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Dobutamine echocardiography in idiopathic dilated cardiomyopathy: clinical and prognostic implications ☆

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Abstract

The dobutamine echocardiographic test (DET) is frequently used in coronary artery disease to detect viable myocardium, but few data are available about its role in idiopathic dilated cardiomyopathy (IDCM). The aims of this study were to evaluate the clinical role of DET and the prognostic implications of the 'contractile reserve' in patients with IDCM treated with optimal medical therapy, including β-blockade (BB). A total of 51 patients with IDCM underwent DET at diagnosis. A positive response to DET (DET +) was judged to be a significant increase (≥ 10 points) in left ventricular ejection fraction (LVEF) with a peak value $\geq 40\%$, and a reversed restrictive left ventricular filling pattern (RFP) if present at baseline study. Improvement at follow-up was defined according to combined clinical and echo-Doppler criteria. In all, 22 patients (43%) were classified as DET + . DET + patients were less symptomatic ($P < 0.001$), with lower heart rate ($P < 0.01$), less enlarged left and right ventricles ($P < 0.0001$ and $P < 0.05$), higher LVEF ($P = 0.0001$), less frequent RFP ($P = 0.01$), and lower pulmonary pressure ($P < 0.01$). At follow-up (34 ± 16 months), 21 patients had improved, while four had died and seven had received a transplant. Among clinical data, NYHA classes I–II (OR = 0.25, $P = 0.07$) and BB dosage (OR = 0.97, $P < 0.005$) were significantly associated with higher transplant-free survival at multivariate analysis. The addition of DET + (OR = 0.34, $P < 0.05$) showed a moderate but significant improvement of sensitivity, but the predictive power of the model remained low (sensitivity, 0.67; specificity, 0.55). Absence of left bundle branch block (OR = 0.27, $P < 0.01$) and BB dosage (OR = 1.03, $P < 0.005$), but not DET + , were predictive of improvement. In patients with IDCM, DET response is associated with a more favourable outcome, since it suggests an earlier stage of the disease. However, in the light of our data, the incremental prognostic power of DET response compared to clinical evaluation at enrolment, despite being significant, seems to be of limited clinical value. Further studies should be carried out in order to clarify the prognostic value of DET in IDCM patients.

Keywords: Idiopathic dilated cardiomyopathy; Contractile reserve; Dobutamine echocardiography; β-Blockers

Abbreviations: DET, dobutamine echocardiographic test; IDCM, idiopathic dilated cardiomyopathy; NYHA, New York Heart Association functional class; EF, ejection fraction; MR, mitral regurgitation; RFP, restrictive filling pattern; HF, heart failure; BB, β-blockers; LV, left ventricle; MED, metoprolol-equivalent dose

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1. Introduction

Several recent studies have shown the clinical usefulness of the dobutamine echocardiographic test (DET) in patients with coronary artery disease in assessing the presence of reversible left ventricular (LV) dysfunction. In fact, both 'stunned' and 'hibernating' myocardium can respond to inotropic drug stimulation by increasing wall motion and improving pump function. This inotropic response has proven to be highly predictive of improvement after the resolution of stunning or hibernation [1,2].

Conversely, only a few studies employed DET in patients with idiopathic dilated cardiomyopathy (IDCM) [3–7]. In some of those studies [5–7], an 'inotropic reserve' was demonstrated in a subset of patients with IDCM. Interestingly, the positive response to this drug could predict a favourable outcome.

β-Blocker (BB) treatment was recently demonstrated as being beneficial in IDCM; in fact, some clinical studies, both controlled and uncontrolled, showed an improvement in symptoms, hemodynamics and survival in patients treated [8–12]. The effects of BB therapy may be related to a 'biological' activity in the myocytes, including modification of gene expression, upregulation of receptors and regression of hypertrophy. However, the possibility of predicting a favourable response to treatment is still not clearly understood [13].

Therefore, the objectives of our study were to evaluate by DET: (1) the frequency and patterns of response to dobutamine in patients with IDCM; (2) the characteristics of patients with a positive DET; and (3) the prognostic role of DET in predicting the outcome of patients receiving tailored medical treatment.

2. Methods

2.1. Patient selection

From February 1988 to October 1996, 230 consecutive patients with a final diagnosis of IDCM were systematically and prospectively enrolled in our Heart Muscle Disease Registry, and treated with tailored medical therapy, including BB in most cases. From May 1994 to October 1996 all patients enrolled underwent DET.

The diagnosis of IDCM was made according to the currently employed criteria [14]. Inclusion criteria were sinus rhythm, adequate echocardiographic images and significantly depressed ($< 40\%$) LV ejection fraction (LVEF). Informed consent for DET was obtained in all cases.

2.2. Initial evaluation

At enrolment, all patients underwent physical examination, rest electrocardiogram, chest X-ray, M-mode, two-dimensional Doppler and colour-Doppler echocardiography, DET, bicycle exercise testing, haemodynamic and angiographic study, including coronary angiography and endomyocardial biopsy to exclude coronary disease and myocarditis according to the Dallas criteria [15].

Heart failure (HF) severity was clinically evaluated according to the New York Heart Association (NYHA) classification and by a HF score according to the classification of Lee et al. [16].

The bicycle exercise test was performed in accordance to a protocol with 10-W steps every minute.

2.3. Echocardiographic examination

Baseline echocardiographic examination was performed immediately before the DET. The M-mode tracings were evaluated according to the recommendations of the American Society of Echocardiography [17]. Standard measurements included LV end-diastolic and end-systolic diameters and shortening fraction, end-diastolic thickness of interventricular septum and left ventricular posterior wall, and end-systolic diameter of left atrium.

