Prognostic Value of Myocardial Viability in Medically Treated Patients With Global Left Ventricular Dysfunction Early After an Acute Uncomplicated Myocardial Infarction

A Dobutamine Stress Echocardiographic Study

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Background—Residual viable myocardium identified by dobutamine stress after myocardial infarction may act as an unstable substrate for further events such as subsequent angina and reinfarction. However, in patients with severe global left ventricular dysfunction, viability might be protective rather than detrimental. The aim of this study was to assess the impact on survival of echocardiographically detected viability in medically treated patients with global left ventricular dysfunction evaluated after acute uncomplicated myocardial infarction.

Methods and Results—The data bank of the large-scale, prospective, multicenter, observational Echo Dobutamine International Cooperative (EDIC) study was interrogated to select 314 medically treated patients (271 men; age, 58±9 years) who underwent low-dose (≤10 μg · kg⁻¹ · min⁻¹) dobutamine for the detection of myocardial viability and high-dose dobutamine for the detection of myocardial ischemia (≤40 μg · kg⁻¹ · min⁻¹ with atropine ≤1 mg) performed 12±6 days after an acute uncomplicated myocardial infarction and showing a moderate to severe resting left ventricular dysfunction (wall motion score index [WMSI] ≥1.6). Patients were followed up for 9±7 months. Low-dose dobutamine stress echocardiography identified myocardial viability in 130 patients (52%). Dobutamine-atropine stress echocardiography was positive for ischemia in 148 patients (47%) and negative in 166 patients (53%). During the follow-up, there were 12 cardiac deaths (3.8% of the total population). With the use of Cox proportional hazards model, delta low-dose WMSI (the variation between rest WMSI and low-dose WMSI) was shown to exert a protective effect by reducing cardiac death by 0.8 for each decrease in WMSI at low-dose dobutamine (coefficient, −0.2; hazard ratio, 0.8; P=0.03); WMSI at peak stress was the best predictor of cardiac death in this set of patients (hazard ratio, 14.9; P<0.0018).

Conclusions—In medically treated patients with severe global left ventricular dysfunction early after acute uncomplicated myocardial infarction, the presence of myocardial viability identified as inotropic reserve after low-dose dobutamine is associated with a higher probability of survival. The higher the number of segments showing improvement of function, the better the impact is of myocardial viability on survival. The presence of inducible ischemia in this set of patients is the best predictor of cardiac death. (Circulation. 1998;98:1078-1084.)

Key Words: dobutamine ■ echocardiography ■ infarction ■ prognosis

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associated with persisting viability in regions with resting dysfunction. Second, only medically treated patients should be included, with follow-up censored at revascularization, because coronary revascularization dramatically changes the natural history of the disease in these patients, obscuring any direct relationship between viability and prognosis. Third, populations of an adequate sample size should be enrolled, because cardiac death is a relatively rare event in these patients. Therefore, to assess the impact of myocardial viability on survival, the data bank of the large-scale, prospective, multicenter, observational Echo Dobutamine International Cooperative (EDIC) study was interrogated to select 314 medically treated patients (271 men; age, 58 ± 9 years) who underwent low-dose dobutamine (±10 μg·kg⁻¹·min⁻¹) for the detection of myocardial viability and high-dose dobutamine (±40 μg·kg⁻¹·min⁻¹ with atropine ±1 mg) for the detection of myocardial ischemia performed 12 ± 6 days after an acute uncomplicated myocardial infarction and showing a moderate to severe resting left ventricular dysfunction (wall motion score index [WMSI] >1.6). Patients were followed up for 9 ± 7 months.

