Cardiomyopathy

Myocardial Contractile Reserve on Dobutamine Echocardiography Predicts Late Spontaneous Improvement in Cardiac Function in Patients With Recent Onset Idiopathic Dilated Cardiomyopathy

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OBJECTIVES
The purpose of this study was to determine whether identification of contractile reserve with dobutamine would predict recovery of myocardial function during follow-up in patients with recent onset idiopathic dilated cardiomyopathy (IDC).

BACKGROUND
The prognosis of patients presenting with new onset IDC is variable and difficult to predict.

METHODS
Twenty-two patients (17 men, 5 women, 46 ± 14 years) with recently diagnosed IDC (4 ± 3 months) underwent dobutamine echocardiography. Left ventricular ejection fraction (LVEF) and LV sphericity before and at peak dobutamine infusion (30 ± 11 µg/kg/min) were determined. A follow-up echocardiographic assessment was done at 6 ± 4 months.

RESULTS
The LVEF on dobutamine was directly related to baseline LV mass expressed as g/ml (Pearson r = 0.65, p = 0.0003). Baseline variables that were significantly predictive of follow-up LVEF were deceleration time (r = 0.69, p = 0.0006), wall motion score index (WMSI) (r = −0.63, p = 0.002), LV mass (r = 0.56, p = 0.008) and LVEF on dobutamine (r = 0.84, p = 0.0001). When either deceleration time or WMSI or LV mass was entered into a regression equation to predict follow-up LVEF, the LVEF on dobutamine added significantly to predictive power. However, if LVEF on dobutamine was entered first, none of the other three variables added significantly to prediction. Baseline LV sphericity at end diastole (ED) (r = 0.13, p = 0.6) did not correlate with follow-up LV sphericity in ED, whereas LV sphericity in ED on dobutamine (ED [r = 0.70, p = 0.0004]) correlated with LV sphericity in ED on follow up.

CONCLUSIONS
This study demonstrates that dobutamine-induced improvement in baseline LVEF and LV sphericity identifies patients with IDC who exhibit substantial improvement in LV function and geometry over time. (J Am Coll Cardiol 1999;34:1537–44) © 1999 by the American College of Cardiology
year (18); however, the value of these variables for predicting the outcome of patients with recent onset IDC is not established.

Changes in the adrenergic system are prognostic markers of cardiac function (19). A rise in circulating catecholamines is accompanied by decreased beta receptor density and downregulation of the beta receptors (20) and is associated with a poor response to beta-adrenergic blocking agents (21) as well as a poor prognosis. A significant improvement in LV function, shape (22,23) and prognosis (24) occurs in response to beta blockade therapy in patients with IDC, presumably from beta-receptor upregulation. Moreover, LV hypertrophy (25) and increased myofibrillar to cell volume ratio at myocardial biopsy are associated with a better outcome in IDC (26). The myocardial contractile response to exogenous catecholamine administration has prognostic value in those with (27,28), or destined to develop (29), chronic dilated cardiomyopathy. When combined, these data suggest that LV hypertrophy and myofibrillar beta-receptors may be critical to the maintenance of both myocardial contractility and LV shape and that they confer a prognostic benefit.

We hypothesized that, in patients with acute IDC, the magnitude of dobutamine-induced changes in LV function and LV geometry would predict the magnitude of spontaneous recovery of LV function. This prospective study was designed to examine the prognostic value of myocardial functional reserve as determined by dobutamine echocardiography in the acute or subacute phases of IDC.

**METHODS**

**Patient population.** Twenty-six consecutive patients (20 men and 6 women) who presented with new onset (4 ± 3 months) IDC were identified over a 28-month period. The diagnosis of IDC was based on:

1) LV ejection fraction (EF) <40%,
2) LV end systolic (ES) diameter >4.5 cm,
3) LV end diastolic (ED) diameter >5.5 cm on echocardiography, and
4) absence of significant coronary artery disease, primary valvular heart disease, long-standing or uncontrolled systemic hypertension, corpulmonale, chronic systemic disease involving the heart muscle, drug abuse, administration of adriamycin and HIV disease.

