The additive prognostic value of restrictive pattern and dipyridamole-induced contractile reserve in idiopathic dilated cardiomyopathy

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Abstract

Background: Diastolic dysfunction and lack of contractile reserve are unfavorable prognostic predictors in patients with dilated cardiomyopathy (DCM).

Aims: This study aims to assess whether diastolic dysfunction and lack of dipyridamole-induced contractile reserve were additive predictors of poor outcome in patients with DCM.

Methods: A total of 116 patients with DCM and ejection fraction (EF<35%) were studied by dipyridamole echo (0.84 mg/kg over 10 min). At rest, a restrictive filling pattern was defined as: E/A ratio >2 and an E-wave deceleration time of <140 ms on transmitral flow velocity profile.

Results: Rest wall motion score index (WMSI) was 2.2 ± 0.3 and decreased to 1.9 ± 0.41 after dipyridamole ($p<0.001$). During follow-up (median 26.5 months), 22 cardiac deaths occurred. At multivariate analysis, dipyridamole-induced contractile reserve yielded significant incremental prognostic value (RR=0.275, $p<0.006$) over NYHA class (RR=1.971, $p<0.03$), angiotensin-converting enzyme inhibitor therapy (RR=0.173, $p<0.001$), and left ventricular end-diastolic diameter (RR=1.131, $p<0.001$). The worst prognostic combination was the presence of restrictive pattern at rest and the absence of contractile reserve (ΔWMSI<0.15).

Conclusion: In patients with DCM, the ominous combination of restrictive transmitral flow pattern and lack of contractile reserve during dipyridamole stress predicts an unfavourable outcome.

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Keywords: Dipyridamole echocardiography; Idiopathic dilated cardiomyopathy; Prognosis; Restrictive pattern

1. Introduction

Idiopathic dilated cardiomyopathy (DCM) is a primary myocardial disease of unknown origin, characterized by a poorly contracting and dilated left ventricle [1]. Yet, indices of global systolic dysfunction as measured at rest are inadequate for depicting the severity of the disease and are poorly correlated with symptoms, exercise capacity, and prognosis [2]. In contrast, the assessment of contractile reserve by pharmacological challenge, rather than baseline indices, might be an important means for quantifying the degree of cardiac impairment and for refining prognostic prediction [3]. Indeed, the extent of inotropic response to high-dose dobutamine stress echocardiography identifies DCM patients with a better outcome [4,5]. On occasion, the efficacy of dobutamine stress echo may be limited by submaximal testing for limiting arrhythmias especially frequent in dilated, poorly functioning left ventricles [4–

7]. In these patients, the use of an alternative inotropic stress can be helpful. Dipyridamole may offer a suitable alternative to dobutamine stress, since it is less arrhythmogenic [8,9], better tolerated [10], and equally effective as dobutamine for prognostic stratification in patients with coronary artery disease (CAD) [11]. The aims of this study were to assess whether diastolic dysfunction evaluated in basal conditions and the lack of contractile reserve during dipyridamole stress echocardiography were additive predictors of poor outcome in patients with DCM. Therefore, we studied 116 patients with DCM who were followed up for a median of 26.5 months in a prospective, multicenter, observational study design.

2. Methods

2.1. Patients selection

From February 1, 1997 to February 1, 2003, 149 patients (99 males, mean age 58 ± 12 years) were prospectively enrolled by four different centers: Pisa CNR ($n=48$), Belgrade ($n=48$), Cesena ($n=27$), and Mestre ($n=26$). The study population consisted of patients with DCM diagnosed according to World Health Organization criteria [12] presenting with: (1) a global severe left ventricular dysfunction [ejection fraction (EF)<35% by biplane area length method on resting echocardiogram] but no history of ischemic heart disease and with angiographically normal coronary arteries (coronary angiography performed any time in the 5 years prior to study enrollment); and (2) transthoracic echocardiogram adequate for assessing resting regional wall function (the echocardiogram was considered adequate if >13 of the maximum 16 segments were visualized in at least one projection). Exclusion criteria were: a technically poor acoustic window, hemodynamic instability, significant comorbidity reducing life expectancy to <1 year, and unwillingness to give informed consent. Upon entering the study, clinical, resting, and stress echocardiography data of patients were collected on the case report forms by the accredited cardiologist–echocardiographer of each center. All patients gave their written consent before performing the test. The study was approved by the Ethic Committee of our institute. Stress echo data were collected and analyzed by stress echocardiographers who were not involved in patient care.

