Prevalence and Clinical Predictors of Reverse Remodeling in Patients with Dilated Cardiomyopathy

Michael Arad MD[1], Tamar Nussbaum MD[1], Ido Blechman BA[1], Micha S. Feinberg MD[2], Nira Koren-Morag PhD[3], Yael Peled MD[1] and Dov Freimark MD[1]

[1]Heart Failure Service and [2]Non-Invasive Cardiology Unit, Leviev Heart Institute, Sheba Medical Center, Tel Hashomer, Israel
[3]Division of Epidemiology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Contemporary therapies improve prognosis and may restore left ventricular (LV) size and function.

Objectives: To examine the prevalence, clinical features and therapies associated with reverse remodeling (RR) in dilated cardiomyopathy (DCM).

Methods: The study group comprised 188 DCM patients who had undergone two echo examinations at least 6 months apart. RR was defined as increased LV ejection fraction (LVEF) by ≥ 10% concomitant with ≥ 10% decreased LV end-diastolic dimension.

Results: RR occurred in 50 patients (26%) and was associated with significantly reduced end-systolic dimension, left atrial size, grade of mitral regurgitation, and pulmonary artery pressure. NYHA class improved in the RR group. RR was less common in familial DCM and a long-standing disease and was more prevalent in patients with prior exposure to chemotherapy. Recent-onset disease, lower initial LVEF and normal electrocardiogram were identified as independent predictors of RR. Beta-blocker dose was related to improved LVEF but not to RR. Over a mean follow-up of 23 months, 16 patients (12%) from the 'no-RR' group died or underwent heart transplantation compared to none from the RR group ($P < 0.01$).

Conclusions: Contemporary therapies led to an an improvement in the condition of a considerable number of DCM patients. A period of close observation while optimizing medical therapy should be considered before deciding on invasive procedures.

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Left ventricular remodeling plays a major role in the pathophysiology of dilated cardiomyopathy. The term was originally used to describe cardiac morphological changes that occur after myocardial infarction, as well as those in non-ischemic cardiomyopathies. Targeting the remodeling process to prevent or even revert it therefore constitutes a primary therapeutic goal. Reverse remodeling is a concept that refers to the functional and structural restoration of the heart [1]. This fascinating phenomenon gained publicity following descriptions of heart recovery after myocardial revascularization, timely valve surgery, and implantation of an assist device. It has been associated with contemporary treatments for heart failure and occasionally occurs spontaneously.

Among the medical therapies, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists improved cardiac function and left ventricular dimension when given separately or together [2,3]. Other studies suggested induction of reverse remodeling with moderate intensity exercise training and possibly with treatment of sleep apnea [4,5]. Hoshikawa et al. [6] showed that the extent of RR within 6 months of starting the therapy is associated with improved long-term prognosis.

Some patients with DCM have a wide QRS due to left bundle branch block or intra-ventricular conduction defect. In these patients, cardiac resynchronization therapy may improve the stroke volume and cardiac output. In the MIRACLE study, researchers showed that patients who received cardiac resynchronization therapy improved their physical fitness and New York Heart Association functional score regardless of drug treatment. These patients also improved their LV ejection fraction and diminished their end-systolic and diastolic dimension [7]. Cardiac resynchronization had a synergistic effect when combined with pharmacological therapy.

The etiology of cardiomyopathy undoubtedly plays a role in the response to and outcome of therapy [8]. Familial cardiomyopathy caused by an indolent gene defect is often considered to have an unfavorable prognosis [9]. A recent study compared the response to treatment of DCM between men and women with or without peripartum cardiomyopathy. At 4 years follow-up, the most pronounced improvement in LVEF was in the peripartum group, followed by other women. The males had the worst prognosis [10].

RR = reverse remodeling
DCM = dilated cardiomyopathy
LV = left ventricular
LVEF = left ventricular ejection fraction

The recently published IMAC study examined the prevalence and clinical impact of LV function recovery in patients with recent-onset DCM. The researchers found that 70% of patients receiving optimal therapy for heart failure improved their LVEF by at least 10% units and 25% of them normalized their LV function. LV dimension on presentation was the strongest predictor of LVEF recovery. Other predictors included race, systolic blood pressure and NYHA class. Over a mean follow-up of 2.2 ± 1.4 years the low rates of death (4%) and heart transplantation (5%) imply that contemporary heart failure therapy has revolutionized the natural history of DCM [11].