Patients were not on inotropic support at the time of enrollment. Of the 26 patients, four were excluded. One had inadequate apical echocardiographic windows, one normalized LV function between enrollment and the scheduled dobutamine study and two did not participate. The mean age of the final 22 study patients (17 men, 5 women) was 46 ± 14 years (range 27 to 70 years). All patients were in normal sinus rhythm except one who had atrial fibrillation at entry and at follow-up examination. Significant coronary disease was excluded by stress thallium in two patients and coronary angiography in 11 patients. Seven of these patients had normal coronary angiograms, two had mild to moderate (≤50%) proximal left anterior descending coronary artery stenoses, one had undergone right coronary artery angioplasty in the remote past and had normal coronary angiogram at the time of onset of IDC and one was post coronary artery bypass surgery, had normal LVEF postbypass surgery and had patent saphenous vein bypass grafts on angiography to all three vascular territories at the time of onset of IDC.

Cardiac medications at the time of dobutamine echocardiography and follow-up procedures included angiotensin-converting enzyme (ACE) inhibitors and diuretics in all patients, and digoxin (n = 19), coumadin (n = 5), aspirin (n = 2), amiodarone (n = 2), beta-blockers (n = 3) and nitrates (n = 4) in others. The medical management of the patients was directed by their internist cardiologist. Two patients (one with and two without spontaneous improvement in LVEF on follow-up) were treated with carvedilol during follow up.

**Study protocol.** The study was approved by the Institutional Review Board at the Cedars Sinai Medical Center and informed patient consent was obtained. All patients underwent an echocardiogram at baseline, during low and peak doses of dobutamine and at follow-up. Follow up was performed at six months and 12 months unless:

1) nonmedical intervention for poor pump function occurred or
2) LVEF normalized before this period.

At follow-up visits, symptoms, medications and intervening events such as rehospitalization, surgery and enrollment for cardiac transplantation were recorded. Normalization of LVEF during follow-up visits occurred in five patients (4 of these patients had a normal LVEF by first follow-up). Left ventricular reduction surgery was performed in three patients. One patient underwent this procedure at three weeks, one at four months and one a year after enrollment in this study. We excluded the patient who underwent LV reduction surgery at three weeks after dobutamine echocardiography from analysis of the final LVEF. This patient had

**Abbreviations and Acronyms**

ACE = angiotensin converting enzyme  
ED = end diastole or diastolic  
EF = ejection fraction  
ES = end systole or systolic  
IDC = idiopathic dilated cardiomyopathy  
LV = left ventricle or ventricular  
NYHA = New York Heart Association  
RV = right ventricle, right ventricular  
WMSI = wall motion score index
her LVEF increase from 25% to 35% on dobutamine infusion.

The interval between the time of diagnosis of IDC and dobutamine echocardiography was 4 ± 3 months and between dobutamine echocardiography and follow-up assessment was 6 ± 4 months.

**Two-dimensional and Doppler echocardiogram.** This was performed at rest in the left lateral decubitus position with a commercially available ultrasound system (Sequoia 256, Mountain View, California) using a variable frequency phased array transducer (2 to 3.5 MHz) and using conventional methods (30–36). Left ventricular ES and ED dimensions and posterior wall ES and ED thickness were obtained in the parasternal long axis views. Parasternal short axis views were obtained at the papillary muscle level. Global LV mass was obtained by tracing LV endocardial and epicardial borders in ED in this view and measuring $L V_{ED}$ length in apical four- and two-chamber views. Left ventricular mass (g/ml) was obtained by dividing global LV mass by $L V_{ED}$ volume. Left ventricular ejection fraction was measured by the modified Simpson method (30) from apical four- and two-chamber views. Wall motion score index (WMSI) was measured as the sum of segmental scores (1 = normal, 2 = mildly hypokinetic, 2.5 = markedly hypokinetic, 3 = akinetic, 4 = dyskinetic) divided by the number of segments visualized (30). Left ventricular sphericity index in ED and ES was defined as the ratio of LV length, from apex to the middle of mitral annular plane to LV width, at mid point of LV length in the four-chamber view. Right ventricular (RV) fractional shortening was calculated as percent RV shortening by measuring maximal RV width in ES and ED in apical four-chamber view.