2.2. Resting and stress echocardiography

After a rest electrocardiogram (ECG) was recorded and intravenous access was secured, all patients at study entry underwent, in the same session, resting echo and stress echo during high-dose dipyridamole infusion (0.84 mg/kg over 10 min). Left ventricular end-diastolic and end-systolic diameters were measured from the M-mode trace obtained from parasternal long axis view. Left ventricular volumes

and EF were assessed by two-dimensional two- and four-chamber views by biplane area–length method. All measurements were obtained following the recommendations of the American Society of Echocardiography [13]. Using the pulsed wave Doppler technique from the apical four-chamber view, the inflow over the mitral valve was obtained, with the sample volume placed at the level of the tips of the mitral leaflets. The E- and A-wave velocities, the E/A ratio, and the E-wave deceleration time were calculated from the last three consecutive cardiac cycles and from the last five consecutive cardiac cycles in case of atrial fibrillation. A restrictive filling pattern was defined as the presence of E/A ratio >2 and an E-wave deceleration time of <140 ms [14]. Two-dimensional echocardiography and 12-lead electrocardiography monitoring were performed in combination with high-dose dipyridamole infusion: 0.56 mg/kg during 4 min, no dose for 4 min, and then 0.28 mg/kg during 2 min. The cumulative dose was therefore 0.84 mg/kg during 10 min [15]. During the procedure, blood pressure and ECG were recorded each minute and aminophylline (up to 240 mg over 3 min) was given at the end of the test. Echocardiography monitoring was performed throughout the dipyridamole infusion and up to at least 5 min after the end of the infusion. Two-dimensional echocardiography images were recorded at baseline and at the end of each dipyridamole dose. The dipyridamole test was considered maximal when the dose of 0.84 mg/kg was reached. In the presence of non-diagnostic endpoints, the test was terminated for limiting side effects and the test was considered submaximal. Nondiagnostic end-points were: intolerable symptoms; limiting asymptomatic side effects: (a) hypotension (relative or absolute) >30 mm Hg fall of blood pressure; (b) supraventricular arrhythmias: supraventricular tachycardia or atrial fibrillation; (c) ventricular arrhythmias: ventricular tachycardia; frequent, polymorphic premature ventricular beats. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography, using a 16-segment model of the left ventricle [16]. In all studies, segmental wall motion was semiquantitatively graded as follows: 1=normal; 2=markedly hypokinetic, marked reduction of endocardial motion and thickening; 3=akinetic, virtual absence of inward motion and thickening; and 4=dyskinetic, paradoxical wall motion away from the centre of the left ventricle in systole. It was agreed a priori to ignore "mild" or "questionable" hypokinesia, which was graded as normal. A wall motion score index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments. A segment was considered to have contractile reserve when improved by one grade or more at peak stress (for instance, a hypokinetic segment becoming normal, or an akinetic segment becoming hypokinetic). In order to quantify the amount of myocardium showing a contractile reserve elicited by high-dose dipyridamole, contractile reserve was assessed also according to a continuous

parameter defined as ΔWMSI, which expresses the difference between rest WMSI and peak dose WMSI. This parameter provides information, not only on the presence of, but also on the extent of contractile reserve of dysfunctional myocardium [17]. Quality control of stress echo performance and reading in enrolled centers has been previously described in depth [18]. Briefly, readers from each recruiting center were selected to meet the predefined criteria for stress echo reading. Then the center started recruiting patients and the reading of the stress echo from the recruiting center was directly entered into the data bank.

