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Prognostic Value of Dobutamine Echocardiography in Patients With Left Ventricular Dysfunction

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Objectives. **This study sought to establish the prognostic implications of ischemic and viable myocardium identified by dobutamine echocardiography in patients with left ventricular dysfunction.**

Background. **Recent studies have suggested that in patients with viable myocardium identified by positron emission tomography, medical treatment is associated with recurrent cardiac events. Dobutamine echocardiography has been used to identify viable myocardium in patients with left ventricular dysfunction, but the prognostic significance of this test is undefined.**

Methods. **One hundred thirty-six consecutive patients (mean [±SD] age 67 ± 7.9 years; 104 men) with moderate or severe left ventricular dysfunction (left ventricular ejection fraction 30 ± 5%) undergoing dobutamine echocardiography were included in the study. Dobutamine was administered using a standard incremental protocol (5 to 40 μg/kg body weight per min intravenously in 3-min stages) with additional atropine (1 mg intravenously) as required. Standard body weight echocardiographic views were digitized on-line and compared using a side-by-side display. Viable myocardium was identified by enhancement of regional function at low dose (<10 μg); scar was diagnosed by akinesia at rest or dyskinesia without change and ischemia as new or worsening dysfunction. One hundred thirty patients (95%) were followed up for 16 ± 8 months after the original study for major cardiac events (cardiac death, myocardial infarction or severe unstable angina requiring late myocardial revascularization).**

Results. **No significant complications occurred during dobutamine echocardiography. Viable myocardium was detected in 26 patients (19%), ischemia in 23 (17%), both viability and ischemia in 13 (10%) and scar in 74 (54%). Of 108 patients treated medically, 46 had viable or ischemic myocardium, and 62 had scar only. There were no significant differences in age or other clinical characteristics, stress response, left ventricular dimensions and ejection fraction between the two groups. Cardiac events occurred in 26 medically treated patients (24%): 18 died of cardiac-related causes; 4 had a nonfatal myocardial infarction; and 4 had late revascularization because of unstable angina. The event rate was greater in patients with viable or ischemic myocardium than those with scar (43% vs. 8%, p = 0.01 by log-rank test). In a Cox regression model, the presence of viable or ischemic myocardium was found to predict subsequent events (relative risk 3.51, p = 0.02) independently of ejection fraction and age.**

Conclusions. **Viable or ischemic myocardium detected at dobutamine echocardiography in patients with left ventricular dysfunction is associated with an adverse prognosis, independent of age and ejection fraction.**

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The long-term outcome of patients with left ventricular dysfunction can be predicted by clinical factors, the severity of left ventricular dysfunction and the presence of residual ischemic myocardium (1–3). Recent studies using myocardial metabolic imaging with positron emission tomography have shown (4–7) that the presence of residual viable myocardium is an adverse prognostic factor, with an effect additive to that of ischemia. Both ischemic and viable tissue may be jeopardized if perfused by a stenosed coronary vessel and are therefore susceptible to recurrent ischemic events.

Whereas positron emission tomography is expensive and not widely available; dobutamine stress echocardiography is an inexpensive and potentially widely available noninvasive test for the diagnosis and evaluation of coronary artery disease. In addition to its established role in the detection of ischemic responses in patients with normal left ventricular function (8–10), dobutamine echocardiography can distinguish viable from nonviable myocardium in patients with left ventricular dysfunction (11,12), and recent studies have demonstrated (13,14) concordance with positron emission tomography with respect to detection of viability. However, in addition to its diagnostic role, dobutamine echocardiography is often used for risk stratification, particularly for preoperative screening in patients who are unable to exercise (15–17). The purpose of the present study was to establish the prognostic implications of identifying both ischemia and viability with dobutamine echocardiography in patients with left ventricular dysfunction.

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Methods

Patient selection. Over a 2-year period, 136 consecutive patients with known or suspected coronary artery disease and at least moderate rest left ventricular dysfunction and without valvular heart disease, recent myocardial infarction or myocardial revascularization (<3 months) underwent dobutamine echocardiography. Patients with a left ventricular ejection fraction <40%, measured off-line, were enrolled for follow-up study. These patients represented the usual spectrum of clinical referrals for dobutamine echocardiography at our institution and were tested either for preoperative risk stratification before noncardiac surgical intervention or for diagnosis or functional evaluation of coronary artery disease, particularly in patients unable to exercise.