A low frequency (2.5 MHz) transducer was used for all Doppler examinations. Severity of mitral and tricuspid regurgitation was assessed visually by color flow Doppler as mild, moderate, moderately severe or severe (31) and graded on a scale from 1+ to 4+. The maximum RV-right atrial gradient was obtained with the continuous wave Doppler using standard method (32). Peak E, peak A and deceleration time were measured by examination of the mitral inflow velocity with the pulsed Doppler technique, and the sample volume positioned at the tips of the mitral leaflets (33). Isovolumetric relaxation time was measured by placing pulsed wave sample volume in the LV outflow tract (34). Due to the merging of E- and A-waves in six patients and atrial fibrillation in one patient, the peak dobutamine E- and A-waves and deceleration time could not be recorded in seven patients. A clear Doppler tricuspid flow signal to record pulmonary artery systolic pressure was recordable in only nine study patients and at peak dobutamine in three study patients.

**Dobutamine echocardiography.** Ten to 40 $\mu g/kg/min$ of dobutamine was infused at incremental doses of 2.5, 5, 10, 20, 30 and 40 $\mu g/kg/min$ at 3-min intervals through a 19-gauge cannula inserted into a forearm vein. Two-dimensional and Doppler images were acquired after each dose of dobutamine. No complications occurred in any patient except one who developed ventricular couplets or triplets with varying morphology. Dobutamine infusion was stopped if maximum dose (40 $\mu g/kg/min$) was reached, LV function normalized, 75% of target heart rate (220 − age) was achieved or complex ventricular ectopy developed.

All studies were stored on 1/2-inch videotape. Selected views in baseline, peak-dobutamine and on follow-up visits were digitized for LVEF measurement, sphericity index, mitral inflow and LV outflow waves and for parameters listed in Appendix 1 (35–37). An average of three measurements was taken for patients in sinus rhythm and six measurements for the patient in atrial fibrillation. We analyzed variables at each dose of dobutamine and found progressive improvement in LV systolic function, dimensions and geometry. Data at baseline and peak dose of dobutamine are presented. To assess the variability in interpretation, all echocardiograms were analyzed independently by two of the investigators (TZN, RJS). The reproducibility of the measurements was calculated on the basis of standard error of the estimate; both interobserver and intraobserver variations were ≤5% for pre- and postdobutamine echocardiography and follow-up LVEF.

**Statistical analysis.** On the basis of final follow-up LVEF, we divided patients into two groups: group 1, follow-up LVEF >40% and group 2, follow-up LVEF <40%. Change in LVEF from baseline was greater than 14% in all patients in group 1 except one whose LVEF increased by 9% and was less than 6% in all patients in group 2 except one in whom LVEF increased by 12%. Baseline variables between these groups and changes in the variables from baseline on dobutamine infusion and on follow-up in the two groups were compared by Student unpaired t test. Using all 21 patients, association between baseline clinical and echocardiographic variables and final LVEF (and with change in LVEF from baseline) was assessed with the Pearson correlations and scatterplots. Multiple regression was performed to predict follow-up LVEF as an outcome variable. To assess the relative influence of significant predictors of follow-up LVEF, several different regression models were fit. Pearson correlation analyses was also performed using LV sphericity in ED or ES or RV fractional shortening as outcome variables. For these three outcome variables only their prior baseline and dobutamine values were used as dependent variables. Data are expressed as mean ± SD. A p value of <0.05 was considered significant.

