The Prognostic Impact of the Evolution of RV Function in Idiopathic DCM

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ABSTRACT

OBJECTIVES In this study, the authors analyzed the prognostic role of right ventricular systolic function (RVF) longitudinal trends in a large cohort of patients affected by dilated cardiomyopathy (DCM).

BACKGROUND RVF is a known prognostic predictor in DCM; however, whether RVF changes over time to better predict the long-term disease progression has not been investigated.

METHODS From 1993 to 2008, we analyzed 512 patients with DCM (46 years of age [36 to 55 years of age], left ventricular ejection fraction 32% [25% to 41%]) with a potential follow-up of ≥72 months and available data at baseline and at least 1 pre-specified follow-up evaluation (i.e., 6, 24, 48, or 72 months). RV dysfunction was defined as RV fractional area change <35% at 2-dimensional echocardiography. The primary outcome measure was a composite of death or heart transplantation.

RESULTS At enrollment, 103 (20%) patients had RV dysfunction. During follow-up, 89 of them (86%, 17% of the overall cohort) normalized RVF at a median time of 6 months, whereas 38 of the remaining 409 patients with normal baseline RVF (9%; 7% of the overall population) exhibited a new-onset RV dysfunction (median time: 36 months). RVF normalization was significantly associated with subsequent left ventricular reverse remodeling that was observed at a median time of 24 months (odds ratio: 2.49; 95% confidence interval [CI]: 1.17 to 5.3; $p = 0.018$). At baseline multivariate analysis, RV dysfunction was independently associated with the primary outcome measure (hazard ratio: 1.71; 95% CI: 1.02 to 2.85; $p = 0.0413$). At time-dependent model, RVF revaluation over time maintained an independent predictive value (hazard ratio: 2.83; 95% CI: 1.57 to 5.11; $p = 0.0006$).

CONCLUSIONS Patients with DCM frequently present RV dysfunction at first evaluation. However, a complete RVF recovery is largely observed early after optimization of medical therapy and predates subsequent left ventricular reverse remodeling. Systematic revaluation of patients including RVF throughout regular follow-up conferred additive long-term prognostic value to the baseline evaluation. (J Am Coll Cardiol Img 2016;9:1034–42) © 2016 by the American College of Cardiology Foundation.

Dilated cardiomyopathy (DCM) is a primary heart muscle disease classically characterized by left ventricular (LV) systolic dysfunction and dilation (1). In the past several decades, the long-term prognosis of DCM has improved impressively, mainly through the effectiveness of treatments on left ventricular reverse remodeling (LVRR) (2). Indeed, LVRR has emerged as an important prognostic predictor in DCM, highlighting the importance of the systematic revaluation of patients during follow-up (3,4). Nevertheless, the prognostic stratification of DCM in clinical practice still remains

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particularly difficult. Recent data suggest that right ventricular systolic function (RVF) is crucial in prognostic assessment of patients with DCM. RV dysfunction, assessed by cardiac magnetic resonance scans, was found in a sizable number of patients with DCM and showed an incremental prognostic value in addition to that of LV evaluation (5). However, these data are limited to highly selected populations. To date, there are no data on the long-term natural history of RVF in patients with DCM undergoing optimal treatment or, similarly, on the prognostic significance of RVF revaluation during follow-up.

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Therefore, the aims of the current study were to analyze the long-term evolution of RVF and to assess the prognostic impact of regular RVF revaluation over time in a large population of patients with DCM.

METHODS

STUDY POPULATION AND DESIGN. We retrospectively analyzed all 657 patients with DCM who were enrolled consecutively in the Trieste Heart Muscle Disease Registry between 1993 and 2008 (2). Patients who underwent extensive clinical and laboratory evaluation at baseline (including invasive tests, when indicated) and with at least 1 available evaluation at any of the pre-specified follow-up times (i.e., 6, 24, 48, 72 months) were considered for the present analysis. Follow-up ended on December 31, 2014, or at the time of death/heart transplantation (D/HT); thus, each patient had a potential minimum follow-up period of at least 72 months.

The institutional ethics board approved the study and informed consent was obtained under the institutional review board policies of the hospital administration.

The diagnosis of DCM was determined according to the World Health Organization criteria (1,6). Enrolled patients presented a left ventricular ejection fraction (LVEF) <50% in the absence of a possible known cause. Ischemic etiology was ruled out by coronary angiography, which was performed systematically in patients ≥35 years, with cardiovascular risk factors and/or without a familial history of DCM. Patients with significant coronary artery disease (stenosis >50% of a major coronary artery), history of severe systemic hypertension (>160/100 mm Hg), biopsy-proven active myocarditis, alcohol intake >100 g/day, significant organic valve diseases, tachycardia-induced cardiomyopathy, congenital heart diseases, and advanced systemic diseases affecting short-term prognosis were excluded (2). The patients' familial histories were strictly investigated and all familial DCM cases fulfilled the published criteria (7).