Methods

Patient Selection
The initial population consisted of 1362 patients admitted to the coronary care unit for an episode of acute myocardial infarction. Of these, 159 were excluded for continuing myocardial ischemia, left ventricular failure, shock, or important cardiac arrhythmias. Of the remaining 1203, 34 patients had a technically poor acoustic window ventricular failure, shock, or important cardiac arrhythmias. Of the initial population consisted of 1362 patients admitted to the national Cooperative (EDIC) study was interrogated to select viability on survival, the data bank of the large-scale, pro-

| TABLE 1. Patient Characteristics |
|------|---------|
| Age, y | 58±9 |
| Sex, M/F | 271/43 |
| O-wave infarction, n (%) | 280 (89) |
| Thrombolytic therapy, n (%) | 198 (58) |
| Patients with previous MI, n (%) | 39 (12) |
| Time to test, d | 12±6 |
| Follow-up, mo | 9±7 |
| Resting WMSI | 1.89±0.2 |
| Low-dose WMSI | 1.76±0.0 |
| Peak stress WMSI | 2.0±0.3 |

MI indicates myocardial infarction.

Dobutamine-Atraxone Stress Echocardiography
After a resting ECG and echocardiogram were performed, intravenous access was secured and dobutamine was infused with 3-minute dose increments, starting from 5 μg·kg⁻¹·min⁻¹ and increasing to 10, 20, 30, and 40 μg·kg⁻¹·min⁻¹ under continuous ECG and echocardiographic monitoring. When no end point was reached, atropine (in 4 divided doses of 0.25 mg up to a maximum of 1 mg) was added to the continuing 40–μg·kg⁻¹·min⁻¹ dobutamine infusion. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model.11 In all studies, segmental wall motion was semiquantitatively graded as follows: 1 = normal; 2 = hypokinetic, marked reduction of endocardial motion and thickening; 3 = akinetic, virtual absence of inward motion and thickening; and 4 = dyskinetic, paradoxical wall motion away from the center of the left ventricle in systole. WMSI was derived by dividing the sum of individual segment scores by the number of interpretable segments.11 Test positivity was defined as the occurrence of at least 1 of the following conditions: (1) new dysynnergy in a region with normal resting function (ie, normokinesis becoming hypokinetic, akinetic, or dyskinetic); (2) worsening of a resting dyssynnergy (ie, a hypokinesia becoming akinesia or dyskinesia; a resting akinesia becoming dyskinesia was not considered a positivity criterion)12; and (3) biphasic response of a resting dysynnergy (ie, a hypokinesia showing normal function at low dose with a following deterioration at high dose, or an akinesia becoming hypokinesia at low dose and returning to the initial condition at high dose).13 Test positivity was defined as “remote” ischemia when the development of asynnergy was not directly adjacent to the infarcted area and was supposed to be related to another vascular region.14 Nonechocardiographic diagnostic end points were the following:15 peak atropine dose, 85% of target heart rate, and achievement of conventional end points (such as severe chest pain and/or diagnostic ST-segment changes). The test was also stopped in the absence of diagnostic end points for 1 of the following reasons: submaximal, nondiagnostic test15; intolerable symptoms; and limiting asymptomatic side effects, consisting of hypertension (systolic blood pressure >220 mm Hg; diastolic blood pressure >120 mm Hg), hypotension (relative or absolute; >30 mm Hg decrease in blood pressure), supraventricular arrhythmias (supraventricular tachycardia or atrial fibrillation), and ventricular arrhythmias (ventricular tachycardia; frequent, polymorphous premature ventricular beats).

The presence of myocardial viability was defined as an improvement in regional function of ≥1 grade at low-dose dobutamine (±10 μg·kg⁻¹·min⁻¹) (ie, a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic).

To quantify the amount of myocardium showing a contractile reserve elicited by low-dose dobutamine, myocardial viability was also assessed according to a continuous parameter defined as ΔWMSI, expressing the difference between resting WMSI and low-dose WMSI. This parameter provides information on not only the presence but also the extent of contractile reserve of the dysfunctioning myocardium. An arbitrary cutoff was set at ΔWMSI=0.25 to identify those patients with an extensive inotropic response.