The two-dimensional echocardiographic examination was performed from all standard approaches and sections. Both ventricular chambers were quantitatively analysed. LV end-diastolic and end-systolic volumes and LVEF were assessed from the apical four-chamber view using the area–length single-plane method [18]. Right ventricular dimensions and systolic function were evaluated by measuring, from the apical four-chamber view, end-diastolic and end-systolic right ventricular areas and the shortening fraction of these areas [19]. From the same section, the end-systolic areas of both atria were obtained.

All measurements were calculated as the mean of three consecutive beats and were normalised for body surface area. Normal values were obtained from 41 normal subjects studied in our laboratory [19]. The limits of normality were considered the mean $\pm$ 2 S.D. Therefore, LVEF was considered normal if $\geq 52\%$, and right ventricular systolic function if the shortening fraction of right ventricular areas was $> 40\%$.

Mildly dilated cardiomyopathy was defined, according to the literature [20], when in the presence of depressed LV systolic function and of LV end-diastolic diameter index not more than 15% from the upper limit of normality (3.2 cm/m^2), i.e. ≤ 3.68 cm/m^2.

LV filling pattern was assessed at Doppler echocar-

diography. When studying the diastolic Doppler mitral curve, the sample volume of pulsed Doppler was positioned between the tips of mitral leaflets from the apical four-chamber view [21,22]. Doppler curves with E + A fusion due to tachycardia were not evaluated for filling pattern. LV restrictive filling pattern (RFP) was considered if E-deceleration time was < 120 ms. This cut-off point was arbitrarily chosen as corresponding to the mean value − 2 S.D. from the data of a series of 79 normal control subjects of similar age (normal E-deceleration time 177 ± 31 ms) [22].

The colour Doppler technique was used to evaluate the severity of mitral regurgitation (MR). It was assessed semi-quantitatively according to the area of regurgitant jet, from the apical four-chamber view [23]. Significant MR was arbitrarily considered if more than 1 + (MR jet area > 4 cm^2).

Intra- and inter-observer variability of LVEF and of E-deceleration time in a group of patients with IDCM was recently published by our group [24], with values of (mean ± S.D.) $0.07 \pm 3.3\%$ and $0.02 \pm 4.0\%$ for LVEF, and 0 ± 22.6 and 8 ± 13.6 ms for E deceleration time, respectively.

2.4. Treatment protocol

Patients were optimally treated with digitalis, diuretics and angiotensin-converting enzyme (ACE) inhibitors. The majority of patients (46/51, 90%), after clinical stabilisation, were also treated with metoprolol or carvedilol at the highest dosage tolerated. Two patients were treated with sotalol because of severe ventricular arrhythmia. BBs were not employed in the remaining three patients because of concomitant amiodarone treatment and significant bradycardia. In order to compare the dosages of different BB, as performed by others for ACE inhibitors [25], a 'metoprolol-equivalent dose' (MED) [8] was arbitrarily calculated by multiplying the carvedilol dosage by a factor of 2 and the sotalol dosage by 0.625. Patients who tolerated a MED ≥ 50 mg/day were arbitrarily considered as tolerant.

2.5. Dobutamine echocardiographic test

Dobutamine was administered using an infusion pump at 5, 10, 15, 20, 25 and 30 μg/kg body weight per minute, with each dosage lasting 5 min. Complete ECG and blood pressure (using a brachial cuff) were monitored. DET was stopped when any of the following criteria was reached:

A. The appearance of:
   - Sustained and/or symptomatic supraventricular and ventricular tachyarrhythmia;
   - Severe and symptomatic systemic hypotension (systolic blood pressure < 90 mm Hg or decrease > 40 mm Hg with respect to the basal condition), which did not respond promptly to liquid infusion;
   - Severe systemic hypertension (systolic blood pressure > 220 mm Hg);
   - Clinical, ECG or echocardiographic changes suggesting myocardial ischemia; or
   - Symptoms judged unacceptable by the patient.
B. Achievement of 75% of age-predicted maximal heart rate.
C. Normalisation of LV pump function (LVEF $\geq$ 52%).
D. Achievement of target dosage of dobutamine.

At the end of DET, the following parameters were measured:

- LV end-systolic and end-diastolic volumes and LVEF;
- E deceleration time of transmitral Doppler curve;
- Severity of MR; and
- Right ventricular areas and shortening fraction of areas.

2.6. Classification of patients

On the basis of the results of the DET, patients were classified into two groups:

A. DET responders (DET +): patients with improvement in systolic and diastolic function, judged by the following combined criteria:
   - Significant increase (≥ 10 points) in LVEF and peak LVEF $\geq 40\%$; and
   - Disappearance of LVRFP (in patients who presented this pattern at baseline study).
B. DET non-responders (DET −): patients without significant improvement in LVEF and/or with persistent RFP during DET.

The interpretation of DET and classification of patients at DET was performed blind to the outcome and follow-up data.

2.7. Follow-up assessment

The main end-points at the follow-up evaluation were:

A. Cardiac mortality or cardiac transplantation. The selection of patients for transplantation was performed according to current criteria, in the presence of severe symptoms of heart failure (NYHA III–IV) and/or VO_2 max < 10 ml/kg min

and/or recurrent hospitalisation for heart failure [26]. Indications for heart transplantation were not influenced by the results of DET.

B. Clinical improvement, in the presence of all the following combined clinical and echo-Doppler criteria:
   1. NYHA class I or II at follow-up (without worsening);
   2. LVEF at follow-up $\geq 40\%$ with increase in EF ≥ 10 points; or
   3. Regression of RFP at follow-up, if present at baseline.

Patients who died or received a transplant before echocardiographic examinations were considered as non-improved.

2.8. Statistical analysis

Baseline descriptive data are presented as mean value $\pm$ standard deviation. Group comparison for continuous data was made using an unpaired Student's *t*-test. The proportions were compared with a χ-square test with Yates correction. Transplant-free survival curves were analysed using the Kaplan–Meyer method and compared with a Mantel Cox test. Baseline and DET data were tested in predicting cardiac mortality or heart transplantation (considered together for the purpose of analysis) by the Cox model. Logistic regression analysis was performed to identify predictive factors for DET response and improvement at follow-up. In order to test the incremental prognostic value of DET, the sensitivity and specificity for each model were estimated, along with their confidence bounds using a bootstrap approach [24] with 0.632 correction and 5000 bootstrap iterations. All analyses were performed using the SPSS package.