After enrollment, if not contraindicated, all patients received angiotensin-converting enzyme inhibitors/angiotensin receptor-blockers and beta-blockers titrated to the highest tolerated dose. An implantable cardioverter-defibrillator was implanted for primary prevention in patients with DCM who were considered at high risk of sudden cardiac death (i.e., persistent LVEF ≤35% and New York Heart Association [NYHA] functional class II to III on chronic, optimal medical treatment) (8). Cardiac resynchronization therapy in our center started in 2005 in patients with conventional indications (persistent LVEF ≤35%, left bundle branch block, and NYHA functional class ≥2) under optimal medical treatment, according to the available evidence (8).

The primary study endpoint was a composite of D/HT. Furthermore, we considered as secondary outcome measures pump failure death or HT

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DCM = dilated cardiomyopathy

D/HT = death/heart transplantation

ICC = intraclass correlation

IQR = interquartile range

LV = left ventricular

LVEF = left ventricular ejection fraction

LVRR = left ventricular reverse remodeling

NYHA = New York Heart Association

RV = right ventricular

RVF = right ventricular systolic function

RV-FAC = right ventricular-fractional area change

TABLE 1 Baseline Characteristics of the Entire Study Population and on the Base of Baseline RV Function

	Study Population (n = 512, 100%)	No Baseline RV Dysfunction (n = 409, 80%)	Baseline RV Dysfunction (n = 103, 20%)	p Value
Age, yrs	46 (36, 56)	46 (36, 56)	45 (31, 56)	0.27
Male	352 (69)	272 (67)	80 (78)	**0.03**
Family history of DCM	113 (23)	88 (22)	25 (25)	0.59
HF duration, months	1 (0, 7)	1 (0, 7)	1 (0, 6)	0.75
NYHA functional class III-IV	123 (24)	68 (17)	55 (54)	**<0.001**
Systolic blood pressure, mm Hg	120 (115, 140)	125 (115, 140)	120 (110, 135)	**0.015**
AF	49 (10)	34 (9)	15 (15)	0.06
LBBB	158 (32)	135 (34)	23 (23)	**0.03**
iLAD, mm/m^2	21 (18, 24)	20 (18, 23)	23 (19, 26)	**0.001**
iLVEDD, mm/m^2	34 (31, 38)	34 (31, 38)	35 (32, 39)	0.55
iLVEDV, ml/m^2	88 (69, 116)	87 (69, 114)	96 (73, 120)	0.20
LVEF, %	32 (25, 40)	33 (26, 41)	27 (21, 37)	**0.003**
RVEDA, cm^2	19 (15, 23)	17 (14, 21)	24 (20, 28)	**<0.001**
RV-FAC %	47 (32, 56)	52 (43, 59)	26 (20, 30)	**<0.001**
Moderate-severe MR	167 (35)	133 (35)	34 (34)	0.98
RFP	83 (16)	51 (16)	32 (42)	**<0.001**
sPAP, mm Hg	32 (23, 45)	27 (20, 33)	42 (32, 52)	**<0.001**
ACEi/ARBs	479 (95)	379 (94)	100 (98)	0.10
β-blockers	422 (84)	336 (83)	86 (84)	0.82
Amiodarone	165 (33)	125 (31)	40 (39)	0.12
MRAs	82 (16)	46 (11)	36 (35)	**<0.001**

Values are median (first, third quartiles) or n (%). **Bold** indicates significant differences.

ACEi = angiotensin-converting enzyme inhibitors; AF = atrial fibrillation; ARB = angiotensin receptor blockers; DCM = dilated cardiomyopathy; HF = heart failure; iLAD = indexed left atrial diameter; iLVEDD = indexed left ventricular end-diastolic diameter; iLVEDV = indexed left ventricular end-diastolic volume; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RFP = restrictive filling pattern; RV = right ventricular; RV-FAC = right ventricular-fractional area change; sPAP = systolic pulmonary arterial pressure.

compared with a composite of sudden cardiac death and malignant ventricular arrhythmias (i.e., aborted sudden cardiac death, ventricular fibrillation/flutter, sustained ventricular tachycardia, or appropriate implantable defibrillator shocks) in a competing risks analysis.

