Prognostic Value of Low-Dose Dobutamine Echocardiography in Patients With Idiopathic Dilated Cardiomyopathy*

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Study objectives: Dobutamine echocardiography is widely used for the evaluation of myocardial contractile reserve. The purpose of the study was to determine the prognostic value of low-dose dobutamine echocardiography in patients with idiopathic dilated cardiomyopathy (IDCM).

Patients: The study group consisted of 77 consecutive patients with recently diagnosed IDCM (mean [± SD] age, 49 ± 9 years; men, 82%) and left ventricular (LV) ejection fractions of < 40%.

Interventions: Two-dimensional and Doppler echocardiographic variables were measured before and after the infusion of dobutamine at the rate of 10 μg/kg/min for 5 min.

Measurements and results: During a mean follow-up period of 63 ± 7 months (range, 49 to 75 months) 30 patients (39%) died and five patients (6%) underwent successful heart transplantation. Using multivariate regression analysis, the only significant factors related to fatal outcome or the need for cardiac transplantation were the following: (1) LV end-systolic volume of > 150 mL after low-dose dobutamine infusion (odds ratio [OR], 2.2; confidence interval [CI], 1.2 to 4.1; p = 0.011); (2) no decrease of LV end-diastolic volume after dobutamine infusion (OR, 1.9; CI, 1.1 to 3.4; p = 0.031); (3) atrial fibrillation (OR, 2.7; CI, 1.4 to 5.3; p = 0.003); and (4) male gender (OR, 2.6; CI, 1.2 to 5.5; p = 0.017). A scoring system was proposed with one point assigned for each of the above-mentioned factors. The mortality rates for total scores of 0, 1, 2, 3, and 4 were 0%, 19%, 48%, 83%, and 100%, respectively.

Conclusion: The response of the LV to low-dose dobutamine infusion adds clinically valuable prognostic information to the evaluation of the patient with IDCM.

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Key words: dobutamine; echocardiography; idiopathic dilated cardiomyopathy; left ventricular function; prognosis

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; E-wave = early wave of mitral inflow; EF = ejection fraction; IDCM = idiopathic dilated cardiomyopathy; LV = left ventricle, ventricular; NYHA = New York Heart Association; OR = odds ratio; RV = right ventricle, ventricular

Idiopathic dilated cardiomyopathy (IDCM) is a primary, global myocardial disorder of unknown cause. The typical manifestation of IDCM is a marked enlargement of left ventricular (LV) end-diastolic and end-systolic volume with a reduction of the ejection fraction (EF).1 The prognosis of patients with IDCM is difficult to predict. Five-year mortality rates vary about 50%.2,3

The New York Heart Association (NYHA) classification,4 echocardiographic variables of LV function5 and shape,6 and invasive measurements2 have been used for prognostic purposes. These parameters, however, do not allow for the differentiation of patients who need cardiac transplantation from those who will respond to medical treatment.7

Specific markers of the adrenergic system play a significant role in heart failure and have the potential to be used for this purpose.8 Exogenous catecholamine administration generates an LV myocardial contractile response and is widely used clinically in patients with coronary artery disease.9 In the early 1990s, the application of β-adrenergic drugs to eval-
ulate the myocardial contractile reserve for the purpose of prognostic stratification of IDCM patients has been proposed. Therefore, we hypothesized that the changes in LV contractile function after dobutamine infusion provide independent prognostic information beyond that obtained with standard echocardiography and may enable the identification of a very high-risk population that may benefit from surgery.

Materials and Methods

The study group consisted of 77 consecutive patients (age, < 60 years) who were admitted to our Department of Cardiology between January 1995 and February 1996 with a new onset of IDCM. In the process of enrollment, patients with suspected alcoholic etiology (n = 3) and coronary artery disease (n = 9) were excluded, based on the patient’s history and the findings of a coronary angiography examination. There were 63 men (82%) and 14 women enrolled in the study. The mean (± SD) age was 49 ± 9 years (age range, 23 to 60 years). Patients were recruited from five hospitals serving a region of 750,000 people.

Symptoms suggesting heart failure were present in the last 1 to 6 months (mean, 3 ± 2 months) before enrollment into the study. All patients were in the NYHA class II or III (mean class designation, 2.6 ± 0.5) at the time of enrollment. No patients had received isotropic support treatment in the last 3 days before enrollment. Medications being received at the time of enrollment included diuretics (n = 77), aspirin (n = 52), digoxin (n = 46), nitrates (n = 26), angiotensin-converting enzyme (ACE) inhibitors (n = 25), acenocoumarol (n = 16), and β-adrenergic agents (n = 8 [discontinued 3 days before patients underwent dobutamine echocardiography]). Sinus rhythm was present in all but 21 patients (27%) who had atrial fibrillation at entry. In 20 of those patients, atrial fibrillation persisted during the follow-up examinations.