2.3. Follow-up data

Follow-up data were obtained in all patients by inclusion criteria. Cardiac mortality was the primary end-point; hospital and physician records and death certificates were

Table 1
Baseline characteristics of study patients

	All patients (n=116)	DET+ (n=71)	DET− (n=45)	p
Clinical data				
Gender (% males)	79 (68.1)	48 (67.6)	31 (68.9)	NS
Age (years)	59±12	59.3±11	59.5±13	NS
Disease duration (months)	42±47	35±38	52±58	0.05
NYHA	2.46±.6	2.35±0.6	2.62±0.7	0.03
Therapy				
Diuretics	107 (92.2%)	63 (88.7%)	44 (97.8%)	NS
ACE inhibitors	104 (89.7%)	62 (87.3%)	42 (83.9%)	NS
Digoxin	72 (62.1%)	42 (59.2%)	30 (66.7%)	NS
Beta blockers	53 (45.7%)	28 (39.4%)	25 (55.6%)	NS
Echocardiographic data				
LVEDD (mm)	68.5±7.4	67.8±7.2	69.8±1.13	NS
LVESD (mm)	54.9±9	53.7±8.5	56.8±9.5	NS
LVEDV (ml)	196.5±81	192±87.4	203±71	NS
LVESV (ml)	140.8±59	135.5±64	149±50.5	NS
LVEF (%)	27.4±6.8	28.6±6.6	25.6±6.8	0.02
WMSI	2.2±.29	2.2±.27	2.3±.3	NS
E-wave velocity (cm/s)	62.5±23.9	60±23	66±24	NS
A-wave velocity (cm/s)	62.4±27.1	65±26	57±27	NS
E/A ratio	1.3±1.04	1.1±09	1.5±1.2	NS
E deceleration time (ms)	173.3±61.8	176±60	169±64	NS
Restrictive filling pattern	37 (31.9%)	21 (29.6%)	16 (35.6%)	NS

DET=dipyridamole stress echocardiography; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; LVEF=left ventricular ejection fraction; WMSI=wall motion score index.

Table 2
Univariate predictors of total and cardiac mortality

	Cardiac mortality		Total mortality	
	p	RR (95% CI)	p	RR (95% CI)
Resting LVEDD (mm)	<0.001	1.140 (1.079–1.203)	<0.001	1.114 (1.062–1.170)
Resting LVESD (mm)	<0.001	1.116 (1.064–1.171)	<0.001	1.091 (1.046–1.138)
Resting LVEF (%)	<0.001	0.886 (0.834–0.941)	0.001	0.910 (0.863–0.960)
E/A ratio	<0.001	1.58 (1.222–2.041)	0.008	1.421 (1.098–1.839)
Dip EF (%)	<0.001	0.9 (0.858–0.945)	0.001	0.929 (0.891–0.969)
Dip WMSI	<0.001	10.01 (3.12–32.1)	0.002	4.650 (1.737–12.452)
ACE inhibitor	0.001	0.196 (0.082–0.470)	0.002	0.265 (0.116–0.608)
Resting WMSI	0.001	22.01 (3.5–138.1)	0.001	14.179 (2.866–70.132)
ΔWMSI 0.15	0.01	0.356 (0.152–0.833)	0.04	0.457 (0.273–0.98)
ΔWMSI	0.01	0.06 (0.07–0.520)	0.2	0.352 (0.74–1.688)
DTE (ms)	0.01	0.988 (0.979–0.997)	0.04	0.992 (0.984–1.00)
Restrictive pattern	0.01	2.83 (1.201–6.668)	0.06	2.023 (0.946–4.325)
NYHA class	0.02	2.037 (1.117–3.712)	0.01	2.027 (1.173–3.501)

LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter; LVEF=left ventricular ejection fraction; WMSI=wall motion score index; DTE=E wave deceleration time.

used to ascertain the cause of death, which was attributed to a cardiac aetiology if a cardiac illness provoked the final presentation, or if death was sudden and unexpected.

2.4. Statistical analysis

The results are expressed as mean±S.D. The individual effect of certain variables on event-free survival was evaluated with the use of Cox regression model (SPSS, Chicago, IL). The analysis was performed according to unmodified forward selection stepwise procedure. In this case, the variables were entered in the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relationship to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (dependent variable); but in this case, the probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the

Table 3
Stepwise predictors of cardiac death

Variables	RR	95% CI	p
NYHA class	1.971	1.039–3.740	0.03
ACE inhibitors	0.173	0.068–0.444	<0.001
LVEDD (mm)	1.131	1.067–1.199	<0.001
ΔWMSI 0.15	0.275	0.109–0.691	0.006

LVEDD=left ventricular end-diastolic diameter; WMSI=wall motion score index.