3. Results

3.1. Study population

DET was performed in 51 patients (33 males, 67%; mean age 45 ± 13 years, range 12–75). Patient characteristics are summarised in Table 1. The majority was clinically stable (69% in NYHA class I or II). However, severe LV dysfunction was common (EF < 25% in 28 patients: 55%) and 17 patients (33%) were classified as 'mildly dilated' (LV end-diastolic diameter index, 3.38 ± 0.23 cm/m^2; LVEF, $26 \pm 7\%$). A LVRFP was present in 19 out of 49 patients[1] (39%), significant MR in 15 patients (29%), and right ventricular dysfunction in 16 cases (31%).

At enrolment, a stable clinical condition was obtained by tailoring the treatment with digitalis (47 patients, 92%), diuretics (34 patients, 67%), and ACE inhibitors (48 patients, 94%). After achieving clinical stability, patients were treated with metoprolol ($n = 35$), carvedilol ($n = 11$) or sotalol ($n = 2$). Among these 48 patients treated with BBs (94%), the mean MED was 89 ± 54 mg/day and 37 of them (77%) could tolerate a MED ≥ 50 mg/day.

3.2. Dobutamine echocardiographic test

In the whole patient population, the maximal drug dosage achieved was 18 ± 5 μg/kg min. During infusion of the drug, heart rate increased from 81 ± 14 to 109 ± 19 bpm, systolic blood pressure from 111 ± 15 to 128 ± 23 mmHg, and the double product (systolic blood pressure × heart rate) rose from 8956 ± 1976 to 13827 ± 2850 mm Hg × bpm.

No patient complained of significant symptoms during the test. In 18 patients (37%), non-sustained ventricular or supraventricular arrhythmia were observed. These types of arrhythmia were always well tolerated and they did not cause interruption of the test.

During DET, LVEF significantly increased (≥ 10 points), reaching a value $\geq 40\%$ in 23 out of 51 patients (45%) (Fig. 1); 10 of them reached a normal EF. On average, the peak LVEF at the end of DET was $39 \pm 11\%$ (range 13–63%), with a mean increase of 14 ± 9 points (range -2–$+32$ points). In 14 out of 19 patients (74%), the LVRFP reversed during the test (Fig. 2), and in 9 out of 15 cases (60%), a regression of significant MR was observed (Fig. 3). Right ventricular dysfunction reversed in 9 out of 16 patients (56%).

Overall, 22 patients (43%) were considered DET responders (DET+), while the other 29 (57%) were classified as DET non-responders (DET−).

The comparison of the baseline clinical, echocardiographic and haemodynamic data between these two groups of patients is shown in Table 1. In DET+ patients, significantly lower NYHA ($P = 0.0007$), HF score ($P = 0.0028$), and X-ray cardiothoracic ratio ($P = 0.0363$) were observed, and the exercise duration at effort test was significantly longer ($P = 0.0322$). Among echo-Doppler parameters, DET+ patients had less severe LV dilation ($P < 0.0001$) and systolic dysfunction ($P = 0.0001$); mildly dilated cardiomyopathy was in fact more frequent in this group of patients (59 vs. 14%; $P = 0.0004$). In addition, the right ventricle was less enlarged ($P = 0.0353$), and right ventricular dysfunction was less frequent (18 vs. 41%: $P = 0.0466$) in DET+ patients. At Doppler study, LVRFP was more frequent in DET− patients (54 vs. 19%;

[1] In two patients the E deceleration time could not be measured because of tachycardia and E + A fusion.

