Introduction and objectives. Myocardial contractile reserve studies with low-dose dobutamine echocardiography have been shown to be useful to assess functional myocardial status. However, the variables associated with contractile reserve after inotropic stimulation are not well known.

Patients and method. We studied 50 patients (35 men, mean age 56.4 ± 9.5 years) with nonischemic dilated cardiomyopathy (NIDC), LVEF 28.7% ± 8.5% and wall motion score index (WMSI) 2.42 ± 0.34 with low-dose dobutamine echocardiography. Left ventricular contractile reserve was assessed by a differential parameter defined as the difference between rest and stress WMSI ($\Delta$WMSI).

Results. After dobutamine infusion the WMSI was 1.95 ± 0.58; from this value we calculated a $\Delta$WMSI of 0.45 ± 0.39. None of the clinical variables showed a relationship with the presence of contractile reserve. In contrast, the following echocardiographic parameters correlated with $\Delta$WMSI: end-diastolic (p = 0.05) and end-systolic (p = 0.02) diameters, end-systolic volume index (p = 0.01) and LVEF (p = 0.002). In the multivariate analysis, only end-diastolic diameter was an independent predictor of contractile reserve (hazard ratio = 0.852; 95% CI, 0.735-0.987; p = 0.03).

Conclusions. Ventricular diameters, end-systolic volume index and LVEF are related with improvements in myocardial contractility after dobutamine infusion, although only end-diastolic diameter was an independent predictor of contractile reserve. Thus, this parameter should receive particular attention in evaluations of the functional status of the myocardium in patients with NIDC.

Key words: Cardiomyopathy. Echocardiography. Stress.
INTRODUCTION

Dobutamine stress echocardiography (DSE) can be useful in evaluating myocardial function. It has recently been shown that there is a relationship between the presence of contractile reserve assessed using DSE and medium-term survival in patients with nonischemic dilated cardiomyopathy (NIDC). Patients with NIDC generally do not have a good prognosis, with high rates of morbidity and mortality in the short to medium term. The clinical management of these patients should therefore incorporate any tools which help to improve prognostic precision. The option of performing a family study should also be evaluated, as a substantial number of NIDC patients who go on to have a heart transplant have a family history of the disease.

The aim of the present study was to analyze the relationship between clinical, electrocardiographic and echocardiographic (systolic and diastolic function) variables, and the presence of myocardial contractile reserve evaluated using DSE, in patients with NIDC.

PATIENTS AND METHODS

Patient selection

Nonischemic dilated cardiomyopathy was diagnosed according to World Health Organization guidelines and patients were included prospectively in the study from in- or out-patient departments. Study inclusion criteria included: a) absence of previous heart disease and normal coronary arteries in the angiographic study (performed on inclusion in the study or within the previous two years); b) absence of valvular or congenital etiology; c) ejection fraction less than or equal to 40%, determined using echocardiography, and d) systolic dysfunction of at least four weeks’ evolution. Exclusion criteria included having an inadequate acoustic window, an unstable clinical or hemodynamic profile, prior history of ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation), and patient’s refusal to participate. The study protocol was approved by the center’s Clinical Trials Committee. Informed consent to participate was requested from all patients. Sixty clinically stable patients with severe systolic dysfunction were studied initially, and 50 were finally included in the study. One patient was excluded due to inadequate acoustic window, three because they were clinically or hemodynamically unstable, and six patients refused to participate or were lost to follow-up.

Study design

Demographic, clinical and electrocardiographic data collected included age and sex, disease duration, functional status (assessed using the NYHA criteria), presence or absence of sinus rhythm and left bundle branch block, current medical treatment, and presence of co-morbid diabetes mellitus, arterial hypertension (AHT) and family history of cardiomyopathy. A baseline transthoracic echocardiogram was performed to measure systolic and diastolic function. This was followed by the low-dose dobutamine stress echocardiographic study.

Echocardiographic protocol

All studies were performed using a Sonos 5.500 (Philips) apparatus with harmonic imaging. Baseline echocardiographic variables included end-diastolic and end-systolic diameters, and ventricular volumes, measured with the area-length method and a 4-chamber view. The ejection fraction was calculated automatically from the volumes obtained by manual tracing of the left ventricular endocardial border in end-systole and end-diastole. Diastolic function was measured by analyzing: a) mitral flow: E and A wave velocity, E/A ratio, E wave deceleration time and isovolumetric relaxation time; b) pulmonary venous flow: S, D and A’ wave velocity, A’ wave duration and S/D ratio, and c) color M-mode E-wave propagation velocity.