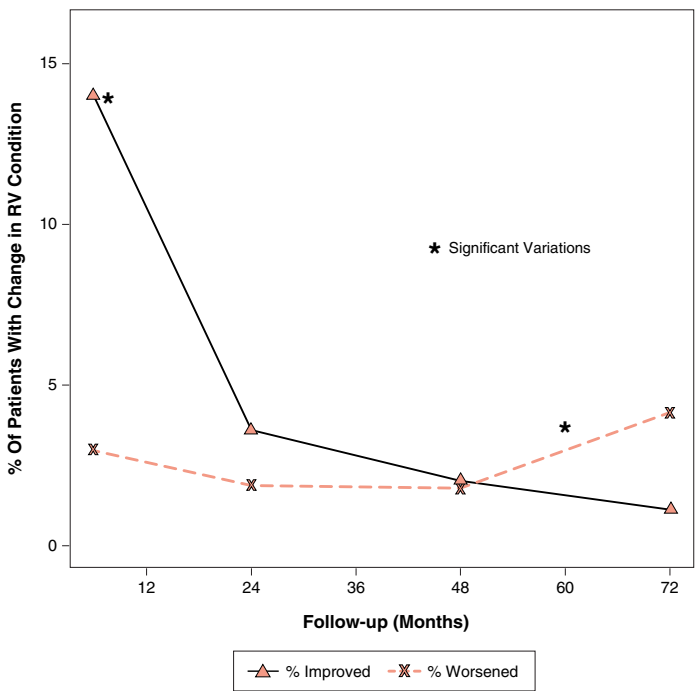
ECHOCARDIOGRAPHIC ANALYSIS. For this specific study, all echocardiographic examinations performed at baseline and at the pre-specified follow-up intervals were reviewed by a level 3-trained echocardiographer with specific expertise in cardiomyopathy imaging. The image analysis was conducted according to current international guidelines (9,10).

RV dysfunction was defined in accordance with current recommendations by a right ventricular fractional area change (RV-FAC) ([end-diastolic area − end-systolic area]/end-diastolic area ×100) <35% (9). LV volumes and LVEF were assessed using Simpson biplane method. LV measurements were indexed according to patients' body surface areas. LVRR was defined by an increase in LVEF ≥10 points (or a follow-up LVEF ≥50% in patients with a baseline LVEF between 45% and 49%), associated with a reduction in indexed LV end-diastolic diameter ≥10% or a follow-up indexed LV end-diastolic diameter ≤33 mm/m^2 (3). LV filling pattern was classified as restrictive in presence of E-wave deceleration time <120 ms or E/A ≥2 associated with E-wave deceleration time ≤150 ms (11). Systolic pulmonary artery pressure was estimated from the maximal continuous-wave Doppler velocity of the tricuspid regurgitation jet using a systolic transtricuspidal pressure gradient calculated by the modified Bernoulli equation and the addition of estimated right atrial pressure (12). Functional mitral regurgitation was assessed using a multiparametric approach by measuring the regurgitant jet area and vena contracta width at color-flow Doppler and, if feasible, by measuring the effective regurgitant orifice area by the proximal isovelocity surface area method (13).

All measurements were obtained from the mean of 3 beats (patients in sinus rhythm) or 5 beats (atrial fibrillation).

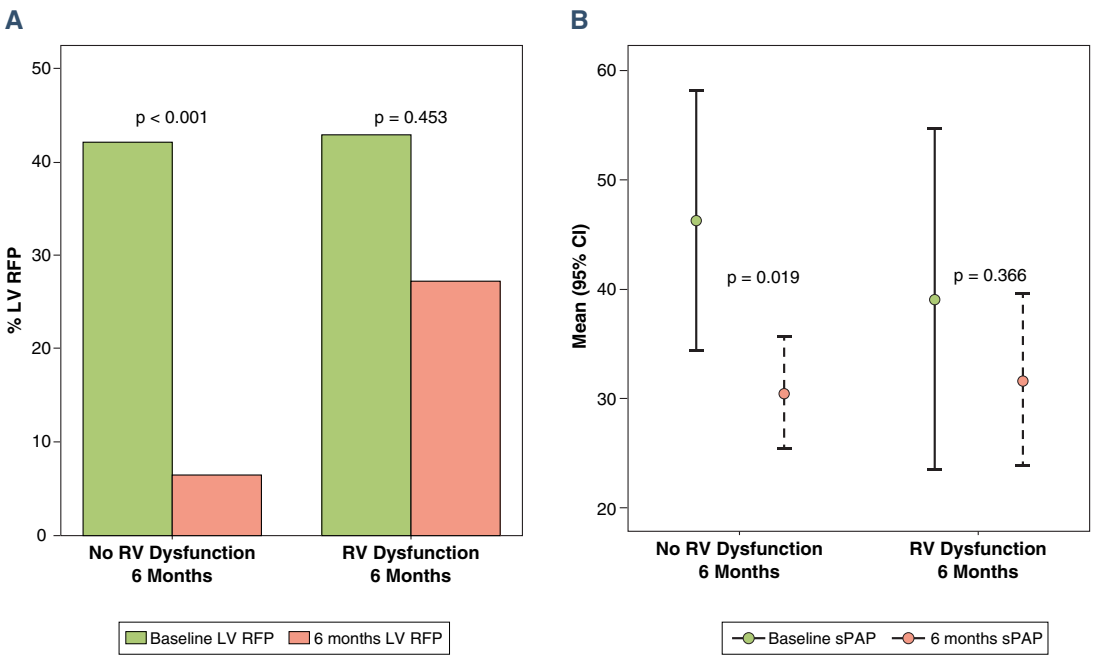
STATISTICAL ANALYSIS. Summary statistics of clinical and laboratory variables at enrollment were expressed as mean and SD, median and interquartile ranges (IQR), or as counts and percentage, as appropriate. Cross-sectional comparisons between groups were made by the analysis of variance test on continuous variables, using the Brown-Forsythe statistic when the assumption of equal variances did not hold, or the nonparametric median test when necessary. Chi-square or Fisher exact tests were calculated for discrete variables. Repeated measures between baseline and follow-up visits were evaluated by means of the paired Student *t* test for continuous Gaussian distributed parameters or the Wilcoxon test, as appropriate. For binary variables, the McNemar test was calculated. Moreover, mixed-effects generalized linear models were estimated to globally evaluate the time effect on RV dysfunction, RV improvement/worsening, and LVEF/LVRR trends (14). Logistic regression was used to investigate whether early RV improvement was associated with subsequent LVRR. Multivariable Cox regression was applied to evaluate predictors of the primary study endpoint, evaluated at baseline and with time-dependent covariates: a full-model strategy was applied by including in the multivariable model all relevant clinical and instrumental parameters. To assess the extent to which the time-dependent analysis leads to a better prediction when compared with the baseline model, patients' data rows were duplicated as necessary, and for the