Table 1
Baseline characteristics of study patients

	All patients ($n = 51$)		DET + ($n = 22$)		DET − ($n = 29$)		P
	M ± S.D.	% (n)	M ± S.D.	% (n)	M ± S.D.	% (n)	
Clinical data							NS
Gender (% males)		67 (34)		77 (17)		59 (17)	NS
Age (years)	45 ± 13		48 ± 12		43 ± 14		NS
Disease duration (months)	19 ± 28		21 ± 30		17 ± 26		0.0007
NYHA	2.06 ± 0.81		1.6 ± 0.6		2.4 ± 0.8		0.0028
HF score (0–13)	2.12 ± 2.1		1.1 ± 1.2		2.9 ± 2.3		NS
S3		67 (34)		55 (12)		76 (22)	0.0887
HR (bpm)	83 ± 12		79 ± 10		85 ± 12		NS
LBBB		61 (31)		64 (14)		59 (17)	0.0363
CTR	0.53 ± 0.05		0.51 ± 0.06		0.55 ± 0.05		0.0322
Exercise duration (s)	554 ± 265		644 ± 233		484 ± 271		< 0.0001
							< 0.0001
Echocardiographic data							NS
LVEDDI (cm/m^2)	4.0 ± 0.5		3.6 ± 0.4		4.2 ± 0.5		NS
LVESDI (cm/m^2)	3.4 ± 0.6		3.0 ± 0.4		3.6 ± 0.5		< 0.0001
LVFS (%)	16 ± 5		17 ± 5		15 ± 5		< 0.0001
PW thickness index (cm/m^2)	0.48 ± 0.09		0.47 ± 0.09		0.49 ± 0.09		0.0001
IVS thickness index (cm/m^2)	0.50 ± 0.09		0.51 ± 0.09		0.49 ± 0.09		0.0033
LVEDVI (ml/m^2)	122 ± 39		97 ± 27		140 ± 37		0.0004
LVESVI (ml/m^2)	93 ± 34		71 ± 22		110 ± 31		0.0353
LVEF (%)	24 ± 6		28 ± 5		22 ± 5		0.0463
LVEF < 25%		55 (28)		32 (7)		72 (21)	NS
Mildly dilated[a]		33 (17)		59 (13)		14 (4)	0.0466
RVEDAI (cm^2/m^2)	11 ± 4		10 ± 3		12 ± 4		NS
RVESAI (cm^2/m^2)	6 ± 4		5 ± 3		7 ± 4		0.0587
RVSF of areas (%)	48 ± 17		52 ± 13		45 ± 20		0.0704
RV dysfunction		31 (16)		18 (4)		41 (12)	0.0135
LADI (cm/m^2)	2.3 ± 0.5		2.2 ± 0.5		2.3 ± 0.5		0.0913
LAAI (cm^2/m^2)	15 ± 4		13 ± 3		16 ± 5		0.0310
EDT (ms)	162 ± 81		186 ± 64		145 ± 88		NS
LVRFP[b]		39 (19)		19 (4/21)		54 (15/28)	NS
E/A ratio	1.4 ± 1.0		1.1 ± 0.7		1.6 ± 1.2		0.0061
MR severity (0–4)	1.3 ± 0.9		1.0 ± 0.8		1.5 ± 0.8		0.0005
MR > 1 +		29 (15)		23 (5)		34 (10)	0.0001
							NS
Haemodynamic data							NS
RAP (mmHg)	5 ± 3		5 ± 3		5 ± 3		NS
Mean PAP (mmHg)	21 ± 8		18 ± 7		24 ± 9		NS
Mean PAWP (mmHg)	12 ± 7		9 ± 5		16 ± 7		0.0150
LVEDP (mmHg)	13 ± 6		9 ± 5		17 ± 6		
Mean AoP (mmHg)	85 ± 11		85 ± 11		85 ± 12		
CI ($ml/min\ m^2$)	3649 ± 654		3650 ± 499		3649 ± 785		
Treatment data							
Metoprolol (mg/day) ($n = 35$)	79 ± 52		98 ± 57		68 ± 48		
Carvedilol (mg/day) ($n = 11$)	58 ± 22		56 ± 24		63 ± 18		
MED (mg/day)	89 ± 54		104 ± 52		78 ± 54		
MED > 50 mg/day		79 (38/48)		95 (20/21)		67 (18/27)	

Abbreviations: AI, area index; AoP, aortic pressure; CI, cardiac index; CTR, cardiothoracic ratio (chest X-rays); DET, dobutamine echocardiographic test; DI, diameter index; EDAI, end-diastolic area index; EDDI, end-diastolic diameter index; EDP, end-diastolic pressure; EDT, E deceleration time; EDVI, end-diastolic volume index; ESAI, end-systolic area index; ESDI, end-systolic diameter index; ESVI, end-systolic volume index; FS, fractional shortening; HF, heart failure; HR, heart rate; IVS, interventricular septum; LA, left atrium; LBBB, left bundle branch block; LV, left ventricular; M, mean; MED, metoprolol-equivalent dose; MR, mitral regurgitation; NYHA, New York Heart Association functional class; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PW, posterior wall; RAP, right atrial pressure; RFP, restrictive filling pattern; RV, right ventricular; S.D., standard deviation; S3, third heart sound.

[a] For definition, see Section 2 in the text.

[b] Out of 49 patients.

$P = 0.0135$) and MR was more severe ($P = 0.0310$). At haemodynamic study, DET − patients showed significantly higher mean pulmonary artery ($P = 0.0061$), capillary wedge ($P = 0.0005$) and LV end-diastolic pressures ($P = 0.0001$).

During DET (Table 2), the patients with positive response to the drug showed significantly lower baseline ($P = 0.0094$) and peak ($P = 0.0326$) heart rate. By definition, DET + patients showed significantly higher peak LVEF (49 ± 6 vs. $31 \pm 7\%$; $P < 0.0001$) and lower peak LV volumes ($P < 0.0001$).

At multivariate analysis (Table 3), independent predictive factors for positive DET response were: a lower basal heart rate (OR = 0.81, 95% CI = 0.69–0.95, $P = 0.0096$); higher LVEF (OR = 1.29, 95% CI = 1.01–1.64, $P = 0.0385$); absence of LVRFP (OR = 0.29, 95% CI = 0.08–1.11, $P = 0.0713$); and lower LV end-diastolic volume index (OR = 0.93, 95% CI = 0.88–0.98, $P = 0.0057$).

3.3. Follow-up data: analysis of survival

During a mean follow-up of 34 ± 16 months, four patients died (three suddenly and one of refractory HF), whilst seven received a transplant. For the overall patient group, survival free from transplantation