Dobutamine stress testing. Dobutamine was administered according to a standard protocol (10), starting at 5 μg/kg body weight per min and increasing to 10 μg/kg per min after 3 min and then incrementally every 3 min to a maximum of 40 μg/kg per min. Atropine (0.5 to 1.0 mg) was administered if heart rate at the 40-μg/kg per min dose was <85% of the age-predicted maximum, according to the equation: Predicted peak heart rate = 220 − Age. The test was performed with standard clinical, hemodynamic and electrocardiographic (ECG) monitoring; symptoms, heart rate, blood pressure and 12-lead ECG were recorded every 2 to 3 min. The end points of the test were completion of the protocol, development of severe angina or extensive ischemia or occurrence of a severe side effect.

Stress electrocardiography. Dobutamine stress ECG results were interpreted as normal, ischemic or nondiagnostic. An *ischemic response* was defined as horizontal or downsloping ST segment depression or elevation >0.1 mV occurring in leads with normal baseline ST segment levels. A *nondiagnostic response* was identified in patients with left bundle branch block or >0.1-mV rest ST segment and T wave deviation, digitalis therapy or paced rhythm and a *negative response* in patients with <0.1-mV stress-induced ST segment depression.

Echocardiography. Echocardiographic images were obtained using standard equipment, and a full rest study was obtained for each patient before the start of dobutamine infusion. Rest left ventricular dimensions at end-diastole and end-systole were measured in the standard parasternal long- and short-axis views. Ejection fraction at rest was calculated from apical views using the modified Simpson's rule.

Rest and stress images were digitized on-line in the parasternal long- and short-axis and apical four- and two-chamber views and placed in a cine loop, quad-screen format (ImageVue, Nova Microsonics). The four screens were successively filled with the rest, two low dose (5 and 10 μg) and peak dose (usually 40 μg) images.

Echocardiographic image analysis was performed by consensus of two investigators experienced in the interpretation of stress echocardiographic images and with no knowledge of both the clinical data and stress ECG findings. The interpretation was based on side-by-side comparison of images in the quad-screen digital display, as well as review of other cardiac cycles, including off-axis projections, from videotaped images. Analysis of regional left ventricular function was performed on a segmental basis using a standard 16-segment model, with regional wall scoring categorized as follows: 1 = *normal;* 2a = *mild hypokinesia;* 2b = *severe hypokinesia;* 3 = *akinesia;* and 4 = *dyskinesia. Ischemia* was defined as the development of a new or worsening wall motion abnormality in one segment or two adjacent segments if the basal inferior or posterior wall was involved, or if the segments were adjacent to significant scar, in which case the possibility of tethering could interfere with interpretation. *Viable myocardium* was defined as an improvement of thickening in at least one segment with rest hypokinesia or akinesia that occurred at the low to intermediate dose (5 to 20 μg). If these segments showed deterioration at peak dose, then this biphasic response was interpreted as showing both viability and ischemia. *Myocardial scar* was identified in segments with rest akinesia or dyskinesia that showed no thickening in response to dobutamine; however, these segments often had passive movement from tethering of normal hyperkinetic adjacent segments. Segments that were normal or mildly hypokinetic at rest and improved in the normal hyperkinetic manner in line with the overall segmental response were described as *normal.*

Follow-up. Patients were followed up by telephone, mail, chart review or contact with the treating physician after a minimal interval of 6 months. Follow-up data were available for 130 (96%) of the 136 patients after a period of 16 ± 8 months (mean ± SD). *Events* were defined as death, myocardial infarction or late myocardial revascularization due to unstable angina. In patients who died in-hospital or at home, the cause of death was elucidated from the medical record, the family and the local physician who signed the death certificate. A designation of *cardiac death* required documentation of significant arrhythmia or cardiac arrest, or both, or death attributable to congestive cardiac failure or myocardial infarction in the absence of any other precipitating factors. In the small number of deaths out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. No attempt was made to further subclassify cardiac deaths into those due to arrhythmia or heart failure because of acknowledged limitations in this area, particularly the inability to determine the terminal event in patients with precedent progressive failure followed by arrhythmia. *Myocardial infarction* was defined as a cardiac event requiring admission to hospital, with development of new ECG changes and cardiac enzyme level increase (creatine kinase >200 U). Hospital admissions for unstable angina or congestive cardiac failure were also documented but not considered "hard" cardiac end points if late revascularization was not provoked.