prediction of the whole model. Variables selected for examination were: age, gender, NYHA class, therapy with ACE inhibitors, β-blockers, digoxin, diuretics, oral anticoagulants, hypertension, diabetes mellitus, alcohol habit, end-diastolic and end-systolic left ventricular diameters, end-diastolic and end-systolic left ventricular volumes, EF, WMSI at rest and at the peak of stress, rest–high-dose stress wall motion index variation (delta high-dose dipyridamole WMSI), EF at the peak of stress and high-dose–rest EF variation and diastolic function at rest: E- and A-wave velocity, E/A ratio, E-wave deceleration time. Continuous variables were compared by unpaired two-sample t test. Proportions were compared by chi-square statistics; a Fischer's exact test was used when appropriate. Kaplan–Meier life table estimates of spontaneously occurring event-free survival were used to summarize the follow-up experience in these patients and to clarify presentation. Differences of these patients

were tested with the log-rank statistic. Receiver-operating characteristics analysis was used to determine the optimal cutoff value for the prediction of cardiac death with respect to the variation of WMSI and the number of segments that showed a transient improvement during test. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity. A P value below 0.05 was considered to be statistically significant.

3. Results

3.1. Feasibility and tolerability of dipyridamole stress echocardiography

No patients had major complications during the test. Only one patient experienced hypotension after low-dose dipyridamole, which was reverted by aminophylline infusion. The test result of this particular patient was included into the analysis with echocardiographic data obtained at peak submaximal test.

3.2. Study population

Out of 149 patients, six were lost to follow-up and, in 27 diastolic parameters, were not available due to atrial fibrillation with mitral inflow deceleration time greater than 140 ms or atrial arrhythmia or E–A fusion. One hundred sixteen patients were enrolled. Patient character-
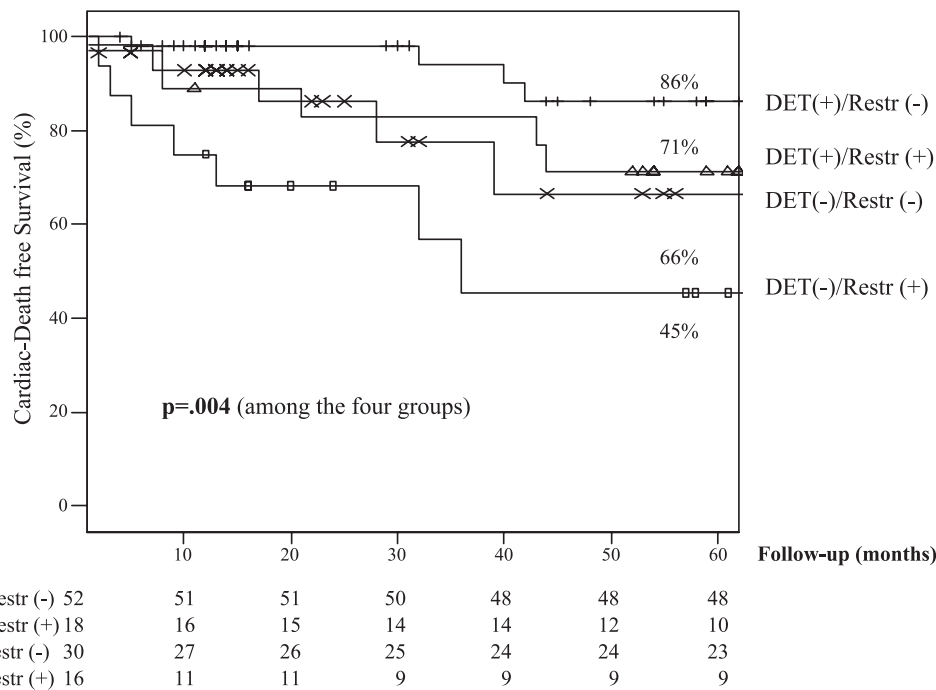

Fig. 1. Kaplan–Meier survival curves (considering cardiac death as an end-point). The presence of little or no contractile response after dipyridamole infusion (DET⁻), here identified as ΔWMSI less than 0.15, and restrictive pattern at rest (Restr⁺) showed a significantly worst outcome than those with contractile response (DET⁺) and absence of restrictive pattern (Restr⁻).

istics are summarized in Table 1. The majority was in functional NYHA class II (58.6%). However, severe left ventricular dysfunction was common (EF<25% in 37 patients: 31.9%).