FIGURE 1 Changes in RVF Over Time



The **solid line** indicates patients' recovering RVF; the **dashed line** indicates patients' worsening RVF. Of note, RVF recovery occurs at a median time of 6 months, whereas the deterioration of RVF was delayed during the follow-up (median time 36 months; IQR: 24 to 48 months). *Significant between-visits variations by repeated measures tests. IQR = interquartile range; pts = patients; RV = right ventricular; RVF = right ventricular systolic function.

FIGURE 2 Changes in the Prevalence of LV Restrictive Filling Pattern and sPAP in Patients With RV Dysfunction at Baseline, According to RVF Evolution at the 6-Month Follow-Up



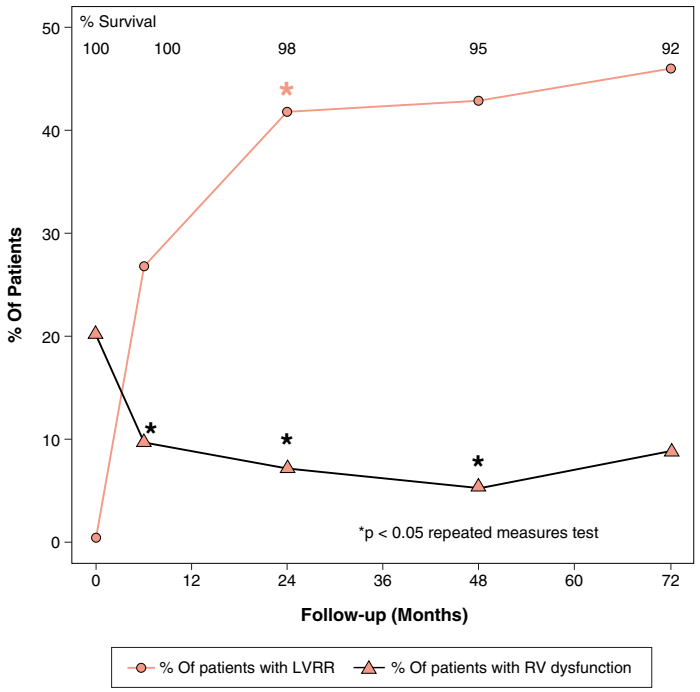
CI = confidence interval; LV = left ventricular; sPAP = systolic pulmonary arterial pressure; other abbreviations as in Figure 1.