Statistical analysis. Baseline clinical and echocardiographic characteristics are given as mean value ± SD for continuous variables and as number (percent) for categoric variables. Patients were classified into those with myocardial scar only and those with either viability or ischemia on dobutamine echocardiography. Differences in continuous variables were compared using the Student *t* test, whereas differ-

ences of categoric variables were compared using the chi-square test; $p < 0.05$ was considered significant.

Patients were then classified into two groups according to the occurrence of events during the follow-up period. Clinical and echocardiographic variables were again compared in a similar manner. To analyze the impact of dobutamine echocardiographic results on cardiac prognosis, cumulative survival estimates were plotted according to the presence or absence of viability or ischemia using the Kaplan-Meier technique. Differences between survival curves were tested with the log-rank chi-square statistic. To adjust for potential confounding from effects of age and ejection fraction, which were postulated to be the two most important predictors of prognosis aside from the dobutamine echocardiographic variables, the Cox proportional hazards model (18) was used. The proportional hazards assumption was found to be valid by constructing a plot of the logarithm of the cumulative hazard over time, as described by Christensen (19). Proportional hazards and Kaplan-Meier analyses were performed using the PHREG and LIFETEST procedures of the SAS 6.08 statistical package (20,21).

Results

Clinical characteristics. Of 136 patients included in the study (104 men, 32 women; mean age [±SD] 67 ± 7.9 years, range 48–87; mean ejection fraction 30 ± 5%), 55 were referred for dobutamine echocardiography as part of a preoperative evaluation, 35 with known coronary artery disease and an inability to exercise were referred for testing as part of usual follow-up protocols, 34 were referred for diagnosis of coronary disease in the presence of left ventricular dysfunction, and, in the latter stages of the study, 12 were referred directly for viability assessment as part of a preintervention workup. One hundred twenty patients (92%) had a previous documented myocardial infarction or ECG and echocardiographic evidence of infarction, and 44 (32%) had undergone previous bypass surgery.

Of 16 patients with left ventricular dysfunction without infarction, 14 had abnormal ECG responses at rest (left bundle branch block in 7, left ventricular hypertrophy and T wave inversion in 5, paced rhythm in 2), 3 had inducible abnormal responses on echocardiography, and 3 had evidence of significant coronary disease at catheterization. Approximately 10 patients had nondiagnostic ECG responses and no echocardiographic regional wall motion abnormalities, and in the absence of catheterization data, may have had either ischemic or dilated cardiomyopathy.

Coronary angiography was performed in 88 patients within 12 months of dobutamine echocardiography. Triple-vessel or diffuse native coronary disease was present in 45 patients, predominant single- or double-vessel disease in 36 and no significant obstruction in 7 (5 of these 7 showed echocardiographic regional wall motion abnormalities).

Dobutamine stress testing. There was no significant augmentation in systolic blood pressure in the overall group in response to dobutamine (rest 138 ± 23 mm Hg vs. peak dobutamine dose 141 ± 28 mm Hg), probably reflecting a number of patients with a moderate hypotensive response countering those with the anticipated increase in systolic pressure. Heart rate increased from 77 ± 11 beats/min at rest to 127 ± 13 beats/min at peak dobutamine dose; 81 patients (60%) achieved a heart rate response >85% age-predicted maximum. A total of 55 patients (40%) had an inadequate heart rate response (85% of age-predicted maximum) despite attainment of the peak dobutamine dose in 29. The submaximal responses were ascribed to early termination from side effects (15 patients), ischemia (11 patients), beta-adrenergic blocker therapy (10 patients), AV node disease with permanent pacemakers (2 patients) and unexplained causes (17 patients).