The diagnosis of IDCM was based on diffuse LV hypokinesis, an LV EF of < 40%, an LV end-diastolic diameter of ≥ 50 mm (and ≥ 27 mm/m²), an LV end-systolic diameter of > 40 mm (and ≥ 22 mm/m²), and the exclusion of other causes for LV deterioration.1

Echocardiography

A two-dimensional echocardiographic evaluation was performed according to the standards of American Society of Echocardiography using a commercially available ultrasonic system (model 128 XP; Acuson; Mountain View, CA). Technically satisfactory echocardiographic images for obtained in all patients. To obtain a stable baseline hemodynamic state, subjects rested in the supine position for 10 min before undergoing the examination. All examinations were recorded on S-VHS video-cassettes, and selected views were digitized (model P-90; TomTec; Munich, Germany) for further evaluation and calculations.

All examinations and offline measurements were performed by the same experienced echocardiographer (JD), except for those used in the interobserver reproducibility study. All measurements were performed in triplicate for patients with atrial fibrillation, measurements were made for five consecutive beats, and a mean value was calculated. LV fractional shortening was calculated by dividing the difference between the end-diastolic and the end-systolic dimensions by the end-diastolic dimension. LV volumes were measured at end-systole and end-diastole using a modified Simpson method using apical four-chamber and apical long-axis views. The LV EF was calculated by dividing the difference between the end-diastolic and the end-systolic volumes by the end-diastolic volume. The LV mass was calculated according to the Penn formula as follows:

\[1.04 \times [(IVS + LVEDD + PW)^2 - LVEDD^2 - 13.5]\]

where IVS signifies interventricular septal thickness in end-diastole, LVEDD signifies the end-diastolic LV dimension, and PW signifies posterior wall thickness in the end-diastole. Peak early wave (E-wave), atrial wave, and deceleration time of the E-wave of the mitral inflow were measured using the pulsed Doppler echocardiography method with the sample volume positioned at the tips of the mitral valve in the four-chamber view. Isovolumetric relaxation time was measured between the end of aortic outflow and the onset of mitral inflow using continuous Doppler echocardiographic sampling in the apical long-axis view. The severity of mitral and tricuspid regurgitation was visually scored on a 4-point scale.13 The right ventricular (RV)-atrial gradient was calculated from the formula 4 × Vmax², where Vmax signifies maximal tricuspid regurgitation flow velocity assessed by continuous-wave Doppler echocardiography and was recorded in 30 patients (39%).

Dobutamine Echocardiography

Dobutamine was infused at the rate of 10 μg/kg/min through a 19-gauge cannula inserted into a forearm vein. All of the echocardiographic measurements that were described above were repeated 5 min after the beginning of infusion. The institutional ethics committee approved the protocol, and all investigated subjects gave written informed consent.

Ambulatory Treatment Regimen

After hospital discharge, the patients were followed-up in the outpatient clinic every 1 to 3 months. The specific medication was changed during follow-up, as appropriate. In particular, β-adrenergic agents (ie, metoprolol, bisoprolol, or carvedilol) and ACE inhibitors (ie, enalapril, lisinopril, or quinapril) were prescribed in adequately high dosages in all patients during the last years of observation in our study (ie, the second half of the follow-up period). Medications being received at the end of the study among the 47 living patients included ACE inhibitors (n = 46), β-adrenergic agents (n = 46), diuretics (n = 43), digoxin (n = 36), acenocoumarol (n = 29), aspirin (n = 18), and nitrates (n = 11).

Heart transplantation was offered to seven patients 1 to 33 months after they had enrolled in the study. The indications for cardiac transplantation were based on clinical evaluations, laboratory testing, exercise testing, echocardiographic findings, and angiographic evaluations, which were restricted to otherwise healthy subjects (with the exclusion of reversible organ damage) with progressive heart failure that was refractory to optimal medical management (ie, a requirement for mechanical ventilation assistance or continuous inotropic support).14 Two of those patients died awaiting an operation. In five patients, heart transplantation was carried out with good long-term results.