baseline model. We evaluated the predictive accuracy of the time-dependent model compared with the baseline model by areas under the curve and the net reclassification index using the R libraries "timeROC" and "survIDINRI," respectively, and considering the time horizon as 146 months (i.e., the median follow-up of the study population). Kaplan-Meier curves and the log-rank tests were calculated and compared between groups of patients defined according to their RV dysfunction presence/evolution. As an additional and secondary analysis, cumulative incidence functions for pump failure death/HT versus sudden cardiac death/malignant ventricular arrhythmias were estimated by means of univariable competing risks regression models, using as the covariate RV dysfunction at baseline and its evolution at follow-up. The approach adopted fits the "proportional subdistribution hazards" method described in Fine and Gray (15); this model directly assesses the effect of the covariate on the subdistribution of a particular type of failure in a competing-risks setting. Interobserver and intraobserver variability regarding RV areas and RV-FAC was verified by randomly selecting a sample size of 50 patients with DCM (3 observations per subject: 2 different operators and a double evaluation by each) to achieve 90% power and, thus, to detect an intraclass correlation (ICC) of 0.8 under the null hypothesis of ICC = 0.5, by using an F-test with a significance level of 0.05 (16). The Kappa agreement was computed for both the RV-FAC and RV dysfunction binary parameter. The intraobserver variability was evaluated by computing the paired correlations between repeated measures of the same operator. IBM SPSS software version 19 (IBM, Armonk, New York), and R statistical package version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria), were used for the analysis.

RESULTS

RV DYSFUNCTION AT ENROLLMENT. The study population included 512 of 657 enrolled patients, with at least 2 evaluations during the follow-up period. Owing to the single baseline evaluation, 123 patients were excluded: no significant baseline differences were found in comparison with the study population (data not shown). Finally, 22 patients were excluded because of poor image quality on their scans. The median follow-up of the study population was 146 months (IQR: 91 to 210 months).

FIGURE 3 Longitudinal Trends of RV Dysfunction and LVRR During the Follow-Up



Note that the rate of RV dysfunction **(black line)** decreased significantly earlier compared with the increasing rate of LVRR **(pink line)** that became significant at 24 months. *Significant between visits variations by repeated measures tests. The top row of numbers indicates the percentage of surviving patients, evaluated at every pre-specified follow-up interval. LVRR = left ventricular reverse remodeling; other abbreviations as in Figure 1.

TABLE 2 Univariate HRs for Death/Heart Transplantation

	HR	95% CI	p Value
Age, yrs	1.06	1.04–1.08	**<0.001**
Male	1.32	0.81–2.14	0.261
Family history of DCM	0.44	0.23–0.85	**0.014**
HF duration, months	1.02	1.01–1.02	**<0.001**
NYHA functional class III-IV	2.21	1.43–3.43	**<0.001**
Systolic blood pressure, mm Hg	0.99	0.98–1.01	0.396
AF	2.51	1.45–4.33	**0.001**
LBBB	1.93	1.25–2.98	**0.003**
iLAD, mm/m^2	1.01	0.99–1.03	0.212
iLVEDD, mm/m^2	1.00	0.99–1.01	0.949
iLVEDV, ml/m^2	1.01	1.00–1.01	**0.011**
LVEF	0.96	0.94–0.98	**<0.001**
RVEDA, cm^2	1.01	0.98–1.03	0.522
RV dysfunction	**1.52**	**0.96–2.47**	**0.08**
RV-FAC	0.98	0.96–1.00	**0.015**
Moderate-severe MR	0.72	0.45–1.16	0.175
RFP	1.61	0.99–2.62	**0.056**
sPAP, mm Hg	1.05	1.01–1.09	**0.012**
ACEi/ARB	2.50	0.61–10.15	0.201
β-blockers	0.96	0.55–1.68	0.886
Amiodarone	1.37	0.89–2.10	0.158
MRAs	1.05	0.58–1.91	0.863

Bold indicates significant differences.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

The baseline characteristics of the patients are reported in Table 1. The median age was 46 years (IQR: 36 to 56 years). Despite a short disease duration (median time 1 month; IQR: 0 to 7 months), the patients presented significantly remodeled LV (LVEF 32%, IQR: 25% to 40%; indexed LV end-diastolic volume 88 ml/m^2, IQR: 69 to 116 ml/m^2). The large majority was optimally treated (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers 95%; beta-blockers 84%) after the first evaluation (i.e., enrollment). During the follow-up, 19% and 8% of patients underwent implantable cardioverter-defibrillator or cardiac resynchronization therapy, respectively.

RV dysfunction was observed in 103 patients at first evaluation (20% of the study population). Compared with patients with preserved RV function, they exhibited a more advanced NYHA functional class, a poorer LV systolic function, and a greater hemodynamic impairment (lower systemic systolic blood pressure, higher prevalence of LV restrictive filling pattern, and higher systolic pulmonary arterial pressures). Interestingly, the rate of left bundle branch block was lower in patients with RV dysfunction (23% vs. 34%; p = 0.003) (Table 1, second and third columns).