Patients were separated into three different groups according to the stress echocardiographic results: group 1, nonviable; group 2, viable and nonischemic; and group 3, viable and ischemic.

Echocardiographic monitoring was performed throughout dobutamine infusion and up to at least 5 minutes after the end of the infusion. Two-dimensional echocardiographic images were recorded at baseline and at the end of each dobutamine step. For each patient, left ventricular function was evaluated at baseline, at low dose for the assessment of myocardial viability in dysynergic segments, and at peak stress.
Quality Control of Stress Echocardiographic Readings

Quality control of the diagnostic performance in the different centers was of critical importance to acquire meaningful information in the data bank. In the enrolled centers, the quality control was performed based on 2 criteria, each one having to be met to fulfill the quality control requirements.\(^{15,16}\)

The first criterion was tested on a videotape with 20 stress echocardiography studies prepared in the coordinating center (Institute of Clinical Physiology in Pisa). In all 20 studies, the readings of 2 experienced independent observers were concordant as to presence and site of coronary stenoses during coronary angiography. The ultimate reading of the 2 observers was arbitrarily assumed to be the “gold standard” against which to evaluate the reading of each participating center. The reader from each center interpreted the videotape in a blinded fashion, with no access to clinical and angiographic data or to the interpretation given by other observers. It was assumed a priori that the minimum threshold of concordance to pass this part of the quality control had to be 90%.

The second criterion consisted of random sampling of 20 consecutive studies from each contributing center. These 20 studies were examined in a blinded fashion by an experienced cardiologist-echocardiographist of the coordinating center, whose reading was arbitrarily assumed to be the “gold standard.” It was assumed a priori that the minimum threshold of concordance to pass the quality control had to be 80%. The lower concordance cutoff compared with the first type of reading is due to the fact that this second set of tapes was not selected on the basis of the superior quality but randomly sampled from each center in a consecutive fashion.

All the 11 enrolled centers met the minimum requirements of quality control.

Follow-Up Data

Follow-up data were obtained from at least 1 of 4 sources: review of the patient’s hospital record, personal communication with the patient’s physician and review of the patient’s chart, a telephone interview with the patient conducted by trained personnel, and a staff physician visiting the patients at regular intervals in the outpatient clinic.\(^{16}\) Events were defined as cardiac-related deaths, nonfatal myocardial infarction, and unstable angina. For patients who died in the hospital or at home, the cause of death was obtained from medical records, families, and local physicians who signed the death certificates. The definition of cardiac-related death required documentation of significant arrhythmias, cardiac arrest, or both or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In case of death out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. Myocardial infarction was defined as a cardiac event requiring hospital admission, with the development of new ECG changes and cardiac enzyme level increases. Unstable angina was defined by accelerating anginal symptoms requiring hospital readmission (no enzyme level elevation or new wall motion dysynchrony on the resting echocardiogram or new Q waves on the resting ECG) or progression of symptoms requiring revascularization. Therefore, the outcome events were hard cardiac events (defined as cardiac-related death or nonfatal myocardial infarction) for infarction-free survival and spontaneously occurring events (cardiac death, nonfatal myocardial infarction, unstable angina) for spontaneous event-free survival. Follow-up was censored at revascularization procedures.

Statistical Analysis

Values are expressed as mean±SD.

The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (BMDP 2L, Department of Biomathematics, University of California at Los Angeles, revised 1987). The analysis was performed according to the unmodified forward-selection stepwise procedure. In this case, the variables were entered into the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relation to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of the equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (dependent variable), but in this case, this probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model. We also analyzed the data according to a modified stepwise procedure in which the significant individual variables were included in the model in the same order in which they are considered by the cardiologist: historical and clinical data first, resting wall function second, low dose (viability) stress echocardiographic data third, and high-dose (ischemia) stress echocardiographic data last.