**RESULTS**

Mean follow-up LVEF of patients who improved (group 1, follow-up LVEF >40%) was 53 ± 11% and of patients who did not improve (group 2, follow-up LVEF <40%) was 21 ± 8%. Table 1 shows the clinical and echocardiographic
parameters of the study population divided into two groups based on the follow-up echocardiogram.

There was no significant difference in baseline demographic or echocardiographic chamber dimensions or function between the two groups. There was, however, a significantly lower baseline LV WMSI and a greater LV mass (g/ml) in group 1. Group 1 also had a longer deceleration time, which correlated with baseline LV mass (r = 0.62, p = 0.003).

Pulmonary artery pressure was 41 ± 11 in group 1 and 35 ± 7 mm Hg in group 2 (p = 0.29).

Effect of gender. Women had a higher baseline LVEF compared with men (31 ± 6% vs. 23 ± 8%, p = 0.05). However, there was no significant difference in LVEF at follow-up (45 ± 6% vs. 34 ± 20%, p = 0.29) or in change in LVEF (13 ± 10% vs. 10 ± 19%) on follow-up in women versus men.

Endomyocardial biopsy findings. Of the eight patients who underwent endomyocardial biopsy, three showed fibrosis, three showed myocyte hypertrophy, one showed inflammation and one was normal. All three patients who showed hypertrophy improved on follow-up visits whereas all three patients who had fibrosis on endomyocardial biopsy did not improve on follow-up.

Response to dobutamine. Table 2 shows the change in hemodynamic and echocardiographic variables in response to dobutamine. Despite no significant difference in changes in heart rate or mean blood pressure at peak dobutamine infusion, a significantly greater improvement in LV WMSI, LVEF and LV stroke volume occurred in group 1 versus group 2. In addition, the ES LV cavity became significantly less spherical in group 1 versus group 2 patients. No significant difference was observed in mitral regurgitation (mean decrease by one grade in both groups). A direct correlation between baseline LV mass/ml and LVEF on dobutamine (Pearson r = 0.65, p = 0.001) was observed. Direct correlations between LVEF on dobutamine and LV sphericity in ED on dobutamine (r = 0.54, p = 0.01) and LV sphericity in ES on dobutamine (r = 0.62, p = 0.001) were also observed. Because of this correlation LV sphericity in ES or ED on dobutamine was not used in the regression model to predict follow-up LVEF.

Serial echocardiographic follow-up study. Follow-up period for patients in group 1 was 6.5 ± 4 months and for those in group 2 was 6 ± 3 months. Table 3 describes the follow-up echocardiographic variables in the two groups. No significant change or slight worsening between initial and follow-up studies occurred in group 2 in WMSI, LVEF and LV cavity dimensions in ES and ED. The LV became more spherical and LV filling continued to have a restrictive filling pattern. In contrast, significant improvement in LV as well as RV systolic function, LV chamber dimensions and LV sphericity occurred in patients in group 1. In addition, LV filling improved from a restrictive to a nonrestrictive pattern. No significant change in LV mass occurred in either group, although compared with baseline, follow-up LV mass was slightly higher in group 1. Figure 1 shows the