Long-term Follow-up Evaluation

All hospitalizations due to cardiac causes that occurred after the initial hospital discharge were defined as adverse events. All subjects who did not comply with regular visits to the outpatient clinic were contacted by telephone. The circumstances of all
causes of death (n = 30) or adverse events (n = 18) were clarified. Cardiac cause was suspected in all patients who died. Sudden death was noted in 24 patients, and heart failure progression refractory to treatment was noted in 6 patients. An autopsy was completed in six patients, confirming a diagnosis of IDCM with end-stage heart failure.

Statistical Analysis

For statistical purposes, the group of patients referred for heart transplantation was clustered with those who died, because of very strict criteria for qualification for surgery. Results are expressed as the mean ± SD. Tests of dependent or independent variables were used to quantify differences between groups. For logistic multivariate analysis, measurements of demographic, clinical, and echocardiographic variables that were obtained at rest and after dobutamine infusion were included. Multivariate logistic regression was performed by forward stepwise analysis and manual elimination of factors that were statistically significant at the level of p > 0.05. Survival and adverse-outcome predictors were evaluated using Kaplan-Meier estimates according to the Cox model (SYSTAT, version 8.0; SPSS Inc; Chicago, IL). The difference associated with the occurrence of predictors was evaluated using a Mantel-Haenszel log-rank test. For continuous quantitative variables, the thresholds that best separated two analyzed groups were determined by testing the whole range of each variable by increments of 25 mL and determining each level by use of a Mantel-Haenszel log-rank test.

For dichotomous variables, McFadden’s $R^2$ value was computed as a transformation of the likelihood ratio statistic intended to mimic an $R^2$ value. A higher $R^2$ value corresponds to more significant results. The $R^2$ value tends to be much lower than the $R^2$ value, however, and a low number does not necessarily imply a poor fit. Values between 0.20 and 0.40 are considered to be very satisfactory.$^{15}$

To assess the interobserver and intraobserver variability, LV function parameters were measured twice in 10 randomly selected studies by the same investigator (>1 month after the initial measurements) and twice in 10 studies by two investigators (JD and JDK) who were blinded to each other’s results. Variability was determined as the absolute difference between measurements divided by the mean value of two observations and expressed as a percentage.

RESULTS

Dobutamine Echocardiography

No adverse events occurred in any patient during dobutamine infusion. Heart rate, BP, respiration rate, or oxygen saturation did not change significantly.

After low-dose dobutamine infusion, the mean LV systolic and diastolic dimensions tended to decrease by $-1 ± 3$ mm (range, $-9$ to $+4$ mm) and by $-2 ± 2$ mm (range, $-9$ to $+3$ mm), respectively. The mean LV systolic and diastolic volumes became smaller by $-23 ± 31$ mL (range, $-138$ to $+43$ mL) and $-16 ± 33$ mL (range, $-112$ to $+62$ mL), respectively. LV fractional shortening and EF increased by $2 ± 1$% (range, $0$ to $4$%) and $6 ± 4$% (range, $0$ to $15$%), respectively. An increase of LV fractional shortening of at least 2% was noted in 31 patients (40%).

Follow-up Evaluation

The follow-up period ranged from 49 to 75 months (mean, $63 ± 7$ months). Among the 77 patients who were followed-up, 30 persons died (39%) $34 ± 20$ months after enrollment. In five patients (6%), heart transplantation was successfully performed $10 ± 13$ months after enrollment into the study. Fourteen patients (18%) were hospitalized due to a cardiac cause (result of heart failure progression, 12 patients; malignant arrhythmias, 2 patients). Uncomplicated outcome was observed, therefore, in 28 patients (36%).

Univariate Analysis

Fifty-one demographic, clinical, echocardiographic (rest and dobutamine) factors were analyzed. From the univariate analysis of demographic and clinical parameters (ie, gender, age, body mass index, body surface area, heart rate, systolic and diastolic BP, atrial fibrillation, NYHA class, time from the beginning of heart failure symptoms) only the male gender (94% vs 71%, respectively; $p = 0.022$), atrial fibrillation (49% vs 10%, respectively; $p < 0.001$), and NYHA class ($2.8 ± 0.4$ vs $2.5 ± 0.5$, respectively; $p = 0.004$) were related to unfavorable outcome (ie, death or the need for heart transplantation).

Table 1 presents a comparison of echocardiographic parameters assessed in IDCM patients with favorable and unfavorable prognoses before and after 10 µg/kg/min dobutamine infusion. Patients with unfavorable outcomes had larger LVs with lower systolic indexes, greater LV mass, a larger left atrium, and a higher degree of mitral and tricuspid regurgitation. These relationships remain statistically significant after correction for body surface area.

