Myocardial Viability During Dobutamine Echocardiography Predicts Survival in Patients With Coronary Artery Disease and Severe Left Ventricular Systolic Dysfunction

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Objectives. The purpose of this study was to assess whether the presence or absence of myocardial viability during dobutamine echocardiography (DE) predicts survival in patients with coronary artery disease (CAD) and severe left ventricular (LV) dysfunction.

Background. In patients with CAD, the presence of myocardial viability during DE identifies viable myocardium and predicts recovery of LV systolic function after revascularization. However, there is little data on the relation between myocardial viability and clinical outcome in patients with CAD and severe LV dysfunction.

Methods. We studied 318 patients with CAD and a LV ejection fraction (EF) ≤35% who underwent DE and were followed for 18 ± 10 months. Patients were classified into four groups. Group I (n = 85) consisted of patients who had evidence of myocardial viability and subsequently underwent revascularization. Group II (n = 119) consisted of patients with myocardial viability who did not undergo revascularization. Group III (n = 30) consisted of patients who did not have myocardial viability and underwent revascularization. Finally, group IV (n = 84) patients lacked myocardial viability and did not undergo revascularization.

Results. The four groups had similar baseline characteristics and rest LVEF. During follow-up there were 51 deaths (16%). The mortality rate was 6% in group I, 20% in group II, 17% in group III and 20% in group IV (p = 0.01, group I vs. other groups).

Conclusions. In patients with CAD and severe LV dysfunction who demonstrated myocardial viability during DE, revascularization improved survival compared with medical therapy.

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left ventricular (LV) function is a major determinant of survival in patients with coronary artery disease (CAD) (1). Patients with severe LV systolic dysfunction (LV ejection fraction [EF] <35%) have particularly high mortality (2–4). It is now well recognized that ventricular dysfunction in some patients with severe CAD may be due to viable, hibernating myocardium rather than irreversible scar (5,6). If ventricular dysfunction is due to hibernation, myocardial contractility frequently improves after revascularization (7–11). Assessment of myocardial viability is increasingly being used to decide whether patients with CAD and severe LV dysfunction should undergo revascularization (12–15). Several studies have shown that myocardial viability during dobutamine echocardiography (DE) accurately predicts recovery of rest LV function after revascularization (10,16–20). However, there is little data on the relation between myocardial viability and clinical outcome in patients treated medically or with revascularization. The purpose of this study was to assess whether the presence or absence of myocardial viability during DE predicts survival in patients with CAD and severe LV dysfunction.

Methods

Study patients. The study group was selected from patients evaluated and managed at the participating institutions who underwent DE between 1993 and 1996 and met the following criteria: 1) presence of CAD, defined as ≥70% stenosis in at least one major epicardial coronary artery; and 2) rest LVEF ≤35% determined visually by two-dimensional echocardiography. Patients with recent myocardial infarction (<1 month) were excluded.

Dobutamine echocardiography. Patients underwent DE according to the local protocol at each institution. The starting dobutamine dose was 2.5 μg/kg/body weight per min in 106 patients and 5 μg/kg per min in 212 patients. Incremental dobutamine doses were then given at either 3-min (n = 266) or 5-min (n = 52) intervals. The majority of patients (79%) were studied using a full dose protocol (dobutamine doses up to
40 μg/kg per min and atropine if the heart rate was <85% of predicted maximal), while the remaining patients underwent a low dose study (dobutamine doses up to 20 μg/kg per min). Differences in DE protocols reflect clinical practice, as there is no “standard” dobutamine protocol for viability assessment. The data on DE were obtained from an interpretation performed at each center at the time of the study. Altogether there were 20 experienced echocardiographers who interpreted these studies. For analysis, the LV was divided into the standard 16-segment model as recommended by the American Society of Echocardiography (21). Wall motion at rest was scored using a 4-grade scoring system (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia). The rest wall motion score index was calculated as the sum of segmental wall motion scores divided by the number of scored segments. For each segment with abnormal rest wall motion, the response to low dose and peak dose dobutamine was assessed and classified as sustained improvement, worsening, biphasic or no change (10). Although there were differences in DE protocols, all centers used 5- and 10-μg/kg per min doses to assess the wall motion response to low dose dobutamine. A patient was considered to have myocardial viability if four or more segments demonstrated improvement, worsening or a biphasic response during DE. We chose this definition based on previous studies demonstrating that evidence of viability in four or more segments during DE is associated with a significant improvement in DE. Patients in group II consisted of 119 patients with myocardial viability who did not have myocardial viability and underwent revascularization. Group III consisted of 36 patients with myocardial viability during DE who subsequently underwent revascularization. Group IV consisted of 30 patients who did not have myocardial viability and underwent revascularization. Group IV patients (n = 84) lacked myocardial viability and were not revascularized. Table 2 compares the clinical, angiographic and rest echocardiographic findings in the four groups. Patients in group III were younger, with a higher rest LVEF.