| Table 1. Baseline Characteristics of Study Population According to Final EF |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Variables                  | Baseline Value              | FU LVEF > 40%               | FU LVEF < 40%               | p Value          |
| Age                        | 48 ± 16                     | 45 ± 12                     | 0.57                        |
| BSA                        | 2.03 ± 0.18                 | 2.01 ± 0.18                 | 0.78                        |
| NYHA class                 | 2.6 ± 0.8                   | 3.1 ± 0.8                   | 0.18                        |
| Dobutamine dose (µg/kg/min)| 27 ± 11                     | 32 ± 11                     | 0.29                        |
| HR (beats/min)             | 85 ± 17                     | 88 ± 16                     | 0.65                        |
| BPmean (mm Hg)             | 89 ± 13                     | 88 ± 17                     | 0.89                        |
| LV mass (g)                | 247 ± 59                    | 208 ± 58                    | 0.13                        |
| LV mass (g/ml)             | 1.25 ± 0.24                 | 0.96 ± 0.27                 | 0.02                        |
| ESsphericity| | 87 ± 18                     | 98 ± 27                     | 0.29                        |
| EF (%)                     | 27 ± 8                      | 24 ± 7                      | 0.25                        |
| WMSI                       | 2.27 ± 0.21                 | 2.51 ± 0.18                 | 0.01                        |
| ESD (mm)                   | 5.4 ± 0.83                  | 5.75 ± 0.83                 | 0.32                        |
| EDD (mm)                   | 6.16 ± 0.9                  | 6.61 ± 0.61                 | 0.18                        |
| SFR (%)                    | 26 ± 6                      | 20 ± 11                     | 0.15                        |
| Emax (cm/s)                | 0.79 ± 0.15                 | 0.89 ± 0.22                 | 0.26                        |
| Amax (cm/s)                | 0.63 ± 0.25                 | 0.46 ± 0.32                 | 0.24                        |
| E/A ratio                 | 1.71 ± 1.34                 | 2.56 ± 1.26                 | 0.17                        |
| Decel TimeMI (ms)          | 159 ± 61                    | 96 ± 22                     | 0.01                        |
| IVRT                       | 82 ± 22                     | 92 ± 22                     | 0.29                        |
| Sphericity indexED         | 1.63 ± 0.14                 | 1.63 ± 0.25                 | 0.95                        |
| Sphericity indexES         | 1.81 ± 0.22                 | 1.81 ± 0.32                 | 0.97                        |
| Mitral regurgitation grade | 1.9 ± 1.62                  | 2.85 ± 0.9                  | 0.07                        |

Values are mean ± SD.

*BP = blood pressure; BSA = body surface area; EDD = end diastolic diameter; EF = ejection fraction; ES = end systolic; ESD = end systolic diameter; FU = follow up; HR = heart rate; IVRT = isovolumetric relaxation time; MI = mitral in flow Doppler; NYHA = New York Heart Association; SFR = right ventricular fractional shortening; WMSI = wall motion score index.

| Table 2. Change in Hemodynamic and Echocardiographic Variables in Response to Dobutamine |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Variables                  | Baseline Value              | FU LVEF > 40%               | FU LVEF < 40%               | p Value          |
| Heart rate*                | 34 ± 17                     | 35 ± 11                     | 0.93                        |
| Blood pressure* (mean)*    | −3 ± 13                     | −0.6 ± 17                   | 0.74                        |
| Ejection fraction*         | 27 ± 14                     | 10.5 ± 5                    | 0.001                       |
| Sphericity indexED*        | 0.35 ± 0.34                 | 0.14 ± 0.23                 | 0.09                        |
| Sphericity indexES*        | 0.60 ± 0.43                 | 0.13 ± 0.21                 | 0.003                       |
| Wall motion score index*   | −0.69 ± 0.29                | −0.37 ± 0.30                | 0.02                        |
| Stroke volume*             | 34 ± 27                     | 6 ± 17                      | 0.012                       |
| ESsphericity*              | −43 ± 16                    | −63 ± 26                    | 0.34                        |
| Fractional shortening RV*  | 16 ± 14                     | 11 ± 12                     | 0.31                        |

Values are mean ± SD.