On completion of the baseline echocardiographic study, the four standard views were obtained in digital format using stress echocardiograph software, and dobutamine infusion was initiated using increasing doses (5, 10 and 20 µg/kg/min) administered in consecutive 5-minute phases. On completion of the stress protocol, off-line images were studied, and the peak wall motion score index (WMSI) was calculated. The WMSI was obtained by summing the score for each segment (1=normokinetic, 2=hypokinetic, 3=akinetik, and 4=dysskinetic) and dividing by 16, as recommended in the American Society of Echocardiography guidelines. Where left bundle branch block was present, scores were calculated by evaluating wall thickening but not wall motion. Dobutamine stress echocardiography was suspended before concluding the 20 µg dose if the drug was poorly tolerated, or where any of the following occurred: arterial hypertension (systolic arterial pressure >220 mm Hg and/or diastolic arterial
pressure >120 mm Hg), arterial hypotension (reduction of >30 mm Hg compared to baseline), supraventricular arrhythmias (supraventricular tachycardia or de novo atrial fibrillation, and ventricular arrhythmias (ventricular tachycardia or frequent polymorphic ventricular tachycardias). All studies were rated by 2 independent observers. In case of disagreement, segments were scored by consensus.

Contractile reserve in each segment was defined as an improvement in function of at least one point after inotropic stimulation. Global contractile reserve was assessed by subtracting baseline WMSI from peak WMSI after dobutamine infusion (ΔWMSI). This parameter had a theoretic range of 0 (total absence of contractile response) to 3 (all dyskinetic segments become normokinetic). Contractile reserve was considered significant where ΔWMSI≥0.44. This cut-point was recently validated by Pratali et al.4

Statistical analysis

Quantitative variables were expressed as means±standard deviations, and categorical variables were expressed as percentages. The Kolmogorov-Smirnov test with the Lilliefors correction was used to test whether quantitative variables were normally distributed. The χ² test was used to compare qualitative variables, and means were compared using Student’s t-test. The relationship between systolic and diastolic function and the contractile reserve index was studied using Pearson’s correlation coefficient. All comparisons were bivariate, and means were compared using Pearson’s correlation coefficient. All analyses were performed using the SPSS 10.0 statistical package (SPSS inc. Chicago, USA).

RESULTS

Population

A total of 50 patients (35 men and 15 women) were included. Mean age was 56.4±9.5 years. On inclusion in the study, 10 patients (20%) were in NYHA functional class I, 34 (68%) were in class II and 6 (12%) were in class III. The electrocardiograph results showed that 39 patients (78%) had sinus rhythm, 8 (16%) had atrial fibrillation and 3 (6%) used pacemakers. A total of 29 patients (58%) had complete left bundle branch block. Three patients (6%) had type 2 diabetes, 17 (34%) had hypertension and 6 (12%) had a family history of dilated cardiomyopathy. Mean disease duration was 30.7±25 months (range, 1-120 months).

<table>
<thead>
<tr>
<th>Table 1. Baseline echocardiographic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
</tr>
<tr>
<td>EDD, mm</td>
</tr>
<tr>
<td>ESD, mm</td>
</tr>
<tr>
<td>EDV, ml</td>
</tr>
<tr>
<td>ESV, ml</td>
</tr>
<tr>
<td>EF, %</td>
</tr>
<tr>
<td>E wave V, cm/s</td>
</tr>
<tr>
<td>A wave V, cm/s</td>
</tr>
<tr>
<td>E/A</td>
</tr>
<tr>
<td>E wave DT, ms</td>
</tr>
<tr>
<td>IVRT, ms</td>
</tr>
<tr>
<td>M-color Pv, cm/s</td>
</tr>
<tr>
<td>S wave V, cm/s</td>
</tr>
<tr>
<td>D wave V, cm/s</td>
</tr>
<tr>
<td>S/D</td>
</tr>
<tr>
<td>A' wave V, cm/s</td>
</tr>
<tr>
<td>A' wave T, ms</td>
</tr>
<tr>
<td>Baseline WMSI</td>
</tr>
<tr>
<td>Peak WMSI</td>
</tr>
<tr>
<td>ΔWMSI</td>
</tr>
</tbody>
</table>

EED indicates end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction; WMSI, wall motion score index; CR, contractile reserve; T, time; DT, deceleration time; IVRT, isovolumetric relaxation time; V, velocity; PV, propagation velocity; EDV, end-diastolic volume; ESV, end-systolic volume.

General echocardiographic data

The group presented serious systolic dysfunction, with a mean ejection fraction (EF) of 28.7±8.5% and a baseline WMSI of 2.42±0.34. There were no relevant complications in terms of study procedures and all patients completed the study up to doses of 20 μg. Baseline echocardiographic values are shown in Table 1. After dobutamine infusion, mean peak WMSI was 1.95±0.58, and mean ΔWMSI was 0.45±0.39. A total of 26 patients (52%) had preserved contractile reserve (ΔWMSI>0.44), whereas 24 (48%) had not (ΔWMSI<0.44).