Logistic Multivariate Analysis

Table 2 presents significant parameters for discriminating patient groups with favorable and unfavorable outcomes. The four steps of analysis included the following data: (1) only demographic and clinical data; (2) only rest echocardiographic variables; (3) demographic, clinical, and rest echocardiographic variables; and (4) all of the above data were taken into consideration. The most significant factors influencing prognosis in IDCM patients were LV end-systolic volume after dobutamine infusion, LV end-diastolic volume changes after dobutamine infusion, the occurrence of atrial fibrillation, and male gender (Table 2). After the exclusion of patients who were qualified for heart transplantation (n = 5), the factors influencing survival in IDCM patients were as above, with an additional factor (NYHA class)
Table 1—Comparison of Echocardiographic Parameters Before and After 5 Min of Dobutamine Infusion (10 μg/kg/min) in Patients With Favorable (n = 42) and Unfavorable (n = 35) Outcomes*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Favorable Prognosis</th>
<th>Unfavorable Prognosis</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Diastolic dimension, mm</td>
<td>59 ± 9</td>
<td>65 ± 11</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic dimension, mm</td>
<td>50 ± 10</td>
<td>56 ± 11</td>
<td>0.003</td>
</tr>
<tr>
<td>LV diastolic volume, mL</td>
<td>217 ± 124</td>
<td>291 ± 146</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic volume, mL</td>
<td>155 ± 103</td>
<td>222 ± 130</td>
<td>0.007</td>
</tr>
<tr>
<td>Diastolic volume change after dobutamine infusion, mL</td>
<td>-26 ± 30</td>
<td>-5 ± 33</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic volume change after dobutamine infusion, mL</td>
<td>-31 ± 30</td>
<td>-14 ± 31</td>
<td>0.009</td>
</tr>
<tr>
<td>FS, %</td>
<td>16 ± 4</td>
<td>13 ± 5</td>
<td>0.01</td>
</tr>
<tr>
<td>EF, %</td>
<td>31 ± 8</td>
<td>27 ± 9</td>
<td>0.02</td>
</tr>
<tr>
<td>Wall stress, kPa</td>
<td>129 ± 45</td>
<td>147 ± 43</td>
<td>0.046</td>
</tr>
<tr>
<td>Mass, g</td>
<td>266 ± 74</td>
<td>327 ± 109</td>
<td>0.003</td>
</tr>
<tr>
<td>PW diastolic/systolic thickness, mm</td>
<td>10 ± 2/11 ± 2</td>
<td>10 ± 2/11 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>PW thickening, %</td>
<td>12 ± 6</td>
<td>11 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>IVS diastolic/systolic thickness, mm</td>
<td>10 ± 1/11 ± 2</td>
<td>10 ± 1/11 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>IVS thickening, %</td>
<td>12 ± 7</td>
<td>11 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>41 ± 6</td>
<td>46 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RV diastolic diameter, mm</td>
<td>22 ± 4</td>
<td>23 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral regurgitation, grade</td>
<td>0.7 ± 0.8</td>
<td>1.3 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tricuspid regurgitation, grade</td>
<td>0.3 ± 0.5</td>
<td>1.0 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximal RV-RV gradient, mm Hg</td>
<td>34 ± 11</td>
<td>40 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>E/A-wave ratio</td>
<td>1.3 ± 1.5</td>
<td>2.5 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>E-wave deceleration time, ms</td>
<td>90 ± 25</td>
<td>81 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>123 ± 25</td>
<td>117 ± 30</td>
<td>NS</td>
</tr>
</tbody>
</table>

*pValues given as mean ± SD, unless otherwise indicated. NS = not significant; FS = fractional shortening; IVRT = isovolumetric relaxation time; PW = LV posterior wall; LA = left atrium; A-wave = atrial wave of mitral inflow.

Table 3 shows ORs with CIs for dichotomous data for all the groups of IDCM patients that were investigated. A scoring system was proposed for simple risk stratification, with 1 point assigned to the patient for each of the following: (1) LV end-systolic volume > 150 mL after dobutamine infusion; (2) no decrease in LV end-diastolic volume after dobutamine infusion; (3) the presence of atrial fibrillation; and (4) male gender. Thus, this yielded a score in the range of 0 to 4. The prevalence of scores 0, 1, 2, 3, and 4 in the entire group of IDCM patients was 9%, 34%, 27%, 23%, and 7%, respectively. Figure 3 presents the mortality rate in the subgroup of patients based on these scores.

The Interobserver and Intraobserver Variability

The interobserver variability values for echocardiography were < 5% for LV and left atrial dimension measurements and < 6% for LV volumetric calculations. The respective variables for intraobserver variability were < 4% and < 6%.