Ninety-four patients attained the peak dose of dobutamine (40 μg/kg per min). Despite selection of patients with moderate and severe left ventricular dysfunction, no major complications occurred during dobutamine stress testing. Five patients had nonsustained ventricular tachycardia, the maximal duration of which was 12 beats, without hemodynamic compromise. Five patients had nonsustained atrial tachycardia, and one developed atrial fibrillation that lasted for 2 h without notable compromise and reverted spontaneously to sinus rhythm. Test termination due to hypotension was more common earlier in the series; subsequently, hypotension without concurrent symptoms or other abnormalities was not used as an end point unless it was severe (systolic blood pressure <100 mm Hg). Furthermore, the use of atropine may have alleviated some vagal responses, allowing completion of the test protocol.

Dobutamine echocardiography. Of the 136 patients in the initial group who underwent dobutamine echocardiography, 26 (19%) were diagnosed as having viable myocardium only, 23 (17%) had an ischemic response only, and 13 (10%) had both viability and ischemia. Sixty-two patients therefore had evidence of myocardial viability or ischemia, or both. Fifty-seven (92%) of these 62 patients had involvement of two or more segments, with single-segment involvement in only 5 (3 with viability, 2 with ischemia), comprising apical anterior and apical lateral segments in 2 each and the proximal anterior septum in 1. Significant comorbidity and medical therapy were evenly distributed between patients with viability or ischemia and those with infarction only (Table 1).

Of 45 patients with severe coronary disease at catheterization, 26 (58%) had jeopardized myocardium at dobutamine echocardiography (19 with ischemia [42%], 7 with viability [16%]). This relatively low rate of ischemia may be partially due to extensive previous infarction because the ejection fraction in this group was 27 ± 4%. Furthermore, 15 (79%) of the 19 patients without jeopardized myocardium did not achieve 85% of age-predicted maximal heart rate compared with 40% in the overall group and 50% in the ischemic group with a submaximal heart rate response.

Echocardiographic findings and hemodynamic responses to dobutamine for patients with viability or ischemia, or both, and those with infarction only are shown in Table 2. There was no

Table 1. Clinical Features of Patients With Ischemic or Viable Myocardium and Those With Myocardial Scar Only

	Overall (n = 136)	Viab/Isc (n = 62)	Scar (n = 74)	p Value (scar vs. viab/isc)
Age (yr)	67 ± 7.9	66 ± 7.5	68 ± 7.9	NS
Diabetes	56/136 (41)	25/62 (40)	31/74 (42)	NS
Hypertension	94/136 (69)	44/62 (71)	50/74 (68)	NS
Hypercholesterolemia	92/136 (68)	43/62 (69)	49/74 (66)	NS
Smoking	61/136 (45)	33/62 (53)	28/74 (38)	0.07
Beta-blockers	19/136 (14)	8/62 (13)	11/74 (15)	NS
ACEI	70/136 (51)	30/61 (49)	40/74 (54)	NS
Nitrates	39/136 (29)	20/61 (33)	19/74 (26)	NS
Digoxin	28/136 (21)	9/61 (15)	19/74 (26)	0.11

Data presented are mean value ± SD or number (%) of patients. ACEI = angiotensin-converting enzyme inhibitor; Viab/Isc = viable/ischemic myocardium.

significant difference between the two groups with respect to left ventricular ejection fraction or rest left ventricular dimensions.

The ECG ST segment changes were not predictive of either ischemia or viability. The ST segment response was nondiagnostic in 56 patients (41%) (left bundle branch or intraventricular block in 26, left ventricular hypertrophy and ST segment changes in 21, diffuse ischemic changes at rest or paced rhythm in 9). Symptoms of chest pain occurred in 25 patients; 9 patients with pain and ST segment depression or elevation had an ischemic response confirmed on echocardiography. However, of the remaining 16 patients with chest pain and no or uninterpretable ST segment changes, only 3 had ischemia detected on echocardiography.