3.3. Rest and dipyridamole echocardiographic findings

In the 116 study patients with interpretable baseline and stress echo tracings and with follow-up information, during dipyridamole stress infusion, heart rate increased from 75 ± 14 to 90 ± 16 beats/min ($p<0.001$), systolic blood pressure decreased from 123 ± 20 to 118 ± 20 mm Hg ($p=0.002$), and diastolic blood pressure decreased from 72 ± 12 to 68 ± 12 mm Hg ($p<0.001$). At baseline, end-diastolic diameter was 68.5 ± 7.4 mm, end-systolic diameter was 55 ± 9 mm, EF was $27.4\pm6.8\%$, and WMSI was 2.2 ± 0.29. On the basis of Doppler transmitral flow patterns, there were 37 patients in the restrictive group and 79 in the nonrestrictive group. At the peak of stress, the EF was $33.6\pm10\%$ ($p<0.001$ vs. rest EF) and WMSI was $1.94\pm.41$ ($p<0.001$ vs. rest WMSI). Overall, 71 patients (61.2%) were considered responders (ΔWMSI$\geq$0.15), while the other 45 (38.7%) were classified as nonresponders (ΔWMSI<0.15). The comparison of the baseline clinical echocardiographic data between the two groups of patients is shown in Table 1. Responders showed lower NYHA class ($p=0.03$) and less severe left ventricular dysfunction ($p=0.02$).

3.4. Follow-up data: cardiac death

One hundred sixteen patients were followed up for a median of 26.5 months. Total mortality was 23% (27
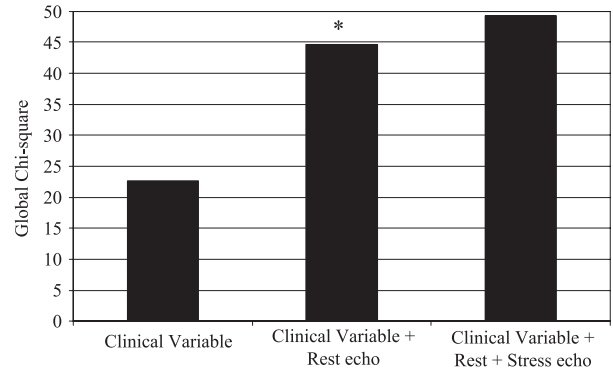

Fig. 3. Bar graph showing global chi-square of significant predictor modelling of cardiac mortality according to an interactive procedure. In the model, stress echocardiographic parameters added non-significant information to clinical variables and rest echocardiographic parameters of systolic and diastolic function. *Significance lower than 0.05.

patients), of which 22 deaths were considered as cardiac deaths (18.9%). Univariate predictors of cardiac death and total mortality are reported in Table 2. Using Cox' proportional hazard model, the NYHA class, therapy with ACE inhibitors, end-diastolic left ventricle diameter, and the presence of contractile reserve were independent predictors of cardiac death (Table 3). Cumulative survival rates considering cardiac death and total mortality, in patients with and without preserved contractile response to dipyridamole infusion and with or without restrictive pattern, are shown in Figs. 1 and 2, respectively. When clinically realistic, sequential models for prediction of cardiac mortality were used, stress echocardiography showed incremental albeit non-significant value vs. clinical evaluation, and resting left ventricular systolic and diastolic