Relationship between ΔWMSI and non-echocardiographic variables

None of the demographic variables or the clinical and electrocardiographic variables correlated with ΔWMSI (Table 2). P values for correlations between age, sex and time with the disease and ΔWMSI were 0.27, 0.37, and 0.60, respectively. NYHA functional class was likewise not associated with ΔWMSI (P=0.54), although a non-statistically significant tendency towards an improvement in function was observed in patients in class I after dobutamine infusion (ΔWMSI of 0.73±0.56 for patients in class I vs 0.47±0.37 for the remaining patients).
The primary endpoint was any of the following events: death, re-admission to hospital for cardiac insufficiency, worsening in functional class or need for a heart transplant. After a mean follow-up of 16.6±7.9 months, only 7 patients (14%) presented any of the events listed: one died (2%), one had worsening in NYHA functional class (2%) and 5 were admitted for heart failure (10%). None of the echocardiographic variables, including ∆MSI, were related to the primary endpoint. Of the clinical, ECG and demographic variables, only the presence of AHT was statistically significantly associated with a poorer evolution (33.3% incidence of events in patients with hypertension vs 6.4% in patients without hypertension; \( P = .029 \)).

**DISCUSSION**

The aim of the present study was to identify clinical, electrocardiographic or echocardiographic parameters which predicted adequate functional response in the myocardium after inotropic stimulation with dobutamine. Dobutamine studies of myocardial contractile reserve have principally been performed in patients with ischemic cardiomyopathy, in an effort to show the presence of hibernating and therefore viable myocardium. Similarly, DSE has been used to evaluate patients with systolic dysfunction before bypass surgery or percutaneous revascularization, and to establish a differential diagnosis between ischemic cardiomyopathy and NIDC. Dobutamine stress echocardiography has also been used in patients with suspected tachycardomyopathy stemming from atrial fibrillation to identify patients who recover function after cardioversion. In NIDC patients, the study of contractile reserve has been used in an attempt to predict late spontaneous recovery in patients with recent onset cardiomyopathy or improvement in left ventricular systolic function after prolonged treatment with beta-blockers. Comparisons with maximum \( O_2 \) consumption have also shown that DSE is useful in evaluating myocardial function in patients with advanced chronic heart failure. In addition, increased survival has been observed in NIDC patients with an adequate myocardial response after dobutamine infusion. However, few studies have attempted to explore the relationship between baseline clinical,
electrocardiographic or echocardiographic findings and the presence of contractile reserve.

Despite the prognostic importance of NYHA functional class in patients with NIDC, in the present study no evidence of a statistically significant relationship between this parameter and the presence of contractile reserve was found. Nevertheless, a non-significant tendency towards an improvement in function was observed after dobutamine infusion in patients in class I: with a greater number of patients this variable may have achieved statistical significance. The DSE showed no relationship between age, sex, time with the disease, presence of sinus rhythm or left bundle branch block, medical treatment used, or the presence of associated factors such as diabetes or arterial hypertension and myocardial contractile response. On the other hand, the echocardiographic parameters were related with contractile response. Our findings indicate that smaller ventricular (end-diastolic and end-systolic) diameters and smaller baseline end-systolic volumes lead to a greater capacity for contractile response in stimulated myocardium. Baseline EF was also related with this response: patients with a more depressed EF showed a weak inotropic response after dobutamine infusion. Of all the echocardiographic variables included in the multivariate analysis, only end-diastolic diameter correlated independently with the presence of contractile reserve. This finding highlights the importance of this parameter when evaluating myocardial function when serious systolic dysfunction is present.

Previous studies have shown that a restrictive diastolic pattern and a reduction in E wave deceleration time are associated with poorer evolution and higher mortality in patients with congestive heart failure. In our series, there was no association between any of the diastolic parameters and inotropic effect) may at least partially explain the beneficial effects of treatment with beta-blockers. The modulating effect of beta-blockers on the expression and stimulation of those receptors suggests that these drugs influence the results of tests such as the DSE, which are based on adrenergic stimulation. In the present study, however, the proportion of patients taking beta-blockers was similar in the group which responded to dobutamine (n=17; 65.4%) and in the group which did not (n=17; 70.8%), indicating that there was no association between the presence of the drug and the test results (P=.27).

Finally, the fact that there was no relationship between presence of contractile reserve and prognosis during follow-up is probably due to the small number of patients in the study, as well as to their clinical and hemodynamic stability and the low rate of recorded events. Interestingly, having a prior history of AHT was associated with a worse prognosis, despite optimal treatment.

Study limitations included the fact that the evaluation of segmental contractility in echocardiography is influenced by observer subjectivity. To mitigate this, all of the studies were performed by the same echocardiographer (MPP) and interpreted by three observers (MPP, AC, DMG). Differences of opinion were resolved by consensus. On the other hand, the fact that a significant number of patients did not have a sinus rhythm or had complete left bundle branch block further complicated interpretation of the studies. This limitation was ameliorated as far as possible by seeking interobserver agreement when interpreting the echocardiograms, and by excluding non-interpretable cases. Likewise, greater importance was given to myocardial thickening than to systolic excursion when each segment was scored, particularly when there was evidence of paradoxical wall movement.

CONCLUSIONS

Baseline ventricular diameters, end-systolic volume and left ventricular ejection fraction correlated significantly with improvements in myocardial contractility after dobutamine infusion, although only end-diastolic diameter independently predicted the presence of contractile reserve. This parameter is of particular relevance when myocardial function is evaluated in patients with nonischemic dilated cardiomyopathy. Future studies should investigate whether periodic monitoring of this parameter would be useful in determining prognosis in these patients.
REFERENCES