* = change; ED = end-diastole; ES = end-systole; FU = follow up; RV = right ventricle.
changes in echocardiographic variables from baseline to follow-up in the two groups. Left ventricular ejection fraction increased by 26 ± 12% in group 1 and decreased by 3 ± 8% in group 2 (p < 0.001). Left ventricular ED dimension decreased in group 1 and increased in group 2 (delta = −0.35 ± 0.88 cm vs. 0.25 ± 0.67 cm, p = 0.09). A decrease in LV dimensions in group 1 was associated with a decrease in ES wall stress, whereas an increase in LV dimensions in group 2 was associated with an increase in ES wall stress (delta = −28 ± 21 vs. 42 ± 99 G/cm², p = 0.043). In addition, LV filling became less restrictive, with a greater decrease in mitral in flow E/A ratio in group 1 versus group 2 (delta = −0.70 ± 1.28 vs. −0.41 ± 1.36, p = NS) and a greater increase in deceleration time in group 1 versus group 2 (delta = 36 ± 72 ms vs. −1 ± 50 ms, p = 0.24).

Figure 2 shows the LVEF at baseline, peak dobutamine and follow up in the two groups. Correlation between dobutamine LVEF and follow-up LVEF was 0.84, between ΔEF on dobutamine (dobutamine EF–baseline LVEF) and follow-up LVEF was 0.71 and between ΔLVEF on dobutamine and ΔLVEF on follow-up (follow-up LVEF–baseline LVEF) was 0.81. Table 4 shows the correlation between baseline clinical and echocardiographic variables as well as contractile reserve of the LV, measured as an increase in LVEF on dobutamine, to LVEF on follow up. Because higher correlations of baseline clinical, echocardiographic and dobutamine echocardiographic variables were found for final LVEF than they were for change in LVEF from baseline, correlations with final LVEF are shown. The baseline variables that were significantly predictive of follow-up LVEF (or change in LVEF on follow-up) were DT with a correlation of 0.69 (and 0.57), WMSI with a correlation of −0.63 (and −0.38), LV mass (g/ml) with a correlation of 0.56 (and 0.48) and LVEF on dobutamine with a correlation of 0.84 (and 0.69) for follow-up LVEF (or change in LVEF from baseline, respectively). Figure 3 shows the correlation between LVEF on dobutamine and at follow-up. Using any of baseline variables DT, WMSI or LV mass to predict follow-up LVEF gave adjusted R-square of 0.47, 0.39 and 0.31, respectively. Left ventricular ejection fraction on dobutamine (or ΔLVEF = dobutamine, LVEF–baseline LVEF) added significantly to predictive power, r² = 0.74, 0.73 and 0.70 with DT, WMSI and LV mass, respectively. However if LVEF on dobutamine (or ΔLVEF = dobutamine LVEF–baseline LVEF) was entered first, none of the other three variables added significantly to prediction. Baseline LV sphericity in ED


Table 4. Correlation Between Ejection Fraction on Follow-Up and Baseline Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pearson Correlation r</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMSI</td>
<td>−0.63</td>
<td>0.002</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>−0.21</td>
<td>0.34</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>0.22</td>
<td>0.34</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.37</td>
<td>0.09</td>
</tr>
<tr>
<td>Fractional shortening RV (%)</td>
<td>0.38</td>
<td>0.08</td>
</tr>
<tr>
<td>E/A ratioMI</td>
<td>0.33</td>
<td>0.18</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>0.69</td>
<td>0.0006</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>−0.43</td>
<td>0.065</td>
</tr>
<tr>
<td>Sphericity index (ED)</td>
<td>0.12</td>
<td>0.61</td>
</tr>
<tr>
<td>Sphericity index (ES)</td>
<td>0.34</td>
<td>0.13</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0.20</td>
<td>0.41</td>
</tr>
<tr>
<td>End systolic wall stress (g/cm²)</td>
<td>−0.31</td>
<td>0.17</td>
</tr>
<tr>
<td>LV mass</td>
<td>0.26</td>
<td>0.25</td>
</tr>
<tr>
<td>LV mass/ml</td>
<td>0.56</td>
<td>0.008</td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.84</td>
<td>0.0006</td>
</tr>
<tr>
<td>Sphericity index&lt;sub&gt;ED&lt;/sub&gt;</td>
<td>0.64</td>
<td>0.0017</td>
</tr>
<tr>
<td>Sphericity index&lt;sub&gt;ES&lt;/sub&gt;</td>
<td>0.71</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

n = 21. Patient who underwent LV reduction surgery at three weeks after dobutamine echocardiography was excluded from analysis.