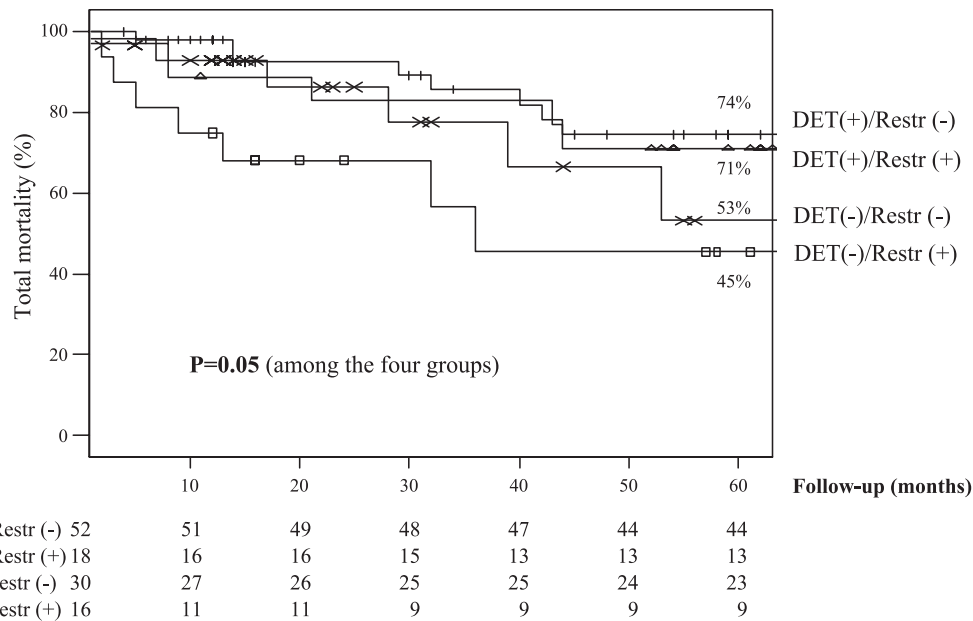|		10	20	30	40	50	60
DET(+)/Restr (-)	52	51	49	48	47	44	44
DET(+)/Restr (+)	18	16	16	15	13	13	13
DET(-)/Restr (-)	30	27	26	25	25	24	23
DET(-)/Restr (+)	16	11	11	9	9	9	9

Fig. 2. Kaplan–Meier survival curves (considering total mortality as an end-point). The presence of little or no contractile response after dipyridamole infusion (DET⁻), here identified as ΔWMSI less than 0.15, and restrictive pattern at rest (Restr⁺) showed a significantly worst outcome than those with inotropic response (DET⁺) and absence of restrictive pattern (Restr⁻).
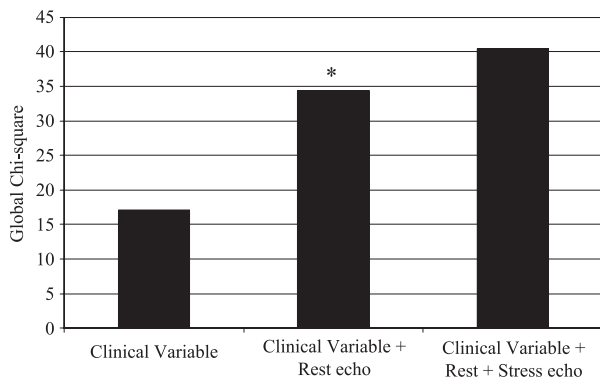
Fig. 4. Bar graph showing global chi-square of significant predictor modelling of total mortality according to an interactive procedure. In the model, stress echocardiographic parameters added non-significant information to clinical variables and rest echocardiographic parameters of systolic and diastolic function. *Significance lower than 0.05.

echocardiographic data (Fig. 3). The same was found for total mortality (Fig. 4).

4. Discussion

High-dose dipyridamole stress echocardiography is safe and well tolerated in patients with DCM. Contractile reserve following dipyridamole and the absence of restrictive pattern on transmitral flow velocity are associated with a better survival in DCM patients. The higher the improvement of function after dipyridamole, expressed by ΔWMSI, the better the impact of inotropic response on survival.

4.1. Comparison with previous studies

Our results suggest that a contractile reserve induced by high-dose dipyridamole stress echo has an impact on survival of patients with DCM. These data are consistent with the study by Sicari et al. [18] with dipyridamole stress echo in patients with ischemic cardiomyopathy. In the study by Sicari et al. [18], the beneficial effect of myocardial viability was observed during low-dose dipyridamole (0.28 mg/kg over 4′)—a dose virtually without ischemic potential—chosen in that study to evaluate selectively inotropic response in patients vulnerable to ischemia with the standard high dose. Furthermore, the beneficial prognostic value of dipyridamole-induced inotropic response was observed by Sicari et al. only in revascularized patients, whereas no beneficial effect was observed in medically treated patients. The best cutoff value for prognostic stratification was 0.20 increase in WMSI—distinctly different from 0.40 observed by the same author with dobutamine stress in a similar cohort of ischemic patients with ischemic cardiomyopathy [19]. Our study is certainly methodologically and conceptually germane to that of Sicari et al. but with some important differences. Firstly, the patients