Variables selected for examination were age, sex, history of angina, previous myocardial infarction, thrombolysis, Q-wave myocardial infarction, WMSI at rest, WMSI at viability, dobutamine-atropine stress echocardiography positivity, WMSI at peak dobutamine, low-dose ΔWMSI (the variation between rest and low-dose WMSI), and dobutamine time (ie, test duration to time of echocardiographically detected ischemia).

Continuous variables were compared by the unpaired two-sample t test. Proportions were compared by the χ² statistic; Fisher’s exact test was used when appropriate. Kaplan-Meier life table estimates of spontaneously occurring event-free survival were used to summarize the follow-up experience in these patients and to clarify presentation. Differences of survival curves were tested with the Mantel-Haenszel statistic. A P value <0.05 was considered statistically significant.

Results

The main clinical and echocardiographic data are reported in Table 1.

Feasibility and Tolerability of Dobutamine-Atropine Stress Echocardiography

In 28 patients, the test was submaximal for the occurrence of limiting side effects; the test results of these patients (10.5% of all studies) were included in the analysis. Three patients had major adverse reactions consisting of ventricular tachycardia.

Stress Echocardiographic Findings

Resting WMSI was 1.89±0.2. At the low-dose stage (10 μg·kg⁻¹·min⁻¹ of dobutamine), WMSI was 1.76±0.3 (P<0.05 versus rest). One hundred fifty-one patients (52%) showed the presence of myocardial viability. Among these patients, 83 (54%) had a low-dose ΔWMSI >0.25, showing an inotropic response to low-dose dobutamine in at least 4 segments with resting dysfunction.

One hundred forty-eight patients (53%) had a positive dobutamine-atropine stress echocardiography result, and 166 had a negative dobutamine-atropine stress echocardiography result. The average WMSI at peak dobutamine-atropine stress echocardiography was 2.0±0.3.

Follow-Up Data

Patients were followed up for 9±7 months. During the follow-up period, 12 patients died of cardiac-related causes, 6 had nonfatal myocardial infarction, 21 developed unstable angina, and 87 underwent a coronary revascularization procedure (bypass surgery in 48 and coronary angioplasty in 39).
Cardiac-Related Death

When cardiac-related death was considered, patients who did not show the presence of an inotropic response at low-dose dobutamine (no viability group) had a higher incidence of cardiac death (9 deaths) compared with those with an inotropic response (viability group) to low-dose dobutamine (3 deaths) (5.5% versus 1.9%, \( P < 0.04 \)).

When myocardial viability was analyzed on the basis of not only its presence but also its extent, no patients with a low-dose \( \Delta WMSI \) value >0.25 experienced cardiac death, while cardiac death occurred in 3 (4.3% of the viability group) of the patients with a low-dose \( \Delta WMSI < 0.25 \). In Figure 1, the cumulative survival rates in patients with a high grade of myocardial viability (>0.25 \( WMSI \) variation), a low grade of myocardial viability (<0.25 \( WMSI \) variation), and no viability (\( P < 0.04 \)) are shown.

Cardiac death occurred in 8 patients with positive and in 4 with negative tests for myocardial ischemia (5.4% versus 2.4%, \( P = 0.2 \)). In Figure 2, the survival rates in patients stratified according to stress echocardiography results for ischemia are shown; survival is worse in patients with compared with those without inducible ischemia. In the stepwise analysis, the most important predictor of cardiac death was \( WMSI \) at peak stress (hazard ratio, 14.9; \( P < 0.0018 \)), while in the same model, low-dose \( \Delta WMSI \) was shown to exert a protective effect on survival (coefficient, −0.2; hazard ratio, 0.8; \( P < 0.03 \)) (Table 2). In Figure 3, the survival rates in patients stratified according to low- and high-dose stress echocardiography results are shown. The best survival is observed in patients with echocardiographic evidence of myocardial viability at low dobutamine dose with no ischemia at high dobutamine dose. The worst survival is observed in patients without echocardiographic evidence of myocardial viability at low-dose dobutamine dose and with inducible ischemia at the high dose.