Cardiac events. Complete follow-up data were obtained for 130 patients (100 men, 30 women; mean age 68 ± 10 years) over a period of 16 ± 8 months. Six patients (4%) were lost to follow up (three from other states, two from overseas). The prevalence of viable or ischemic myocardium and other echocardiographic variables in the 6 patients lost to follow-up were similar to those in the remaining 130.

Of the 130 patients, 22 were referred for intervention within 3 months of dobutamine echocardiography (10 for coronary angioplasty, 11 for bypass surgery, and 1 for cardiac transplantation). All 11 patients who underwent bypass surgery had evidence of myocardial ischemia or viability on dobutamine echocardiography, but only 4 of 10 patients undergoing coronary angioplasty had detectable ischemia or viability. Patients with intervention may have influenced the results of long-term follow up and were thus analyzed separately. Late cardiac death occurred in three patients (14%) who underwent intervention, and one required repeat coronary angioplasty within 6 months of the index procedure.

Of the remaining 108 patients who had medical therapy on an intention-to-treat basis, 46 had viable or ischemic myocardium, and 62 had scar only on dobutamine echocardiography. In this group, there were 26 cardiac events in 26 patients (24%) (18 cardiac-related deaths due to myocardial infarction, congestive cardiac failure or arrhythmia; 4 nonfatal myocardial infarctions; 4 episodes of unstable angina requiring late revascularization). Fourteen patients required subsequent hospital admission for congestive cardiac failure (eight patients) or angina (six patients), but in the absence of documented infarction or coronary intervention, these events were not considered cardiac end points. Of these 14 patients, 6 had evidence of myocardial viability or ischemia, and the remaining 8 had myocardial scar alone.

Table 3 summarizes the distribution of clinical variables in

Table 2. Echocardiographic Features of Patients With Ischemic or Viable Myocardium and Those With Myocardial Scar Only (mean ± SD)

	Overall (n = 136)	Viab/Isc (n = 62)	Scar (n = 74)	p Value (scar vs. viab/isc)
LVEDV (ml)	171 ± 44	174 ± 43	169 ± 44	NS
LVESV (ml)	122 ± 36	125 ± 35	120 ± 36	NS
Ejection fraction (%)	30 ± 5	29 ± 5	30 ± 6	NS
Stroke volume (ml)	49 ± 11	50 ± 11	49 ± 11	NS
Rest heart rate (beats/min)	77 ± 11	75 ± 11	79 ± 11	NS
Rest SBP (mm Hg)	138 ± 23	138 ± 21	138 ± 25	NS
Peak heart rate (beats/min)	127 ± 13	126 ± 13	127 ± 14	NS
% age-predicted heart rate	83 ± 9	82 ± 8	83 ± 9	NS
Peak SBP (mm Hg)	141 ± 28	139 ± 27	143 ± 29	NS

LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; SBP = systolic blood pressure; Viab/Isc = viable/ischemic myocardium.

Table 3. Clinical Features of Patients With and Without Cardiac Events

	Events (n = 26)	No Events (n = 82)	p Value
Age (yr)	69 ± 6	68 ± 8	NS
Diabetes	10 (38)	34 (41)	NS
Hypertension	19 (73)	61 (74)	NS
Hypercholesterolemia	18 (69)	55 (67)	NS
Smoking	17 (65)	31 (38)	0.01
Beta-blockers	3 (12)	9 (11)	NS
ACEI	19 (73)	40 (49)	0.03
Nitrates	4 (15)	22 (27)	NS
Digoxin	6 (23)	15 (18)	NS

Data presented are mean ± SD or number (%) of patients. ACEI = angiotensin-converting enzyme inhibitor.