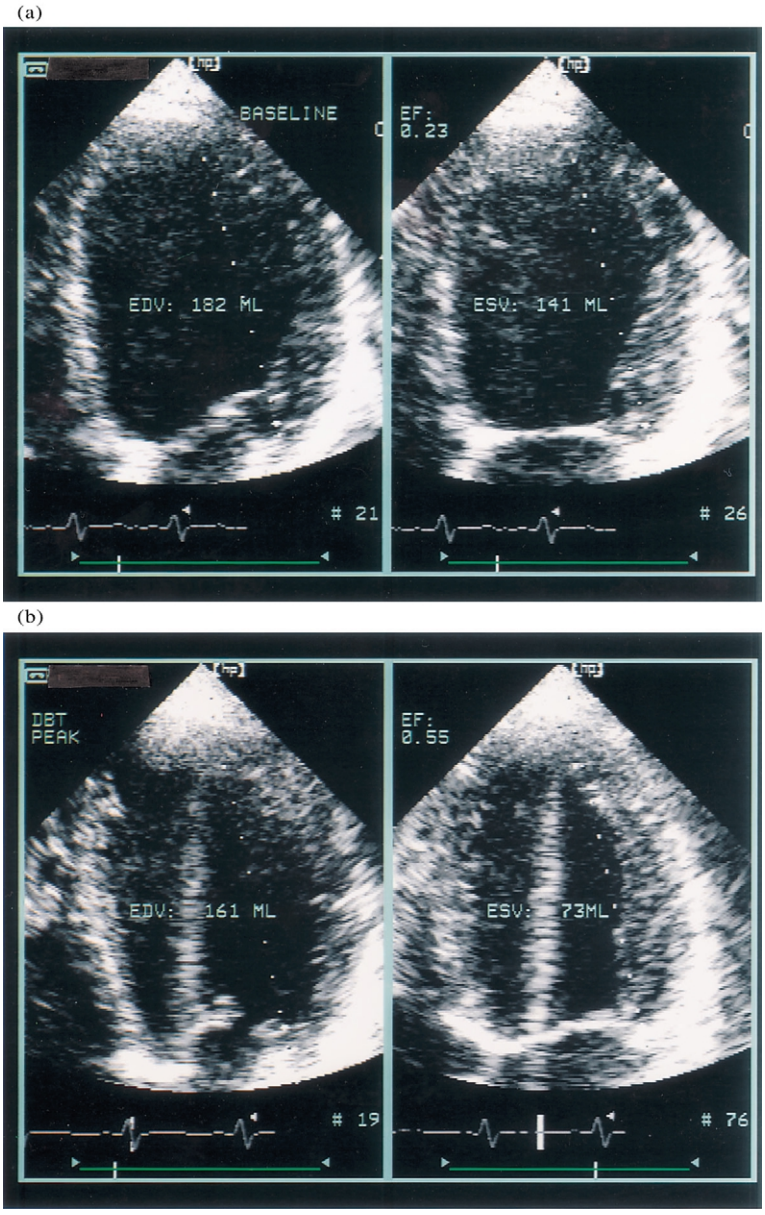

Fig. 1. Echocardiographic frames of the left ventricle (left frame, end-diastole; right frame, end-systole) from apical four-chamber view in a study patient with IDCM and positive response to DET: (a baseline study; and (b) control at the end of dobutamine infusion (20 μg/kg min). At the baseline study, the EF was severely depressed (23%), but significantly improved during DET (55%).

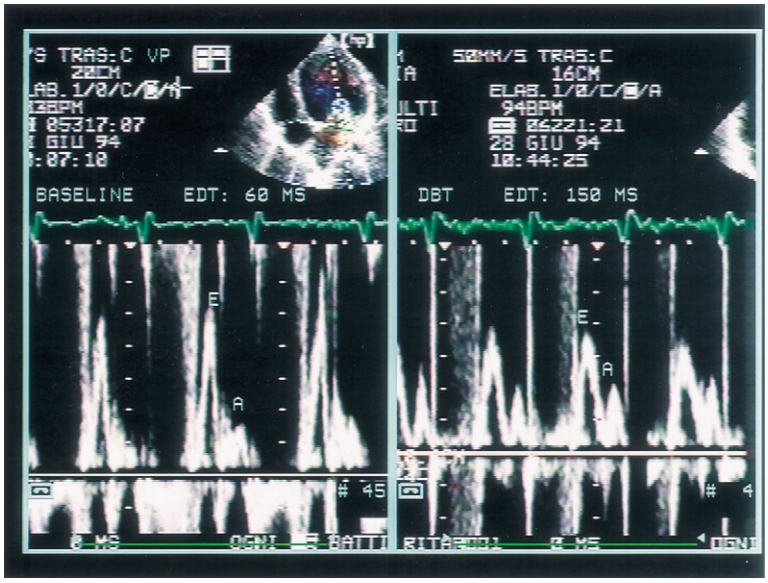

Fig. 2. Example of disappearance of restrictive left-ventricular filling pattern during DET. At baseline Doppler study (left frame) the transmitral curve showed an increased E/A ratio (3.3) and an extremely shortened E deceleration time (60 ms). During DET (right frame), the E/A ratio decreased (1.75) and E deceleration time increased (150 ms).

was 82% at 1 and 2 years, and 69% at 3 years. Three other patients are currently on a waiting list for transplantation.

Transplant-free survival was significantly better for DET + than for DET − patients (100% at 1 and 2 years and 92% at 3 years vs. 69% at 1 and 2 years and 56% at 3 years, respectively; $P = 0.0094$) (Fig. 4).

Predictive factors for transplant-free survival (Cox analysis) are shown in Table 4.

At multivariate analysis (Table 3), the clinical model included two parameters independently related to transplant-free survival: (1) NYHA class I or II (OR = 0.251, 95% CI = 0.05–1.17, $P = 0.078$); and (2) MED (OR = 0.97, 95% CI = 0.94–0.99, $P = 0.017$). When added to the clinical model, DET response was independently related to transplant-free survival (OR = 0.34, 95% CI = 0.12–0.94, $P = 0.038$) (Table 3).

The clinical-plus-DET model showed an incremental value with significant improvement in sensitivity with respect to the clinical model (from 0.55 to 0.67;