TABLE 3 Cox Models and Predictive Accuracy Evaluation: Independent Prognostic Role of RV Dysfunction Revaluation

Cox Models	HR	95% CI	p Value
Baseline model			
Age at enrollment*	2.54	1.79–3.60	**<0.0001**
HF duration*	1.07	1.03–3.60	**0.0005**
LVEF*	0.67	0.46–0.97	**0.0356**
RV dysfunction	1.71	1.02–2.85	**0.0413**
NYHA functional class III-IV	1.40	0.83–2.35	0.2016
iLVEDD*	1.02	0.85–1.14	0.8420
Moderate-severe MR	1.06	0.48–1.35	0.4048
β-blockers	0.99	0.78–2.91	0.2256
Time-dependent model			
Age at enrollment*	2.55	1.78–3.65	**<0.0001**
HF duration*	1.07	1.03–1.11	**0.0002**
LVEF*	0.56	0.39–0.80	**0.0015**
RV dysfunction	2.83	1.57–5.11	**0.0006**
NYHA functional class III-IV	2.23	1.10–4.54	**0.0266**
iLVEDD*	1.07	0.76–1.49	0.6951
Moderate-severe MR	1.03	0.44–1.47	0.4770
β-blockers	1.21	0.91–1.64	0.1830

Bold indicates significant differences. *HR estimated for IQR intervals.
IQR = interquartile range; other abbreviations as in Tables 1 and 2.

THE NATURAL HISTORY OF RV DYSFUNCTION. Data from the pre-specified follow-up evaluations were available in 455, 360, 331, and 264 patients at 5 (IQR: 4 to 7), 25 (IQR: 22 to 29), 47 (IQR: 43 to 52), and 71 (IQR: 66 to 76) months, respectively.

Interestingly, longitudinal trends of RV dysfunction presented 2 distinct patterns: 89 of 103 patients with baseline RV dysfunction (86%; 17% of the overall cohort) normalized RVF in the short-term (median time 6 months; IQR: 5 to 7 months), whereas in 38 of 409 patients with preserved RVF at enrollment (9%; 7% of the total population), RV function deteriorated at a later follow-up (median time 36 months; IQR: 24 to 48 months) (Figure 1). Finally, RVF was stable throughout the follow-up period in the remaining patients, and none showed a decline in RVF after the initial improvement.

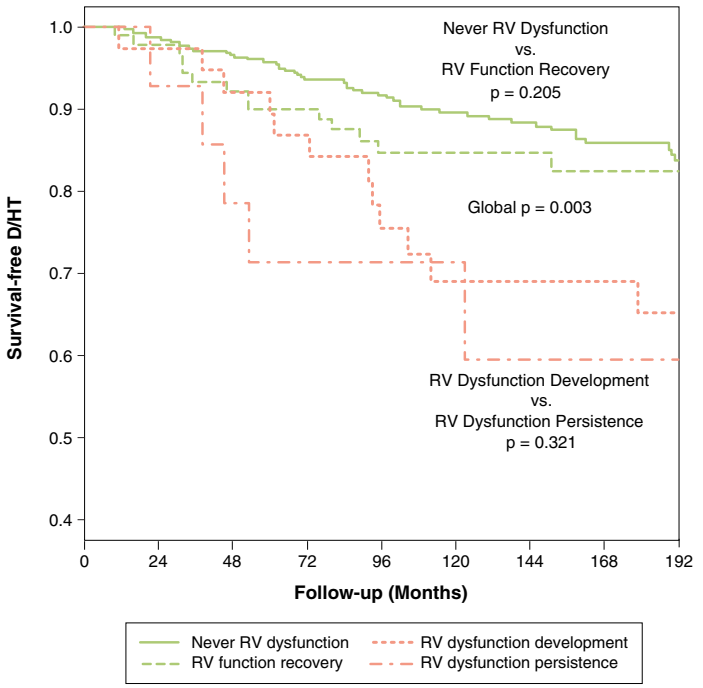
The recovery of RVF was associated with a parallel improvement of the echocardiographic parameters related to hemodynamic status (specifically, the LV restrictive filling pattern [$p < 0.001$] and the systolic pulmonary arterial pressure [$p = 0.019$]) (Figure 2). It is noteworthy, as shown in Figure 3, that RVF normalization occurred mostly within 6 months, thereby preceding the LVRR that was observed at a median time of 24 months (IQR: 18 to 30 months). Moreover, RVF recovery at 6-month follow-up was significantly associated with the subsequent LVRR (odds ratio: 2.49; 95% confidence interval [CI]: 1.17 to 5.3; $p = 0.018$).