**Patient groups.** Within 3 months after DE, 115 patients (36%) underwent coronary revascularization either by coronary artery bypass graft surgery (n = 79) or percutaneous transluminal coronary angioplasty (n = 36). The decision for revascularization was not randomized and was made by the patients’ physicians. Based on DE findings and revascularization status, patients were classified into four groups. Group I consisted of 85 patients with myocardial viability during DE who subsequently underwent revascularization. Group II consisted of 119 patients with myocardial viability who did not undergo revascularization. Group III consisted of 30 patients who did not have myocardial viability and underwent revascularization. Group IV patients (n = 84) lacked myocardial viability and were not revascularized. Table 2 compares the clinical, angiographic and rest echocardiographic findings in the four groups. Patients in group III were younger, with a higher rest LVEF.

**Mortality.** Among 318 patients followed for 18 ± 10 months, there were 51 deaths (16%). Figure 1 shows survival in the four groups over time. Differences in survival between patients in group I and the other three groups increased over time (99% vs. 94% at 6 months, 96% vs. 89% at 12 months, 92% vs. 83% at 18 months and 92% vs. 78% at 2 years, p = 0.01). Among revascularized patients, mortality was similar between those treated by bypass surgery and coronary angioplasty (8% vs. 11%, p = NS).

**Independent predictors of mortality.** To assess the value of myocardial viability compared with known predictors of out-

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**Table 1. Indications for Dobutamine Echocardiography**

<table>
<thead>
<tr>
<th>Indication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of myocardial viability</td>
<td>169 (53)</td>
</tr>
<tr>
<td>Evaluation of known CAD</td>
<td>76 (24)</td>
</tr>
<tr>
<td>Evaluation of suspected CAD</td>
<td>73 (23)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease.
come in patients with CAD, Cox multivariate analysis was done (Table 3). After adjustment for age, LV function and severity of CAD, the absence of the group I characteristic (myocardial viability during DE followed by revascularization) remained an independent predictor of mortality. Age and LVEF predicted mortality only in patients who were not revascularized. Among nonrevascularized patients, age and LVEF were 64 ± 11 years and 28 ± 7%, respectively, in survivors, compared with 69 ± 9 years and 24 ± 7%, respectively, in nonsurvivors (p = 0.01 for age and p = 0.001 for LVEF). Among revascularized patients, age and LVEF were similar between survivors and nonsurvivors (age 62 ± 10 years vs. 63 ± 10 years, p = 0.9; LVEF 28 ± 7% vs. 29 ± 8%, p = 0.8). In revascularized patients the only significant predictor of mortality was the absence of myocardial viability (Table 4).

Table 2. Comparison of Baseline Characteristics of Patient Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group I (n = 85)</th>
<th>Group II (n = 119)</th>
<th>Group III (n = 30)</th>
<th>Group IV (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 10</td>
<td>65 ± 11</td>
<td>60 ± 9</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>DM</td>
<td>24%</td>
<td>27%</td>
<td>27%</td>
<td>21%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>57%</td>
<td>61%</td>
<td>67%</td>
<td>57%</td>
</tr>
<tr>
<td>CHF</td>
<td>59%</td>
<td>56%</td>
<td>60%</td>
<td>56%</td>
</tr>
<tr>
<td>Angina</td>
<td>54%†</td>
<td>32%</td>
<td>43%</td>
<td>20%</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>25%</td>
<td>28%</td>
<td>13%</td>
<td>21%</td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td>17%</td>
<td>18%</td>
<td>37%</td>
<td>22%</td>
</tr>
<tr>
<td>Q waves on ECG‡</td>
<td>44%</td>
<td>40%</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>Three-vessel CAD</td>
<td>39%</td>
<td>49%</td>
<td>41%</td>
<td>54%</td>
</tr>
<tr>
<td>Rest WMSI</td>
<td>2.3 ± 0.4</td>
<td>2.3 ± 0.4</td>
<td>2.1 ± 0.4</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Rest LVEF</td>
<td>27 ± 6%</td>
<td>26 ± 7%</td>
<td>30 ± 7%*</td>
<td>27 ± 8%</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; DM = diabetes mellitus; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; MI = myocardial infarction; WMSI = wall motion score index. *p < 0.05 compared with all other groups. †p < 0.01 compared with group IV. ‡Only patients with interpretable electrocardiograms. Data are presented as the mean value ± SD or percentage of patients.

Discussion

Our study demonstrated that in patients with CAD and severe LV systolic dysfunction who had evidence of myocardial viability on DE, revascularization improved survival compared with medical therapy. In the absence of myocardial viability, mortality was similar in patients who did and did not undergo revascularization.