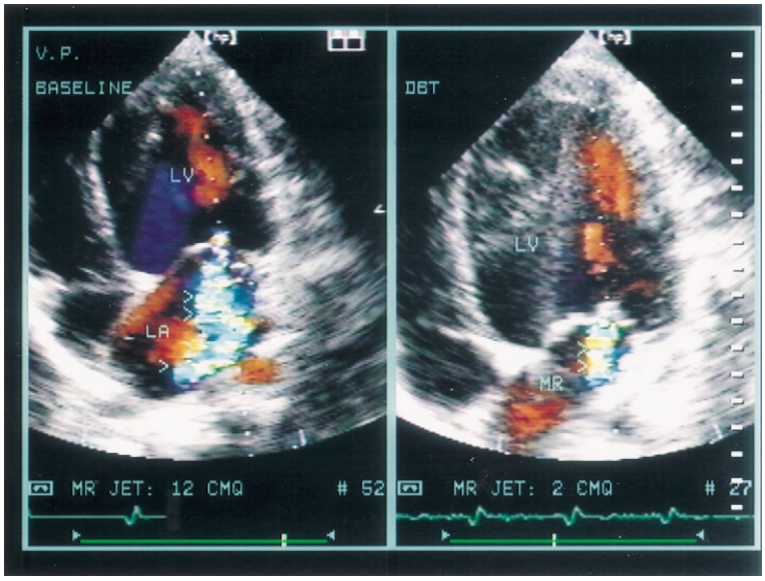

Fig. 3. Improvement in MR during DET in a study patient with IDCM. At baseline colour-Doppler study (left frame), MR was moderately severe (3 + ; MR jet area = 12 cm^2). During DET (right frame), MR was only mild (1 + ; MR jet area = 2 cm^2).

Table 2
Parameters during DET

	DET + ($n = 22$)	DET − ($n = 29$)	P
Max. DBT dosage (μg/kg min)	18 ± 5	19 ± 5	NS
Total dose of DBT (μg)	207 ± 106	229 ± 108	NS
Baseline HR (bpm)	75 ± 12	85 ± 15	0.0094
Baseline SBP(mmHg)	112 ± 15	111 ± 15	NS
Baseline DP	8336 ± 1561	9427 ± 2149	0.0500
Peak HR (bpm)	103 ± 20	114 ± 17	0.0326
Peak SBP (mmHg)	133 ± 26	124 ± 20	NS
Peak DP	13529 ± 3174	14053 ± 2613	NS
Peak LVEDVI (ml/m^2)	81 ± 25	129 ± 42	< 0.0001
Peak LVESVI (ml/m^2)	42 ± 16	90 ± 35	< 0.0001
Peak LVEF (%)	49 ± 6	31 ± 7	< 0.0001
LVEF variation (points)	21 ± 5	9 ± 6	< 0.0001
LVRFP regression	100% ($n = 4/4$)	67% ($n = 10/15$)	

Values are mean ± S.D. DBT, dobutamine; DP, double product; SBP, systolic blood pressure. For other abbreviations see Table 1.

95% CI from 0.51–0.59 to 0.63–0.70) in the prediction of transplant-free survival (Table 5).

3.4. Analysis of improvement

Clinical and echocardiographic data at follow-up were available in 42 patients. No follow-up echocardiographic data were available in three patients. The remaining six patients died or received a transplant before clinical and echocardiographic check-ups. They were included in the analysis and classified as non-improved (see Section 2).

According to clinical and echo-Doppler combined criteria (see Section 2), 21 out of the 48 patients (44%) were considered improved, whereas 27 (56%) had not improved at follow-up. LVEF increased to a value ≥ 40% in 22 patients, and RFP and right ventricular dysfunction reversed in 8 out of 12 patients (67%) and in 11 out of 14 patients (79%), respectively. One patient, in whom LVEF improved at follow-up, but LVRFP persisted, was considered as non-improved.

Table 6 compares the baseline data of improved and non-improved patients. Among improved patients, left bundle branch block was less frequent than in non-improved patients ($P = 0.0004$). Furthermore, the improved patients showed less dilated LV and higher LVEF ($P = 0.0065$). Among haemodynamic parameters, LV filling and pulmonary artery pressures were significantly lower in the patients who subsequently improved.

As regards therapy, the patients who improved were treated less frequently with digitalis and diuretics. Furthermore, the mean BB dosage was significantly

Table 3
Multivariate analysis

	β coefficient	S.E.	P	OR	95% CI
Model for DET response					
LVEDVI	−0.0754	0.0273	0.0057	0.93	0.88–0.98
HR	−0.2110	0.0815	0.0096	0.81	0.69–0.95
LVEF	0.2544	0.1229	0.0385	1.29	1.01–1.64
LVRFP	−1.2321	0.6832	0.0713	0.29	0.08–1.11
Clinical model for transplant-free survival					
MED	−0.0337	0.0141	0.017	0.97	0.94–0.99
NYHA I–II	−1.3834	0.786	0.078	0.25	0.05–1.17
Model for transplant-free survival (clinical + DET)					
MED	−0.0264	0.0092	0.0040	0.97	0.96–0.99
DET +	−1.0894	0.5261	0.0384	0.34	0.12–0.94
Clinical model for improvement at follow-up					
MED	0.0321	0.0112	0.0040	1.03	1.01–1.06
LBBB	−12981	0.4928	0.0084	0.27	0.10–0.72

OR, Odds ratio; S.E., standard error. For other abbreviations, see Tables 1 and 2.

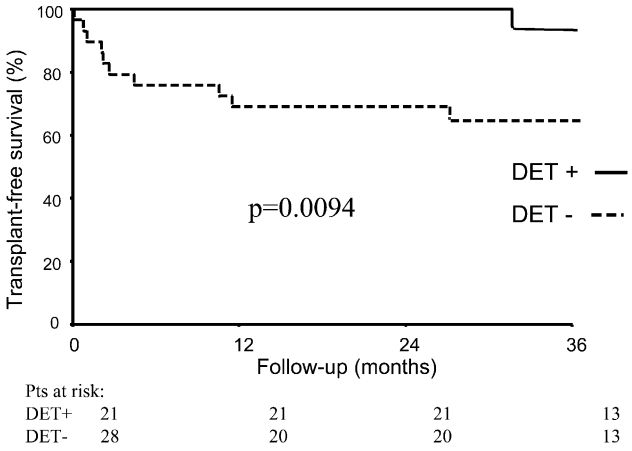

Fig. 4. Cumulative survival curves (free from heart transplantation) in DET + and DET − patients. Transplant-free survival was significantly better in patients who responded to DET ($P = 0.0094$).

higher (MED, 121 ± 53 vs. 66 ± 42 mg/day; $P = 0.0004$). All improved patients, but only 64% of non-improved patients, tolerated at least 50 mg MED ($P = 0.0021$) (Table 6).