The phenomenon of reverse remodeling and its long-term consequences are not yet completely understood. RR occurs in only a fraction of DCM patients receiving optimal heart failure therapy. While RR might identify a subgroup with a better prognosis, it may be difficult to predict those expected to improve. The purpose of our study was to determine the etiological and clinical factors predicting occurrence of RR in an unselected cohort of patients with non-ischemic DCM.

PATIENTS AND METHODS

The investigational part of the study conforms to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board.

We collected the data from all patients with dilated cardiomyopathy who had been evaluated or followed at the Sheba Hospital Heart Failure Clinic between 2004 and 2008. Significant coronary disease was eliminated by angiography or radionuclide scan. Prior to diagnosis of DCM, patients suspected of having an acute myocardial injury such as myocarditis, hypertensive crisis, sepsis, stress-induced cardiomyopathy or peripartum cardiomyopathy were reevaluated within 3 months to document reversibility of myocardial function.

Cardiomyopathy patients followed by our unit usually undergo echo-Doppler studies every 6–24 months or as clinically indicated. For the purpose of the present study, to investigate reverse remodeling we identified those patients who had data from at least two echo-Doppler exams separated by at least 6 months. Due to the unavailability of on-site echo studies in some of the patients, echo reports by outpatient clinics were also accepted. LVEF was determined by Simpson's method or eyeballing and LV end-diastolic dimension from the parasternal long axis view. Because of the unavailability of a core lab to compare different studies, we based our definition of RR on echo measurements that would not likely result from inter- or intra-observer differences. We therefore defined reverse remodeling of the left ventricle as an increase in LVEF by at least 10% units concomitant with a decrease in the LVEDD by at least 10% relative to the baseline measurement [12,13]. We validated our parameter against other volumetric and functional measures of RR used in the literature by analyzing the echo-Doppler recordings of a series of patients studied in our echo lab (data not shown). The measures used in this study appear to be well reproducible when compared to Simpson's calculations, and more robust compared to a ≥ 15% decrease in the end-systolic volume commonly used to define RR in prospective studies [7].

The echo-Doppler study that was used for DCM diagnosis was defined as Echo1. The first follow-up echo-Doppler, which met the criterion for RR, was defined as Echo2. If no RR occurred, the last echo available at the time of closing the database was taken as Echo2. A minimum 6 month interval between Echo1 and Echo2 was established.

Epidemiological and clinical data, including the principal complaint on presentation, NYHA class and baseline electrocardiogram, were recorded. We documented comorbidities and potential causes of secondary cardiomyopathy such as hypertension, diabetes, history of substance abuse, chemotherapy exposure, sustained tachyarrhythmia, association with pregnancy, or endocrinopathy. Familial cardiomyopathy was defined according to the consensus document [14]. When several members of a family were followed in our clinic only the proband was included in the database. Skeletal myopathy (characterized by muscle weakness or an unexplained persistent creatine kinase elevation) and early conduction system disease were noted. Coexistent coronary artery disease was defined as stenosis not involving a proximal section of a major coronary artery and the inability to attribute myocardial dysfunction to scar tissue according to a radionuclide perfusion scan.

LV hypertrophy on ECG was defined by voltage criteria of Sokolow-Lyon. Low voltage ECG was defined as maximal QRS deflection of ≤ 5 mm in limb leads or SV1+RV5/6 ≤ 15 mm [15].

Patients were treated according to contemporary Heart Failure guidelines [16]. Therapies and interventions were recorded at the time of Echo2. While most drug categories were defined by a binary variable, the dose of beta-blockers, ACE inhibitors and ARBs were also presented by a fraction of the maximal recommended dose in each category. Since no quantitative data were available for the duration of rehabilitation therapy, cardiac rehabilitation was defined as the patient's presence in the rehabilitation facility.

Outcome measurements were obtained from the patient's chart and ascertained by phone, if necessary. They included NYHA functional class recorded at the time of Echo2, and the combined end-point of death, heart transplantation, or implantation of an assist device.

NYHA = New York Heart Association

LVEDD = LV end-diastolic dimension
ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blockers

DATA ANALYSIS

The primary objective of the study was to define the predictors of RR from among the epidemiological, clinical, ECG and echo parameters collected on baseline and from drug and other treatments. We had two secondary end-points: a) to determine the effect of RR on the outcome measures, and b) to define 'improved EF' as an increase in LVEF by at least 10% of units irrespective of the ventricular dimension and study the predictors of 'improved EF' and its effect on the outcome measures.