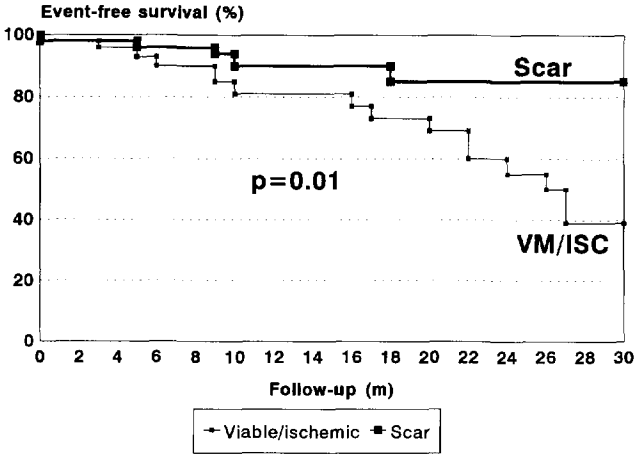

Figure 1. Life table demonstrating event rates in patients with infarction only (Scar) and those with viable or ischemic myocardium (VM/ISC).

medically treated patients with and without cardiac events. There was no significant difference between the prevalence of risk factors or medication usage between patients with and without events, except that smokers were disproportionately represented among patients with events. Likewise, analysis of echocardiographic variables, including left ventricular ejection fraction showed no significant difference between the two groups (Table 4). In patients with a cardiac event, there was a trend toward increased left ventricular end-diastolic (183 ± 41 vs. 167 ± 44 ml) and end-systolic volume (130 ± 37 vs. 119 ± 35 ml), but all other variables were similar.

The peak dose of dobutamine (40 μg/kg per min) was achieved in 75 (69%) of 108 patients undergoing follow-up echocardiography. In the 33 patients with early termination of the test before maximal dobutamine dose, 11 had cardiac events compared with 15 events in the 91 patients with the maximal dobutamine dose (33% vs. 20%, p = 0.04). Similarly, 63 (58%) of 108 patients followed up for primary cardiac events achieved >85% of age-predicted maximal heart rate, and 45 (42%) had a submaximal heart rate response. There were 16 cardiac events in the 45 patients with inadequate heart rate response as opposed to 10 events in the 63 patients with adequate heart rate response (36% vs. 16%, p = 0.02). In the 45 patients not attaining 85% age-predicted maximal heart rate, 21 had evidence of ischemia or viability as opposed to 23 of the 63 patients with adequate heart rate response (47% vs. 37%, p = 0.29). In the group with inadequate heart rate, the finding of echocardiographic, ECG or symptomatic ischemia often led to termination of the test before attainment of target heart rate and may account at least in part for the bias toward ischemia/viability and events in this group.

Relation between dobutamine echocardiography and cardiac events. Of 26 medically treated patients with an event, 20 (77%) had myocardial viability or ischemia detected during dobutamine echocardiography, and 6 (23%) had myocardial scar only. The event rate was greater in patients with viable or ischemic myocardium than in those with scar (43% vs. 8%, p = 0.01), and Kaplan-Meier survival analysis confirmed a significantly worse outcome (p = 0.01 by log-rank test) in the group with viability or ischemia than in the group with scar (Fig. 1). In a Cox regression model that included age, left ventricular ejection fraction and presence of ischemic or viable myocardium, the presence of viability or ischemia was found to predict subsequent events (adjusted relative risk 3.5, 95% confidence interval 0.10 to 0.80, p = 0.02), independent of ejection fraction or age (Table 5). Moreover, although analysis of the overall group of 46 patients with viability or ischemia showed an increased prevalence of cardiac events, subgroup analysis showed no significant difference between patients with viability and ischemia with respect to cardiac events (Fig. 2).

The relation of dobutamine echocardiographic results to

Table 4. Echocardiographic Features of Patients With and Without Cardiac Events

	Events (n = 26)	No Events (n = 82)	p Value
LVEDV (ml)	183 ± 41	167 ± 44	NS
LVESV (ml)	130 ± 37	119 ± 35	NS
Ejection fraction (%)	29 ± 6	30 ± 5	NS
Stroke volume (ml)	52 ± 9	48 ± 12	NS
Rest heart rate (beats/min)	76 ± 11	77 ± 11	NS
Rest SBP (mm Hg)	136 ± 25	140 ± 23	NS
Peak heart rate (beats/min)	121 ± 13	128 ± 14	NS
% age-predicted heart rate	80 ± 8	84 ± 8	NS
Peak SBP (mm Hg)	135 ± 25	144 ± 29	NS
Viab/Isc myocardium	20 (77%)	26 (32%)	< 0.0001

Data presented are mean ± SD or number (%) of patients. Abbreviations as in Table 2.