Rationale for myocardial viability testing. Patients with CAD and LV dysfunction have high mortality and morbidity and consume substantial health care resources owing to frequent hospital admissions for congestive heart failure, arrhythmias and recurrent ischemia (2–4). The prevalence of heart failure, in particular, is increasing at an alarming rate, with the estimated treatment cost in the United States being over 10 billion dollars each year (4). Because ischemic LV dysfunction is the most common cause of heart failure, one can readily recognize the importance of proper management of this group of patients. Large trials comparing medical and surgical therapy for CAD have excluded patients with a LVEF <35% (23). In fact, surgical treatment has been considered contraindicated in such patients in the past (24). Recently, with improvements in surgical technique and better myocardial preservation, it has been shown that bypass surgery may be performed with acceptable mortality, even in patients with severe ventricular dysfunction (7,25). Observations from the Coronary Artery Surgery Study registry suggest that, compared with medical therapy, revascularization may improve survival in patients with severe LV dysfunction (26). However, both initial operative mortality and overall long-term absolute mortality were significantly higher in patients with a lower LVEF (26). Thus, identification of subsets of patients with CAD and LV dysfunction who benefit the most from revascularization is important to optimize patient outcome and utilization of health care resources. The presence of myocardial viability has been shown to predict improvement in LV function after coronary revascularization (9–11). Several modalities have been investigated

Table 3. Independent Predictors of Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>0.93 (0.90–0.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.00–1.06)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nongroup I patients</td>
<td>1.65 (1.06–2.82)</td>
<td>0.02</td>
</tr>
<tr>
<td>Three-vessel CAD</td>
<td>1.22 (0.81–1.80)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

CI = confidence interval; other abbreviations as in Table 2.

Table 4. Independent Predictors of Mortality in Revascularized Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (0.96–1.10)</td>
<td>0.4</td>
</tr>
<tr>
<td>Three-vessel CAD</td>
<td>0.6 (0.16–2.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.98 (0.90–1.10)</td>
<td>0.8</td>
</tr>
<tr>
<td>Nongroup I patients</td>
<td>3.6 (1.0–13.0)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 2 and 3.

Figure 1. Comparison of Kaplan-Meier survival curves in the four patient groups.

Figure 2. Comparison of Kaplan-Meier survival curves in the four patient groups.
for the identification of viable myocardium before revascularization. These have included methods assessing perfusion and metabolic activity with positron emission tomography or radio-nuclide techniques and those demonstrating myocardial viability during DE (9–11,27,28). Considerable resources are spent on “viability testing” and some patients are denied revascularization owing to a lack of myocardial viability (12). However, it remains unclear whether testing for myocardial viability has an impact on outcome of coronary revascularization.

Owing to low cost, portability and wide availability, DE is particularly attractive for the assessment of myocardial viability. We and other investigators have shown that the response of the dysfunctional myocardium to dobutamine is a strong predictor of recovery of contractile function after revascularization (10,16–18). More recently, comparative studies between DE and thallium-201 scintigraphy have demonstrated that myocardial viability on DE is more specific for prediction of recovery of function than myocardial thallium uptake (28,29). Previously, no study has assessed whether preoperative assessment of myocardial viability by DE predicts clinical outcome after revascularization.

**Myocardial viability and prognosis.** This is the largest study to date on the prognostic value of myocardial viability in patients with CAD and severe LV dysfunction. We studied the impact of viable myocardium on outcome both with and without revascularization. Patients with myocardial viability who were revascularized had significantly improved survival compared with those who were not revascularized. The prognostic value of myocardial viability was independent of known indicators of outcome, including age, LV function and severity of CAD. An interesting observation was that the difference in survival between group I and II patients did not become evident until several months after revascularization. Partly, this may reflect initial surgical mortality in group I. In addition, viable, hibernating myocardium may demonstrate persistent LV dysfunction immediately after revascularization owing to concomitant stunning after restoration of coronary blood flow (30). Recovery of LV function after revascularization is often slow and may take weeks to months (10,30–32).

There are several potential mechanisms by which revascularization may improve survival in patients with viable myocardium. Revascularization of viable myocardium improves rest LV function, which is a powerful determinant of prognosis (6,7,23). Even if rest function does not improve, we have shown that revascularization enhances cardiac reserve in patients with preoperative evidence of myocardial viability (30). Patients with severe CAD and viable myocardium have a high incidence of ischemic events with medical therapy, which may further reduce LV function or precipitate fatal arrhythmias (33). By relieving ischemia, revascularization may prevent a further decline in LV function and reduce arrhythmogenicity (8,34,35). In addition, revascularization may have a favorable impact on ventricular remodeling, a known marker of adverse outcome (8).