**Table 2. Stepwise Predictors of Cardiac Death**

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>( \chi^2 )</th>
<th>( P )</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta WMSI )</td>
<td>−0.2</td>
<td>4.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak ( WMSI )</td>
<td>2.70</td>
<td>9.8</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

**Discussion**

The results of the present study show that in medically treated patients with moderate to severe global left ventricular dysfunction early after acute uncomplicated myocardial infarction, the presence and extent of myocardial viability identified as inotropic reserve after low-dose dobutamine are associated with a higher probability of survival. The higher the number is of segments showing improvement of function, the better the impact of myocardial viability on survival. In this set of patients, the presence of inducible ischemia identified by the \( WMSI \) at peak stress strongly added prognostic power to myocardial viability recognized by low-dose dobutamine, identifying those patients at higher risk of cardiac death.

**Spontaneous Events**

Patients with positive test results had a higher incidence of spontaneous events than those with negative test results for myocardial ischemia, but this difference did not reach statistical significance (14.8% versus 10.2%, \( P = 0.635 \)) (8 cardiac-related deaths, 3 nonfatal myocardial infarctions, and 11 repeat hospital admissions for unstable angina in patients with positive results versus 4 cardiac deaths, 3 nonfatal myocardial infarctions, and 10 repeat hospital admissions for unstable angina in patients with negative test results for myocardial ischemia). When variables were entered into the model according to an interactive clinically realistic approach, after age, sex, and clinical variables were considered, dobutamine stress echocardiography still added significant prognostic information through peak stress \( WMSI \) (global \( \chi^2 \), 8.76; hazard ratio, 2.68; 95% CI, 0.919 to 7.925; \( P < 0.01 \)).
Prognostic Impact of Myocardial Viability After Acute Myocardial Infarction

The meaning of myocardial viability early after an acute myocardial infarction is still unclear. A large body of evidence collected on selected patient populations shows that the presence of myocardial viability, recognized by low-dose dobutamine, might exert a protective effect owing to the potential recovery of stunned myocardial regions and antiremodeling effect on left ventricular volumes. Carlos et al. performed dobutamine from 2 to 7 days after myocardial infarction, showing that in patients with severe resting dysfunction, myocardial viability is associated with a better survival, at least in populations largely submitted to revascularization procedures.

In light of this evidence, one would expect myocardial viability to carry a potential positive prognostic impact. If a segment has an inotropic reserve after dobutamine infusion, it is likely to recover, and left ventricular function will improve. This should be mirrored by a longer survival, given the hyperbolic relationship linking resting left ventricular function to cardiac death, with better function being associated with longer survival. In reality, the prognostic meaning of viability is not always beneficial but should be put in the larger context provided by the clinical picture (recent versus chronic myocardial infarction), resting left ventricular function (preserved versus severely depressed), type of treatment (medical versus revascularization), and prognostic end point considered (unstable angina versus cardiac death).

In the present subset analysis of the EDIC data bank, we selected only those patients with a moderate to severe left ventricular dysfunction (mean resting WMSI=1.9), whereas in the previous EDIC study, unselected patients had preserved left ventricular function (mean resting WMSI=1.5). The beneficial effect of functional recovery on survival, if any, is expected to be mild in patients with preserved global left ventricular function, who are on the flat part of the hyperbolic curve relating left ventricular function to cardiac death, whereas it appears to be critical in patients with severe left ventricular dysfunction, in whom even the recovery of a limited area might imply a significantly better survival. In fact, no patient with a high number of segments showing contractile reserve at low-dose dobutamine experienced cardiac death (Figure 1), whereas those without myocardial viability or with moderate low-dose improvement had a worse outcome. According to the data presented, the “paradox” of the impact of viability on prognosis in patients evaluated early after an acute myocardial infarction can be solved if one takes into account that viability can be both “good” (associated with better outcome) and “bad” (associated with worse outcome), depending on the patient under study and the outcome end point considered. In patients with good ventricles, viability is basically neutral on survival and is associated with a higher ischemic instability (“viability is bad for good ventricles”). In patients with depressed resting function, the presence of myocardial viability recognized by low-dose dobutamine stress echocardiography is associated with a better survival. When only survival is considered, myocardial viability is good for bad ventricles: the more the viability, the better the prognostic benefit.