A favourable response to DET was more frequent among improved patients (62 vs. 33%; $P = 0.05$). However, frequent 'false positive' and 'false negative' DET responses were observed (nine and eight cases, respectively).

At multivariate analysis (Table 3), the two parameters predictive of improvement were absence of left bundle branch block at ECG (OR = 0.27, 95% CI 0.10–0.72, $P = 0.0084$) and MED (OR = 1.03, 95% CI 1.01–1.06, $P = 0.004$). No significant additional prognostic value of DET was found (Table 5).

4. Discussion

In the present study, we investigated whether DET could help in the identification of those patients with IDCM who have a better prognosis and higher probability of improvement on tailored medical treatment.

4.1. DET in IDCM

The favourable action of dobutamine on a failing ventricle in increasing its systolic pump function [27], manifesting the so-called 'contractile reserve', mainly

Table 4
Comparison between patients who survived vs. those who died or received a transplant

	Survived ($n = 40$)			Dead or transplant ($n = 11$)			P
	% (n)	M ± S.D.	95% CI	% (n)	M ± S.D.	95% CI	
Clinical data							
Follow-up (months)		40 ± 8			9 ± 11		< 0.0001
NYHA		1.9 ± 0.8	1.7–2.2		2.5 ± 0.8	2–3.1	0.0229
NYHA I–II	80 (32)			27 (3)			0.0005
S3	58 (23)			100 (11)			0.0074
Echocardiographic data							
LVEDVI (ml/m^2)		116 ± 38	104–128		143 ± 39	116–169	0.0449
LVESVI (ml/m^2)		87 ± 31	77–97		115 ± 35	92–139	0.0114
Mildly dilated	40 (16)			9 (1)			0.0556
LVEF (%)		26 ± 5	24–27		20 ± 6	16–24	0.0015
LVEF < 25%	48 (19)			82 (9)			0.0437
LVRFP	33 (13/39)			60 (6/10)			0.1278
RVEDAI (cm^2/m^2)		10 ± 3	9–11		13 ± 4	10–16	0.0278
DET data							
DET +	53 (21)			9 (1)			0.0094
Peak LVEDVI (ml/m^2)		101 ± 39	89–114		134 ± 49	101–167	0.0233
Peak LVESVI (ml/m^2)		62 ± 32	52–72		95 ± 45	65–125	0.0081
Peak LVEF (%)		41 ± 10	38–44		31 ± 12	23–39	0.0095
Peak LVRFP	5 (2/39)			30 (3/10)			0.0201
Treatment data							
Metoprolol (mg/day)		93 ± 51	72–113		32 ± 15	20–44	0.0025
MED (mg/day)		103 ± 51	86–119		34 ± 15	22–45	0.0003
MED > 50 mg/day	90 (35/39)			33 (3/9)			0.0001

See Table 1 for abbreviations.

Table 5
Incremental value of DET vs. clinical model

	Sensitivity	95% CI	Specificity	95% CI
Model for transplant-free survival				
Clinical model (NYHA + MED)	0.55	0.51–0.59	0.43	0.34–0.52
Additional value of DET +	0.67	0.63–0.70	0.55	0.48–0.65
Model for improvement at follow-up				
Clinical model (LBBB + MED)	0.74	0.52–0.96	0.54	0.61–0.87
Additional value of DET +	0.76	0.58–0.90	0.54	0.59–0.89

depends on two factors: (1) the integrity of contractile fibres; and (2) the density of adrenoceptors, the blockade of which (if present) must be overrun. In fact, the effect of an adrenergic β_1 stimulation can be significantly decreased in the presence of a 'down-regulation' of adrenergic receptors [28]. In addition, the drug can improve myocardial performance by other mechanisms, such as a mild to moderate vasodilatation [27,29,30], a positive effect on diastolic function ('lusitropic' effect) [27,30–32] and a decrease in the severity of MR [33–35].

Dubois-Randé et al. [5], infusing intracoronary dobutamine in a small series of patients with IDCM, observed a significant increase of peak LV dP/dt in some patients, suggesting the presence of a 'contractile reserve'. More recently, other authors have confirmed this observation in IDCM using DET [3–7]. However, some of these studies were focused on the differential diagnosis with coronary artery disease [3,4].

The present study shows a spectrum of responses to the drug in patients with IDCM. In fact, an improve-

Table 6
Comparison between improved and non-improved patients

	Improved ($n = 21$)			Not improved ($n = 27$)			P
	% (n)	M ± S.D.	95% CI	% (n)	M ± S.D.	95% CI	
Clinical data							
Follow-up (months)		40 ± 7			28 ± 19		0.0049
LBBB	38 (8)			85 (23)			0.0004
Echocardiographic data							
LVEDVI (ml/m^2)		104 ± 35	88–120		133 ± 40	117–148	0.0121
LVESVI (ml/m^2)		77 ± 28	64–89		104 ± 34	90–117	0.0048
LVEF (%)		27 ± 6	25–30		23 ± 5	20–25	0.0065
FE < 25%	33 (7)			70 (19)			0.0099
Mildly dilated	52 (11)			22 (3)			0.0304
DET data							
DET +	62 (13)			33 (9)			0.0500
Peak LVEDVI (ml/m^2)		87 ± 31	73–101		122 ± 46	104–140	0.0048
Peak LVESVI (ml/m^2)		51 ± 25	40–63		82 ± 41	65–98	0.0047
Peak LVEF (%)		43 ± 10	39–48		36 ± 12	31–40	0.0221
Haemodynamic data							
RAP (mmHg)		3 ± 2	3–4		5 ± 3	4–6	0.0477
Mean PAP (mmHg)		17 ± 6	14–21		23 ± 9	19–26	0.0327
Mean PAWP (mmHg)		9 ± 5	7–12		14 ± 6	11–16	0.0213
Therapy data							
Metoprolol (mg/day)		110 ± 56	76–144		60 ± 42	40–80	0.0073
Carvedilol (mg/day)		70 ± 19	46–94		45 ± 19	21–69	0.0705
MED (mg/day)		121 ± 53	96–146		66 ± 42	48–84	0.0004
MED > 50 mg/day	100 (20)			64 (16)			0.0021
Digitalis	80 (17)			100 (27)			0.0145
Diuretics	50 (11)			85 (23)			0.0083

