusion scintigraphy increased the annual risk 6- to 12-fold. It should be appreciated, however, that this analysis was restricted to patients without perfusion abnormalities at rest and during stress. If similar patients were studied with DSE (normal function at rest and during stress), the annual event rate of cardiac death or infarction was only 1.3% during a mean follow-up of 36 months (the Figure). The annual cardiac event rate increased to 6% in patients with NWMA and to 8% in patients with RWMA and NWMA. This suggests that the predictive value of both noninvasive tests (DSE and perfusion scintigraphy) are, in fact, similar. A recent study[17] comparing DSE and ^{99m}Tc sestamibi SPECT in a subgroup of our study population (n=220) showed a comparable predictive value for both imaging modalities with the use of dobutamine stress.

Both imaging modalities provide similar incremental prognostic information. The choice of technique should be made on the basis of availability, local experience, skill, and cost. Perfusion imaging may be preferred in patients with poor echographic image quality.

Regional DSE Ischemia

Previous studies with perfusion scintigraphy stressed the importance of the location and extent of ischemia.[10] In particular, ischemia in the territory of the left anterior descending artery was related to late cardiac events. In this study, comparison of anterior (anterior, septal, lateral, and apex) with posterior (inferior and posterior) induced ischemia showed no difference in late cardiac events. Furthermore, the extent of ischemia during DSE was only weakly related to late cardiac death or infarction. Ischemia in only 1 segment had a lower risk than in 2 ischemic segments (HR, 2.9 versus 4.0; $P=0.001$) for late cardiac events, but additional ischemic segments did not increase the annual rate. This may be related to the higher specificity of DSE for severe CAD compared with perfusion scintigraphy.

Feasibility and Safety of DSE

DSE has a high feasibility in patients with adequate echocardiographic images. The test was inconclusive in only 6.3% of all patients. This was due mostly to insufficient heart rate increase despite the use of atropine and dobutamine. Most of these patients were taking β-blockers. The test might be repeated after cessation of β-blockers, although a normal test without "target heart rate" achievement will probably rule out severe CAD.[1]

As in previous studies,[18] the most frequent side effects were severe hypotension (4.4%) and cardiac arrhythmias (5%). Both side effects were not related to the induction of ischemia. Hypotension was usually well tolerated, did not interfere with the test, and did not influence the prognostic value of DSE. Cardiac arrhythmias were more frequent in patients with extensive RWMA but were not related to ischemia or the addition of atropine and were mostly self-limiting.

Study Limitations

The present data apply only to patients with adequate echocardiographic images in whom all myocardial segments were visible. Our results, obtained in a single center with a high volume of DSE, and other echo studies do not necessarily apply to other centers.[19] However, major improvements are expected in echo quality with the introduction in the clinical area of second harmonic imaging and contrast echocardiography.[20]

Conclusions

The risk of future cardiac events can be assessed by DSE, distinguishing subgroups of patient with high (>30% in 5 years), median (12% in 5 years), and low (8% in 5 years) risk. In particular, patients with normal results during DSE have a good prognosis.

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