Table 5. Cox Proportional Hazards Model Results for Relative Risk of Viable or Ischemic Myocardium, Age and Ejection Fraction

	Relative Risk	p Value
Viability/ischemia	3.51	0.02
Age	1.03	0.28
Ejection fraction	1	0.88

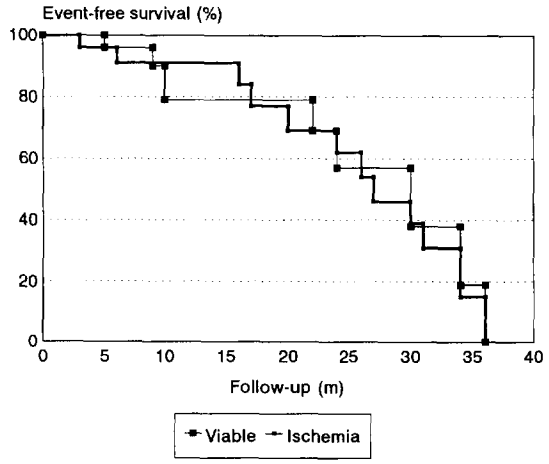

Figure 2. Comparison of event rates in patients with viable or ischemic myocardium.

outcome appeared to be unrelated to reason for testing. Of 53 patients who underwent testing for preoperative risk stratification, 22 (42%) had evidence of viable or ischemic myocardium. Twelve (46%) of these 22 patients had their management strategy altered by the results of dobutamine echocardiography (operation deferred in 4 pending coronary intervention, operation canceled in 5, operative strategy simplified in 3). Of 48 patients proceeding with noncardiac (predominantly vascular) surgery, 10 had viable or ischemic myocardium. No perioperative cardiac-related deaths or myocardial infarctions occurred in this group. Of 11 patients with atrial arrhythmias or exacerbation of congestive cardiac failure in the perioperative period, only 3 had myocardial viability or ischemia at dobutamine study, but left ventricular ejection fraction (24%) was lower in this group. At long-term follow-up, 10 (19%) of 53 patients experienced a cardiac event; 7 of 9 with a cardiac-related death and 1 with late coronary angioplasty in this subgroup had viable or ischemic myocardium on dobutamine echocardiography. This event rate was not significantly different from that in the remaining patients.

Discussion

The results of the present study show that the presence of viable or ischemic myocardium detected at dobutamine echocardiography in patients with left ventricular dysfunction is related to an increased incidence of cardiac events at long-term follow-up among those receiving medical therapy. Moreover, this finding appears to be independent of age and left ventricular ejection fraction. To our knowledge, the prognostic significance of viability detected by dobutamine echocardiography has not been shown previously.

Prognostic significance of ischemia at stress echocardiography. In different clinical scenarios, with different stress modalities, the finding of ischemia at stress echocardiography has been associated with subsequent cardiac events and an adverse long-term outcome, whereas the absence of ischemia implies a more favorable long-term prognosis (22). Among 360 patients with overall normal left ventricular function who underwent treadmill stress echocardiography, Krivokapich et al. (23) showed a threefold increase in the incidence of cardiac events in patients with positive stress echocardiographic responses. Similarly, Severi et al. (24) showed that ischemia during dipyridamole echocardiography has incremental prognostic benefit above and beyond that provided by routine exercise stress electrocardiography. Ischemia at dobutamine echocardiography may be used to identify patients with a greater likelihood of future cardiac events in groups with a high pretest probability of coronary disease (25), patients with stable long-term coronary disease (26) and patients undergoing major vascular surgery (15–17). Thus, the existing data indicate that in patients with essentially normal ventricular function, an ischemic response at dobutamine echocardiography implies a poorer prognosis.