For abbreviations see Tables 1 and 2.

ment in LVEF and in diastolic function (disappearance of RFP, suggesting a decrease in filling pressure [21]) and a decrease in MR severity were observed in several patients (Table 2; Figs. 1–3). A positive response to DET, with a combined improvement in systolic and diastolic parameters (see Section 2), was observed in 43% of our cases.

Interestingly, patients who improved during DET were functionally less compromised (lower NYHA and HF score and longer exercise duration) and showed a significantly lower basal heart rate, in association with a less severe biventricular dilatation and systolic dysfunction and less frequent RFP (Table 1). These data are in accordance with those of Marmor et al. [36] in ischemic CMP and of Scrutinio et al. [7] in IDCM, who showed that a response to dobutamine correlated to a lower NYHA functional class, and to a higher MVO_2, respectively. A reduced response to adrenergic inotropic drugs in more severe cases may suggest a more pronounced 'down-regulation' of adrenergic myocardial receptors and/or more extensive myocardial damage [28,37].

4.2. Prognostic significance of DET in IDCM

A major objective of the present study was to assess the prognostic role of the response to DET in predicting survival and functional improvement in patients with IDCM and tailored medical treatment. In our study, DET response showed a stronger relationship to transplant-free survival than to functional improvement on tailored medical treatment. However, in both models the incremental predictive prognostic power of DET was quite low.

NYHA class and BB dosage were the two independent clinical parameters significantly related to transplant-free survival, but the power of the model was quite low (sensitivity, 0.55; specificity, 0.43) (Table 5). An incremental prognostic value of DET response with respect to the clinical model was significant only in terms of sensitivity, but without a clinically relevant improvement in prognostic power (sensitivity, 0.67; specificity, 0.55) (Table 5). The reasons for this observation are complex and probably related to neurohumoral factors, immune and inflammatory mechanisms involved in the progression of myocardial damage.

Considering the prediction of improvement at follow-up, the incremental value of DET was not significant, DET response frequently resulting in 'false positive' and 'false negative'. For 'false positive' DET responses (nine patients), progression of the myocardial disorder could play a determining role. For 'false negative' cases (eight patients), a β_1 'down-regulation' could have limited the agonistic effect of dobutamine on LV dysfunction [38]. The present study does not confirm the results of Naqvi et al. [6]. In that study, the improvement in LVEF at DET could predict the spontaneous improvement in LVEF during follow-up. Possible explanations for this apparent discrepancy are as follows: (a) differing patient selection criteria: in the Naqvi et al. study, only patients with a short history of heart disease were studied, whereas our patient population was an unselected series of cases of IDCM; (b) different treatment protocols: BBs were used in only a few patients in that previous study, while they were employed in the majority of our cases; and (c) longer duration of follow-up in our population (34 vs. 6 months), with higher possibility of subsequent progression of the disease in some patients with initial improvement.

Finally, the present study demonstrates the prognostic importance of treatment with an adequate dosage of BB. In fact, similar to the experience of Bristow et al. [39], the patients who tolerated higher doses of BB showed higher transplant-free survival and higher probability of improvement (Tables 3 and 6). However, contrary to that study [39], in our patients, the final dosage of BB was not randomly assigned, but was adjusted in each patient in order to obtain a maximal tolerated dosage without significant side effects [8]. Consequently, we cannot exclude the possibility of a selection of patients who could tolerate higher dosages of BB with a less advanced stage of the disease and a better prognosis.

4.3. Limitations of the study

This study has some possible limitations. The first concerns the relatively low number of patients and adverse events. In addition, the effects of dobutamine on the heart were assessed by echocardiographic and Doppler parameters that are non-invasive, but that cannot permit a direct analysis of haemodynamic determinants of systolic and diastolic ventricular function, contractility, preload, afterload, relaxation, stiffness and ventricular interdependence [29,30,36].

As shown in Table 1, the patients who responded favourably to DET were, on average, less functionally compromised. The earlier stage of the disease could probably have influenced the different outcome of these patients. DET response showed a significant incremental value in prognostic assessment with respect to clinical variables (Table 5).

4.4. Clinical implications

The results of this study have several implications that are clinically useful in the management of patients affected by IDCM.

The first consideration is that LV dysfunction is frequently reversible during inotropic stimulation in these patients. This 'contractile reserve' is probably

influenced by several factors, varying from patient to patient, such as the extent of sympathetic activation and 'down-regulation' of adrenergic receptors in the myocardium, and the anatomic substrate of the disease. In fact, it can be assumed that a severely fibrotic or atrophic myocardium is not responsive to inotropic stimulation, as in post-infarction ischemic heart disease.

The positive response of LV systolic function, diastolic parameters and severity of MR with dobutamine explains the favourable pharmacological action of the drug in clinical practice, at least for acute administration.

In addition, partially in accordance with the experience of others [5–7], the presence of contractile reserve in IDCM assessed by DET response is associated with a more favourable prognosis, presumably since it suggests a less advanced stage of the disease. However, the contribution of DET in the prognostic stratification of optimally treated IDCM patients does not appear to be very relevant in everyday clinical practice.

Further prospective studies should be carried out in order to clarify the prognostic value of DET in the setting of IDCM.

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