An important finding of our study was that revascularization did not improve survival in patients without preoperative evidence of myocardial viability. The finding is suggestive but not conclusive, because only a small number of patients without myocardial viability underwent revascularization. However, these patients were younger and had better LV function than the patients’ in all the other groups. This finding has important implications for patient management and should be confirmed in a prospective, randomized study.

Patients with myocardial viability who were treated medically had a high mortality. Viable myocardium in patients with severe CAD exists in a precarious state and is prone to ischemia, infarction and a further decline in LV function (6,23,33). Williams et al. (33) reported findings in 108 patients with LV dysfunction who were medically treated. The risk of adverse cardiac events was higher in patients with ischemia or viability during DE compared with those without ischemia or viability. In contrast, in our study, mortality was high in medically treated patients both with and without myocardial viability and was predicted by known prognostic variables—namely, age and LV function. This difference may, in part, be related to inclusion of ischemic events and late revascularization as end points in the study of Williams et al. (33). The finding of high mortality in our medically treated patients with a LVEF <35% is supported by several large studies (1–3).

**Comparison with previous studies.** Few data are available regarding the impact of myocardial viability on clinical outcome and prognosis. Nesto et al. (36) were the first to report improved survival with revascularization in patients who demonstrated preoperative inotropic reserve, assessed by epinephrine infusion or as post extrasystolic potentiation. The current data on myocardial viability and prognosis are largely confined to small, retrospective studies that utilized positron emission tomography or thallium scintigraphy for viability assessment. In a study of 36 patients, only those with preoperative evidence of myocardial viability by positron emission tomography showed improvement in heart failure after bypass surgery (37). D’Carli et al. (38) showed that revascularization was associated with improved survival in patients with evidence of myocardial viability by positron emission tomography. Lee et al. (13) retrospectively studied 129 patients with LV dysfunction who underwent positron emission tomography. Seventy patients showed evidence of viability and 49 of these were revascularized. On follow-up, ischemic events occurred in 48% of patients not revascularized compared with 8% of those revascularized. However, the study did not show a difference in survival after revascularization between patients with and without viability. Elitzman et al. (14) studied 82 patients with CAD and LV dysfunction using positron emission tomography. Among those with myocardial viability, the incidence of cardiac events was 12% in patients who were revascularized and 50% in those not revascularized. Recently, a “viability index” derived from thallium uptake during rest redistribution scintigraphy was shown to predict cardiac event-free survival after bypass surgery in 70 patients with LV dysfunction (15).

Our study adds significantly to these reports in several respects. This is the first study to demonstrate improved survival with revascularization in patients with CAD and LV
dysfunction who demonstrate myocardial viability as assessed by DE. We studied a large number of patients and used all-cause mortality as the end point. We compared survival in patients treated both medically and with revascularization. Most previous studies on myocardial viability have included patients with moderate LV dysfunction. Assessment of viability in such patients is not important because the operative risk is low and the benefit of revascularization is well demonstrated. In contrast, we only studied patients with severe LV dysfunction (LVEF ≤ 35%). It is in this subgroup of patients that evaluation of myocardial viability is important to identify those likely to benefit from revascularization.

**Study limitations.** There are several important limitations of our study. The decision to revascularize was not randomized, and in most cases the results of DE were available to the patients' physicians. Although ideally this study should have been done with random assignment of treatment, it is nearly impossible at present to randomize patients with evidence of “myocardial viability” to medical therapy. However, patients in the four groups were well matched regarding baseline characteristics as well as prevalence of three-vessel CAD and severity of LV dysfunction. Patients in group III (no myocardial viability, revascularized) were somewhat younger, with a slightly higher LVEF. Despite these characteristics, patients in group III had a higher mortality compared with group I (myocardial viability, revascularized). Although the echocardiographic studies were interpreted without blinding to clinical data, the interpretation was performed before intervention and thus was blinded to outcome.

The echocardiograms were interpreted locally at each center by multiple readers. We did not study the interobserver variability of the readers who interpreted the echocardiograms. All centers that participated in this study have extensive experience in performance and interpretation of DE. The studies were read by experts who consistently interpret large volumes of stress echocardiograms. Single-center interobserver variability data, showing good concordance, have been published by many investigators, including the authors of this report (10,16,39). Interinstitutional variability in interpretation of dobutamine echocardiograms has also been previously published (40). That study had several limitations, including use of videotape rather than digital images, re-recording of images and even inclusion of patients with nonvisualization of all segments in one or more vascular territories. Despite these limitations, agreement between observers was over 70%. We also based the classification of dobutamine echocardiograms on change in wall motion rather than absolute wall motion score; the former is associated with greater interobserver variability. Those with viability should be considered for revascularization. Those with viability are unlikely to benefit from revascularization, and transplantation may be a better alternative in such cases. These findings should be confirmed in a prospective, randomized study.

**References**