Study Limitations

A limitation of this study is the low number of events (only 12 deaths), which may determine instability of results by multivariate analysis. However, the literature is inflated by studies in which the assessment of the outcome is based on soft events, which are of questionable clinical significance. We had to recruit 314 patients by strict selection criteria to obtain meaningful statistical sample size in a relatively homogeneous patient cohort. We identified myocardial viability through the inotropic response to low-dose dobutamine. This is a generally accepted clinical approach, but it certainly is less than ideal for several reasons. First, myocardial viability may be present in the absence of an inotropic response, especially in patients with β-blockers, which totaled 11% of our population. Second, an inotropic stress such as dobutamine can induce an improvement in an asynergic region even in the absence of significant viability; this may occur in transmural or horizontal tethering, for instance, in subendocardial infarctions. However, our intention was not to establish the pathophysiologic meaning of the dobutamine-induced improvement but rather to assess the hard prognostic impact of a response frequently found in stress echocardiography practice—but of uncertain meaning as yet. We included in the present study only patients with depressed left ventricular function, defined as a resting WMSI >1.6. Within the study population, we defined the extent of myocardial viability on the basis of a variation in WMSI >0.25. In both cases, we considered in a binary fashion a continuous variable somewhat artificially introducing threshold criteria in a parameter continuously describing resting function and inotropic response. However, these same criteria were previously used by our and other groups to define a depressed resting function and a “significant” viability response. In addition, a 0.25 value corresponds on
average to 4 segments showing viability, which is equivalent to 25% of the ventricle. Other studies with PET scanning have demonstrated that >20% of the ventricle needs to show evidence of viability for ventricular function to improve after revascularization. The fact that a cutoff value of 0.25 worked well in differentiating patients with low versus high risk of death agrees nicely with the results of PET studies.

Dobutamine echocardiography was performed at various intervals after the index infarction. The response of dysfunctioning but viable myocardium to dobutamine early after acute myocardial infarction may differ from that at discharge. However, this relatively wide variability reflects the lack of an established consensus on the timing for risk stratification and the different logistical situations, ranging from unrestricted bed availability to the pressing demand for coronary care unit space, which can obviously influence the timing of testing. The best time to perform stress tests varies, depending on physician preferences, patient characteristics, and local laboratory expertise.

Clinical Implications

In the prognostic algorithm of risk stratification after myocardial infarction with pharmacological stress echocardiography, the detection of myocardial ischemia plays a fundamental role, identifying those patients at higher risk of hard cardiac events in the first year after the acute event. WMSI at peak stress was the best predictor of cardiac death; this is consistent with a large body of evidence collected both on a multicenter basis and in single institutions, with exercise, dipyridamole, or dobutamine stress. The present data provide new information on the risk stratification of patients early after an acute myocardial infarction. On the basis of the available data, the place of myocardial viability in this prognostic stratification of patients recovering after an acute myocardial infarction is strictly linked to the underlying resting function. As shown in a previous report from EDIC, in patients with preserved left ventricular function, myocardial viability predicts softer end points (mainly unstable angina) with no capability to predict cardiac death. In patients with severely depressed left ventricular function, myocardial viability significantly reduces the mortality rate. However, even in these patients, the beneficial prognostic impact of myocardial viability on survival is outperformed by the negative impact of extent and severity of induced ischemia as assessed through peak WMSI. The more practically relevant implication of these data emphasizes the pivotal role of the quest for myocardial ischemia in risk stratification of the patients recovering from acute myocardial infarction.

References


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