Discussion

In our study, we sought predictors of long-term adverse outcomes in the group of 77 patients with recently diagnosed IDCM. The mortality rate in our study was rather low compared with the 50% 2-year mortality rate that was published in the early 1980s, the 57% 5-year mortality rate published in the late 1980s, and the 56% 5-year mortality rate published in the mid-1990s. This may be explained partly by improvements in modern medical care, based on published clinical trials and clinical guidelines. Patients who showed progressive deterioration in their clinical status were referred for cardiac transplantation.

The most significant finding in this study is that poor LV response to dobutamine infusion predicted...
an unfavorable outcome. We have demonstrated that, besides gender and the prevalence of atrial fibrillation, the volumetric parameters of LV function that were measured during low-dose dobutamine infusion are the most important predictors of unfavorable outcomes. Our findings are consistent with those of earlier studies.7,10,19 This study has the advantage of the longest follow-up period and the largest sample size available in the literature, allowing the development of a practical prognostic applicable to almost every patient with this condition.

Among the four most powerful predictors of unfavorable outcome, two factors are not related to echocardiography. Male gender represents one of the classic predictors of poor outcome in IDCM. Our study also identified atrial fibrillation as an independent and powerful risk factor, which was confirmed in the retrospective analysis of the Studies of Left Ventricular Dysfunction trial.20 Atrial fibrillation appeared even more predictive than male gender in our group of patients.

Resting echocardiography has an established position as a prognostic indicator in patients with IDCM.1,5,6,17,18,21 Enlargement of the LV with contractile dysfunction 5,6,21 was found to be the most important predictor of death. Although these parameters were of prognostic value in our patients, neither was found to be independently related to unfavorable outcome in the multivariate analysis. These factors lost their predictive power, probably because all our patients had advanced LV enlargement and dysfunction. Other parameters, therefore, became more powerful. One of those factors, left

Table 2—Multivariate Analysis of Demographic, Clinical, and Echocardiographic Parameters in IDCM Patients in the Assessment of Unfavorable Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic volume after dobutamine infusion ≤150 mL</td>
<td>2.2</td>
<td>1.2–4.1</td>
<td>0.011</td>
</tr>
<tr>
<td>LV end-systolic volume after dobutamine infusion &gt;150 mL</td>
<td>1.9</td>
<td>1.1–3.4</td>
<td>0.031</td>
</tr>
<tr>
<td>Occurrence of atrial fibrillation</td>
<td>2.7</td>
<td>1.4–5.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.6</td>
<td>1.2–5.5</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*Positive t ratio indicates factor correlated with worse prognosis. See Table 1 for abbreviations not used in the text.
†McFadden’s $R^2 = 0.296$.
‡McFadden’s $R^2 = 0.187$.
¶McFadden’s $R^2 = 0.297$.
||McFadden’s $R^2 = 0.374$.

Figure 1. Kaplan-Meier analysis showing survival in patients with IDCM in the group with LV end-systolic volume > 150 mL and < 150 mL after dobutamine infusion.

Figure 2. Kaplan-Meier analysis showing survival in patients with IDCM in the group with decreases and increases of LV end-diastolic volume after low-dose dobutamine infusion.

Table 3—Effects of Demographic, Rest, and Dobutamine Echocardiographic Parameters on Unfavorable Outcome of IDCM Patients
dilated LV cavity.29 The standard evaluation of the RV from the parasternal long-axis view is not sufficient for prognostic purposes, as confirmed by the RV dysfunction and varying time intervals from the time of onset of the disorder to the time of diagnosis may extend the application of our results.

All patients were hospitalized in the same hospital and were treated by the same staff, therefore, a bias resulting from specific priorities or skills cannot be excluded. We have included patients with atrial fibrillation, which makes echocardiographic quantification difficult. Our study was focused on in-hospital predictors of outcome, therefore, no data regarding medical treatment after discharge were included in the analysis. Changing drug applications depending on actual clinical status and published trials will make such analysis particularly difficult.

CONCLUSIONS

Our study indicated the important prognostic value of variables derived from low-dose dobutamine echocardiography in IDCM patients, which seems to be a more powerful test than resting echocardiography. We have extended the practical aspects of this test by proposing a prognostic score to serve as a therapeutic guide. We propose pharmacologic treatment in patients with scores of 0 and 1. Heart transplants should be reserved to those patients with scores of 3 or 4.

REFERENCES
7. Naqvi TZ, Forrester JS, Siegel RJ. Myocardial contractile reserve on dobutamine echocardiography predicts late spon-