Prognostic significance of viable myocardium. Viable myocardium may be identified by positron emission tomography (PET) (27,28), and the presence of either viable or ischemic myocardium detected by PET is associated with subsequent cardiac events in patients who do not undergo myocardial revascularization. The response of dysfunctional myocardium to low doses of dobutamine (5 to 10 μg/kg per min) is also indicative of viable myocardium (29), and findings consistent with myocardial viability at PET have been shown to correlate with the results of dobutamine echocardiography. The results of the present study suggest that the prognostic implications of viability or ischemia at dobutamine echocardiography are comparable to those reported with PET. Moreover, the prognostic implications of viable myocardium at dobutamine echocardiography (which demonstrates improvement at low doses or a biphasic improvement with subsequent deterioration) were comparable to those of ischemic tissue in the present study.

Although the relation of these findings to the underlying pathophysiologic mechanisms of viable myocardium is unclear, the similar behavior of perfusion–metabolism mismatch, "dobutamine-viable" and "dobutamine-ischemic" tissues might suggest that these states may not be as separate as has been traditionally implied. Indeed, teleologically, the adverse outcome of patients with ischemic segments might be explained if the area acts as a substrate for malignant arrhythmias, subsequent myocardial infarction (leading to deteriorating left ventricular function), or remodeling. All these phenomena may be explained if the segment is perceived as a jeopardized region, corresponding to the presence of incomplete infarction (30).

Clinical significance. In addition to the major end points in the present study (death, myocardial infarction and unstable angina requiring revascularization), "soft" end points, such as hospital admission with cardiac failure or milder exacerbations of angina, are a continuing burden with respect to the cost of medical treatment. However, we did not use these soft end points or symptom analyses in our study, because of the varying

thresholds of both medical and nonmedical guidelines for admission in these circumstances.

The natural history of patients with ischemic cardiomyopathy is associated with a very poor long-term outcome (31,32), and the risk of bypass surgery is certainly greater than that in patients with normal ventricular function (33). Nonetheless, large studies of myocardial revascularization (32) have shown that the use of bypass surgery to treat ischemia in patients with severe left ventricular dysfunction is associated with improvement in survival. Uncontrolled studies based on PET data suggest that the revascularization of viable segments should also be considered on prognostic grounds. Whether the same benefit of revascularization can be shown for viable segments demonstrated by dobutamine echocardiography remains to be defined; we studied a group with more end-stage disease and a relatively low rate of surgical revascularization, which inhibited our ability to demonstrate a prognostic benefit in favor of revascularization.

Many patients with viable myocardium in the present study were unsuitable for myocardial revascularization because of other medical problems. In patients undergoing medical treatment, the therapeutic implications of finding viable and ischemic myocardium remain to be defined. In particular, the prognostic benefits of therapy with angiotensin-converting enzyme inhibitors or low doses of beta-blockers in the presence of jeopardized myocardium are uncertain. Currently, therefore, the only intervention that appears to influence outcome in patients with viable and ischemic myocardium is myocardial revascularization.

Study limitations. 1) The present study included a heterogeneous group of patients with various etiologies of left ventricular dysfunction. Although most patients had significant coronary disease by ECG, echocardiographic and coronary angiographic criteria, we could not ascertain an ischemic etiology of left ventricular dysfunction in all patients. Indeed, even in patients with coronary disease (especially if there is a discrepancy between the extent of disease and the severity of left ventricular dysfunction), it may be difficult to ascertain whether left ventricular dysfunction is due to ischemia/infarction rather than hypertension, diabetes or another cause. Thus, selection of patients with purely ischemic ventricular dysfunction may be difficult. Nonetheless, the present study design has the advantage of mimicking the use of dobutamine echocardiography in clinical practice to identify the presence of an ischemic component in patients with left ventricular dysfunction of unknown cause. 2) The group largely comprised elderly patients with significant left ventricular dysfunction, and the presence of a relatively narrow range for both age and ejection fraction may explain the apparent lack of influence of both these variables on outcome. Caution should be used in the extrapolation of these data to other patient groups; for example, the referral pattern for dobutamine echocardiography at a tertiary care hospital may not parallel the patients studied in office practice.

Conclusions. Dobutamine echocardiography may be used to identify ischemic and viable myocardium. The results of the present study indicate that medical treatment of patients with jeopardized myocardium is associated with subsequent events, independent of other prognostic factors, including age and left ventricular function.

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