THE PROGNOSTIC ROLE OF RVF REVALUATION OVER TIME. A baseline prognostic multivariable model was initially obtained, including all the significant and clinically relevant predictors of D/HT at univariate analysis (Table 2). Through this model, independent prognostic predictors were a longer duration of disease, older age, a lower LVEF, together with RV dysfunction (hazard ratio: 1.71; 95% CI: 1.02 to 2.85; $p = 0.0413$) (Table 3). When the reassessment of RVF was considered in a time-dependent Cox model, it globally maintained an independent predictive value (hazard ratio: 2.83; 95% CI: 1.57 to 5.11; $p = 0.0006$). Even if the addition of RV dysfunction alone to the baseline and time-dependent models did not significantly increase the areas under the curves, the global time-dependent model showed an area under the curve of 0.83 (95% CI: 0.76 to 0.90) versus 0.78 (95% CI: 0.69 to 0.87) of the baseline model ($p = 0.09$), with a net reclassification index of 0.30 with respect to the baseline model (95% CI: 0.10 to 0.52; $p = 0.04$).

Figure 4 shows the long-term survival-free from HT curves of patients, according to the evolution of RVF. Patients with early recovery of RVF presented a similar events rate to those who had never experienced RV dysfunction ($p = 0.205$). On the other hand, the survival curves of patients with new-onset RV dysfunction diverged significantly beyond the 48-month follow-up, then approaching in the long-term the survival rates of patients with persistent RV dysfunction ($p = 0.321$).

Finally, impaired RVF, particularly a new-onset RV dysfunction after the initial evaluation, was mainly related to pump failure death or HT ($p < 0.001$ at baseline and $p < 0.0001$ at follow-up), whereas it was not related to major ventricular arrhythmic events, except for a trend in the very long term ($p = 0.618$ at baseline and $p = 0.07$ at follow-up) (Online Figure 1).

FIGURE 4 Kaplan-Meier Survival Curves: Long-Term Prognostic Role of RV Dysfunction Revaluation



Long-term survival curves according to the RV function evolution. Patients with early recovery of RV function (i.e., at a median of 6 months during follow-up) under treatment presented HT survival-free comparable with those who never experienced RV dysfunction ($p = 0.205$). The HT survival-free curves of patients with new-onset RV dysfunction (i.e., at a median of 36 months at follow-up) diverged significantly thereafter, approaching, in the long-term, the survival rates of patients with persistent RV dysfunction ($p = 0.321$). D/HT = death/heart transplantation; dysf = dysfunction; other abbreviation as in Figure 1.

DISCUSSION

MAIN FINDINGS. The present study describes for the first time the natural history of RV dysfunction in a

large series of recently diagnosed patients with DCM, who were followed systematically over the long-term. The principal results were that: 1) the regular RVF revaluation over time provided an independent long-term prognostic value; and that 2) the RV function improvement under optimal treatment temporally preceded LVRR. These findings should be considered of remarkable importance in the long-term risk stratification and management of patients with DCM.

RV DYSFUNCTION AT ENROLLMENT. Few data exist about the prevalence of RV dysfunction in patients with DCM. In this large-cohort study, 20% of patients with DCM presented with impaired RV at the first evaluation. Notably, our findings refer to a stage close to the onset of the disease (median 1 month). Nevertheless, similar rates of prevalence were reported recently in a highly selected DCM population that was evaluated using cardiac magnetic resonance (5). Although cardiac magnetic resonance is considered to be the most accurate approach for the assessment of RV systolic function (17), RV-FAC obtained by transthoracic echocardiography has been demonstrated to strongly correlate with cardiac magnetic resonance (18). Furthermore, echocardiography still represents the first-line examination in patients with DCM: widely accessible also in secondary-level centers and less suffering from limitations in patient selection. Patients presenting with RV dysfunction at enrollment were contextually characterized by a higher grade of congestion and a more impaired hemodynamic condition. It is noteworthy that, at baseline, we observed a lower prevalence of left bundle branch blocks in patients with an impaired RV. In our opinion, this suggests that worse RVF might mostly be the expression of hemodynamic impairment, rather than of extensive biventricular structural damage.

THE NATURAL HISTORY OF RVF. In our cohort, RVF recovery largely occurred in the first few months during follow-up (**Figure 1**), which was likely from the beneficial hemodynamic effects of anti-neurohormonal therapy on peripheral resistance, LV filling pressures and, consequently, on RV afterload and ventricular interdependency (**Figure 2**) (19). This conclusion is also supported by the correlation between the evolution of RVF over time and pump failure death or HT, rather than to arrhythmic events (Online Figure 1).

Concerning the timing of the response to evidence-based therapy, in the current study, we observed a significant relationship between the improvement in RVF and LVRR. Of interest, the RV response occurred earlier than LVRR, which was indeed detectable at a median time of 24 months (**Figure 3**). LVRR represents, in fact, the intrinsic effect of pharmacological/nonpharmacological therapies on the LV structure; for this reason, it may need up to 24 months or even more to be expressed fully (3,20,21). Finally, RVF recovery remained stable throughout the observation period.