(r = 0.13, p = 0.6) or ES (r = 0.26, p = 0.25) did not significantly correlate with the follow-up LV sphericity in ED or ES, but LV sphericity on dobutamine in ED (r = 0.70, p = 0.0004) and ES (r = 0.69, p = 0.0005) did correlate with the follow-up LV sphericity. The baseline RV fractional shortening correlated with the follow-up RV fractional shortening (r = 0.49, p = 0.02), whereas fractional shortening on dobutamine did not (r = 0.37, p = 0.09) correlate with follow-up RV fractional shortening.

**Status at follow-up.** No cardiac events occurred in any of the 10 patients with follow-up LVEF >40%. Six patients were in New York Heart Association (NYHA) class I, of these five had complete normalization of LVEF and four were in NYHA class II. Five of the 11 patients with follow-up LVEF <40% had events. Two patients had recurrent admissions for congestive heart failure, another one was admitted with congestive heart failure and ventricular tachycardia, one with hypotension and congestive heart failure, and one was listed for heart transplantation. Of these, two patients underwent LV reduction surgery. Of the remaining six patients, two remained in NYHA class II, two improved from class III to class II and two improved from class III to class I.

**DISCUSSION**

The major finding of this study is that early after the diagnosis of IDC, the LV contractile response and change in LV geometry in response to dobutamine predicted late recovery of LV function. Both the response to dobutamine infusion and the late clinical and hemodynamic improvement were directly related to baseline LV mass per unit volume. Other echocardiographic parameters did not predict future cardiac function.

**Prognostic value of contractile reserve.** Our findings extend the results of earlier studies (27,28) that demonstrated the prognostic value of contractile reserve in IDC. These prior studies were performed in patients with long-standing dilated cardiomyopathy, whereas we limited our assessment to patients with recent onset dilated cardiomyopathy and we also assessed LV mass and LV geometry and RV function. Our study also extends a previously established correlation between LV hypertrophy and contractile reserve (38), to demonstrate that there is a further correlation between LV mass, response to inotropic stimulation and spontaneous late recovery of LV function.

The potential for substantial, and even complete, recovery of cardiac function in patients with acute and subacute IDC has been established by several investigators (4–6). Similar to the findings of previous reports (9,10), we found a restricted mitral inflow pattern to be associated with poor LVF on follow-up. Furthermore, improvement in systolic function was associated with resolution of the restrictive LV filling (14), a less spherical LV geometry and decrease in wall stress.

**Prognostic value of LV mass.** In addition, we found preservation of LV mass to be associated with an improvement in LV function. The presence of LV hypertrophy in IDC has been associated with a good prognosis in previous studies (25,26,38). Pelliccia et al. (26) showed in 30 IDC patients that the ratio of myofibrillar volume to total cell volume was significantly lower in patients who had poor
prognosis at one year than those who recovered. Similarly, others have reported that low myofibril volume (39) and electron microscopic evidence of myofilament loss indicate a poor prognosis in patients with IDC (40). Restoration of LV mass by recombinant growth hormone therapy also improves cardiac hemodynamics and clinical function in patients with ischemic cardiomyopathy (41). Our study findings suggest that the presence of LV hypertrophy implies the presence of myocardial contractile reserve, which in turn predicts recovery of LV function.

**Myocardial response to dobutamine.** The mechanism by which greater baseline LV mass relates to subsequent recovery of function is not clear. The dobutamine dose, change in heart rate, mean blood pressure, reduction in mitral regurgitation and the decline in ES wall stress in response to dobutamine was similar in both groups. Thus the factor differentiating the patients who recovered LV function from those who did not was principally the myocardial inotropic response. The LV mass in IDC may determine the contractile response to dobutamine and reflects both beta receptor number and integrity and the potential for recovery of LV function. This capacity for recovery may be independent of subsequent pharmacologic therapy with ACE inhibitor and beta blocker therapy because the treatment pattern in both groups was similar and most of our patients were on ACE inhibitor therapy.