involved in our study are with nonischemic DC. Literature widely reports on the prognostic value of myocardial viability, assessed with different techniques in ischemic cardiomyopathy [20,21], but there is only very limited information on viability with DCM, which accounts for 25% of all heart failure patients [4,22–24]. Secondly, in our patients with normal coronary arteries (by selection), we decided to use high-dose (0.84 mg/kg) dipyridamole stress because there is no ischemic vulnerability. Moreover, in these patients with chronically elevated plasma adenosine levels, a higher dipyridamole dose allows achieving a significant rise in plasma endogenous adenosine [25], and this dose amplifies the inotropic response observed with standard dose. Thirdly, our results showed a beneficial protective effect of dipyridamole-induced response in medically treated patients, in striking contrast with the results obtained by Sicari et al. [18] in ischemic cardiomyopathy. Although this disease is mainly characterized by systolic dysfunction, abnormalities in diastolic function were also reported. The importance of the assessment of diastolic function in DCM patients has been demonstrated in previous works where the restrictive pattern resulted in a useful noninvasive sign of increased left ventricular stiffness and a powerful independent adverse prognostic factor [14,26–29]. To our knowledge, this is the first work that has demonstrated that a combined assessment of diastolic function in basal condition and contractile reserve, which are additive predictors of poor outcome in patients with DCM.

4.2. Pathophysiological mechanisms

Three separate, nonmutually exclusive mechanisms may explain the capability of dipyridamole infusion to recruit a contractile reserve in segments with resting dysfunction: a hemodynamic, a neurohormonal, and a direct cardioprotective effect.

Dipyridamole is responsible for an increase in regional coronary flow mirrored by an increase in function through the so-called garden hose or Gregg phenomenon. Although this phenomenon has been experimentally [30] and clinically [31] described in patients with CAD, it may well come into play also in nonischemic DCM.

Endogenous adenosine accumulation may induce a direct sympathoexcitatory effect through stimulation of adrenergic chemoreceptors [32]. In this way, dipyridamole acts, at least in part, as a "mini-dobutamine" stress, raising the systemic plasma catecholamine concentration independently from the systemic hemodynamic effect [33].

Last, and probably not the least, dipyridamole might exert a direct cardioprotective effect through a calcium antagonist and anti-inflammatory effect of endogenous adenosine [34] and through a direct, strong, and adenosine-independent antioxidant effect of dipyridamole per se [35–37].

4.3. Study limitations

Our study had several limitations. First, central laboratory examination of stress echocardiograms was not available; therefore, interinstitutional variability in interpretation affects the results. However, interobserver agreement is substantially higher when explicit reading criteria, similar to those adopted in the current study, are used [38]. In addition, each interpreting cardiologist met quality control criteria before entering the study. Another limitation is that no clinical chemistry values were included in the analysis, including plasma BNP levels [39]. However, the value of these indices was much less clear at the time of the study onset than it is today. Finally, diastole is a complex phenomenon that is difficult to analyze from any single variable. There is no doubt that evaluation of pulmonary venous Doppler curves gives additional information on left ventricular diastolic pressure [40]. However, for the sake of simplicity and feasibility, systematic analysis of these curves was not performed in this study.

4.4. Clinical implications

DCM patients with preserved contractile reserve following dipyridamole infusion are at substantially lower risk of mortality when compared to patients without contractile reserve. Therefore, dipyridamole stress echo can be used for risk stratification in these patients whenever dobutamine stress echo is contraindicated, or difficult to interpret, or submaximal for limiting side effects [4]. As a further (at least theoretical) advantage, the inotropic response to dipyridamole is less affected by concomitant β-blocker therapy, since the adenosine inotropic action is independent of β-adrenergic receptors and, at least in ischemic patients, it was shown to be relatively insensitive to chronic β-blockade [41]. However, this issue can be fully addressed only through future studies comparing these two methods in the same population. The prognostic evaluation of the patient with DCM is multifaceted and should be addressed via the complex puzzle of clinical, systolic, and diastolic echocardiographic parameters, and contractile reserve, in order to identify those patients at higher risk of death in whom a more aggressive approach is needed.

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