On the other hand, a minority of patients presenting with normal RVF experienced a reduction in RV systolic function, which usually occurred beyond the 48-month evaluation. Therefore, deterioration in RVF might reflect the intrinsic progression of the cardiomyopathy process that typically characterizes DCM in the long term (22).

THE PROGNOSTIC IMPACT OF RVF REVALUATION. In the present study, we confirmed the adverse impact of impaired RVF on survival rates in patients with DCM (5,23). Our population, compared with previously described series, included a larger number of patients more extensively treated with beta-blockers and with a shorter duration of disease. Moreover, it must be noted that in the multivariable model, baseline RV dysfunction showed a stronger impact than other previously demonstrated prognostic factors, such as NYHA functional class, functional mitral regurgitation, LV restrictive filling pattern, and LV dimensions.

Notably, we demonstrated for the first time the strong independent prognostic impact of serial RVF reassessment over time. This emphasizes the importance of a comprehensive echocardiographic evaluation, which should always include a careful assessment of both the right and left chambers at baseline and systematically during the follow-up, to improve the accuracy of clinical management and risk stratification of patients with DCM.

The intriguing hypothesis that specific genetic mutations might determine different phenotypes specifically affecting the RV in DCM, or causing overlap syndromes such as biventricular or left dominant arrhythmogenic cardiomyopathy (24), will require further, more focused studies. Unfortunately, in our series, only a few cases underwent comprehensive genetic testing; however, such testing was beyond the aims of the present study.

STUDY LIMITATIONS. This study suffers from the limitations related to its observational nature. A possible selection bias of the population is limited, however, by the fact that all of the patients were enrolled consecutively in the same institution (a referral center for cardiomyopathies) using homogenous inclusion criteria. The length of the enrollment period could be considered a limitation, but we believe that it is simultaneously an important

strength because it allowed us to analyze the evolution of RVF in the very long-term, in one of the largest existing DCM populations.

A total of 123 eligible patients were excluded from the initial population owing to the lack of follow-up assessment of RVF. However, no significant differences were found when they were compared with the study population; therefore, these patients can be fully considered as missing at random and not influencing the study results. Besides, the number of patients who underwent a complete RV evaluation at each pre-specified interval was sized adequately for the aims of this study (89% at 6 months, >300 within 48 months, and >250 at 72 months).

The assessment of RVF was obtained by using 2-dimensional echocardiography evaluation of RV-FAC. Because of several limitations related to this approach (25), we performed an interobserver and intraobserver variability analysis that indicated a good performance level (ICC for RV-FAC 0.86; 95% CI: 0.73 to 0.92; Kappa agreement for RV dysfunction 0.745; $p < 0.001$; intraobserver correlation for RV-FAC and RV dysfunction >0.90 and >0.81, respectively). Finally, we analyzed 50 patients with DCM with available RVF assessment by using both cardiac magnetic resonance and echocardiography (with a maximum interval between the 2 imaging studies of 1 month): a good correlation between the 2 techniques was obtained for both RV fractional area shortening and RV dysfunction (Spearman Rho correlation coefficient 0.74; $p < 0.001$).

The measurement of tricuspid annular plane systolic excursion as a simple parameter of RVF was not considered in our series because it was available only in a minority of patients and its reliability in assessing global RVF is questionable.

RV strain, strain rate and 3-dimensional echocardiography data were available only for a few patients. There is a growing body of data on the reliability of these techniques, and they will actually improve RV echocardiography in the future (26,27).

The effect of cardiac resynchronization therapy on RVF was not evaluated because it was not the specific aim of our study; however, it represents an interesting issue that needs to be investigated further in large-scale studies.

CONCLUSIONS

RVF is frequently impaired in recently diagnosed patients with DCM, with a prevalence of about 20% in our population. However, it largely and rapidly improves under evidence-based medical treatment, showing a strong relationship with subsequent LVRR. Serial revaluation of RVF during the follow-up emerged as a powerful determinant of long-term prognosis. These findings strongly suggest that systematic RVF reassessment may assist clinical decision-making, and that RV reverse remodeling should be considered an important therapeutic target in the early management of DCM.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Right ventricular dysfunction is present in 20% of recently diagnosed patients with DCM; however, it promptly improved in the majority of patients under optimal treatment.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with baseline evaluation, re-evaluation of right ventricular function during regular follow-up has independent power in prognostic stratification of DCM patients.

TRANSLATIONAL OUTLOOK 1: Future genotype-phenotype correlation studies are needed to prospectively identify DCM patients with right ventricular involvement as an expression of specific mutations rather than of hemodynamic impairment.

TRANSLATIONAL OUTLOOK 2: Studies on reliability of cardiac magnetic resonance, right ventricular strain, strain rate, and 3-dimensional echocardiography data during follow-up of DCM patient are needed to confirm our results.

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APPENDIX For a supplemental figure, please see the online version of this article.