In our study, baseline RV function and improvement in response to dobutamine was not significantly different in both groups of patients, but improvement in LVEF was associated with a concurrent improvement in RV function. These differences in the RV versus LV responsiveness may represent the limitations of echocardiography for the assessment of RV function or relate to the smaller myocardial mass of RV wall and its lower beta receptor density.

**Study limitations.** Because patients may have asymptomatic LV dysfunction for varying time intervals before their diagnosis, our study findings may be considered to be more relevant to “newly diagnosed” rather than “new onset” IDC. Although our findings establish a correlation between contractile reserve with LV mass, our proposed mechanism involving beta-receptor density is speculative, because we did not measure beta-receptor density, adenylcyclase activity or G protein activity. The failure of contractile reserve with dobutamine does not preclude recovery from heart failure, because four patients in group 2 improved functional class despite poor LVEF. Other echocardiographic methodologic limitations include:

1) potential imprecision in the measurement of RV function by echocardiography, which may have accounted for the weak predictive value of RV contractile reserve in our study, and
2) the limited ability to record discrete pressure gradients between right atrium and RV and between left atrium and LV at peak dobutamine infusion due to a reduction in the tricuspid and mitral regurgitation envelopes.

Although we measured LV mass per unit ml at the time of baseline echocardiography, the correlation of LV mass with dobutamine response and with follow-up LVEF is a post-hoc analysis and not based on a priori hypothesis.

As with many cases of dilated cardiomyopathy, the etiology is unknown in our patients. Thus, the recovery process and time is likely to be different based on underlying etiology. Finally, because the sample size is small and the follow-up period is relatively short, our findings need to be confirmed in a larger cohort of patients.

**Implications.** Our findings confirm the limited prognostic value of clinical and conventional echocardiographic parameters in patients with new onset IDC. Conversely, this is the first study to demonstrate that contractile reserve on dobutamine echocardiography has important prognostic value in patients with newly diagnosed IDC. The data suggest that dobutamine echocardiography is a useful test in the assessment of patients with recently diagnosed IDC and may also be useful as part of pretransplant evaluation in patients with IDC. Conservative management without potentially unnecessary transplantation might be considered in patients who show improvement in LV contractility and geometry in response to dobutamine. The absence of a significant response to dobutamine may imply a poor chance of recovery, suggesting a greater role for transplantation or LV reduction surgery. This approach to management could help triage patients with new onset IDC.

**APPENDIX**

**APPENDIX 1: ECHOCARDIOGRAPHIC MEASUREMENTS**

LV mass (g) (35): \[ V = \frac{5/6A}{L} \times L, L = LV \text{ length from base to } LV \text{ apex.} \]

\[ LVM = [V_t (ep) - V_c (en)] \times 1.05, \]

\[ V_t = \text{total } LV \text{ volume, } V_c = \text{ chamber volume, midparasternal short axis view.} \]

\[ 1.05 = \text{ specific gravity of the cardiac muscle.} \]

**Left ventricular end-systolic meridianal wall stress (g/cm²)** (36):

\[ \text{ESWALL\_STRESS} = \left(\frac{1.35 \times (MBP \times (LV_{ES}))}{(4 \times (LVPW_{ES}) (1 + LVPW_{ES}/LV_{ES}))}\right) \times (2DBP + SBP)/3, \]

\[ \text{DBP} = \text{ diastolic blood pressure and } SBP = \text{ systolic blood pressure.} \]

1.35 is the factor to convert pressure from mm Hg to g/cm².

**Right ventricular shortening fraction (FSRV) (37)**: \[ 100\% \times (RV_{ED} - RV_{ES})/RV_{ED} \]

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