RR or 'improved EF' were set as dichotomous variables. Data are reported as mean ± SD for continuous variables and frequency (percentage) for dichotomous variables. Student's *t*-test or chi-square/Fisher test was used as appropriate to compare the various parameters between the different groups. The parameters that emerged as potential univariate predictors were included in a multivariate logistic regression. Variables were introduced into the model according to a Forward method. A P value < 0.05 was considered statistically significant.

RESULTS

We identified 233 DCM patients who had been evaluated or treated in our Heart Failure/Cardiomyopathy Clinic between 1 July 2004 and 1 July 2008. The 188 patients who continued a regular clinical and echocardiographic follow-up and had at least two echo-Doppler exams separated by ≥ 6 months constituted the study group. Except for a higher proportion of females (38 vs. 22%, $P = 0.043$) and higher prevalence of pregnancy-associated presentation (12 vs. 2%, $P = 0.021$), these patients did not significantly differ from those who were excluded due to absence of follow-up.

Reverse LV remodeling (RR) occurred in 50 patients (26%). Although most cases of RR occurred within 3 years, several patients had a late improvement, i.e., 5–10 years after the first echo. The mean time interval between the two echo exams did not differ between the RR group and no-RR groups: 33 ± 28 months vs. 32 ± 25 months respectively. When comparing between Echo1 and Echo2 in patients with RR, reverse remodeling was associated with a marked decrease in LVEDD, left atrial size, severity of mitral regurgitation, and pulmonary artery pressure (data not shown). An increase in LVEF by ≥ 10% occurred in 87 (46%) of the DCM cohort.

Table 1 compares the baseline characteristics of patients with RR or improved LVEF and their correspondent controls. Patients who improved were slightly older, with a significantly shorter disease duration and a lower prevalence of familial cardiomyopathy. Chemotherapy and pregnancy were related to improved LVEF while coexistent coronary disease had an adverse effect.

Congestive heart failure on presentation, represented by higher heart rate, respiratory distress and gallop on auscultation, were associated with better chances of undergoing RR [Table 2]. Interestingly, lower initial LVEF and severe diastolic dysfunction, as well as normal ECG or LV hypertrophy according to ECG voltage criteria, predicted a stronger likelihood to improve. We also studied the association of RR with evidence-based and other treatments that the patients received in the period prior to Echo2 [Table 2]. Since all possible attempts were made to adhere to Heart Failure guidelines, we did not find a significant relationship between the occurrence of RR and the percentage of patients treated with ACE inhibitors, ARBs, beta-adrenergic blockers or mineralocorticoid antagonists. We therefore proceeded to examine the effect of dosage and found that a higher dose of beta-blockers but not ACE/ARB was significantly associated with improved LVEF. Interestingly, the use of dihydropyridine calcium-channel blockers was positively associated, while allopurinol was negatively associated with RR. In this cohort neither cardiac resynchronization therapy nor participation in a cardiac rehabilitation program was related to improved LV structure or function.

Table 1. Univariate predictors of reverse remodeling: baseline characteristics

	Reverse remodeling			Improved LVEF		
	Yes (n=50)	No (n=138)	*P*	Yes (n=87)	No (n=101)	*P*
Age at diagnosis (yr)	49 ± 14	45 ± 17	0.09	49 ± 16	44 ± 16	0.03
Female	22 (44%)	50 (36%)	0.3	39 (45%)	33 (33%)	0.09
Body surface area (m^2)	1.8 ± 0.2	1.9 ± 0.3	0.07	1.9 ± 0.2	1.9±0.3	0.2
Body mass index (kg/m^2)	26 ± 5	27 ± 6	0.3	27 ± 6	27 ± 6	0.5
Disease duration (yr)	2.0 ± 4.1	4.4 ± 5.7	0.009	2.5 ± 4.4	5.0 ± 6.0	0.004
Familial cardiomyopathy	4 (8%)	33 (24%)	0.02	10 (11%)	27 (27%)	0.009
Myopathy	2 (4%)	16 (12%)	0.1	7 (8%)	11 (11%)	0.5
Conduction disease	3 (6%)	16 (12%)	0.3	5 (6%)	14 (14%)	0.07
CAD/ischemia*	2 (4%)	11 (8%)	0.3	2 (2%)	11 (11%)	0.02
Hypertension	20 (40%)	55 (40%)	0.986	39 (45%)	36 (36%)	0.2
Diabetes	9 (18%)	33 (24%)	0.4	16 (18%)	26 (26%)	0.2
Hyperlipidemia	18 (36%)	53 (38%)	0.8	30 (34%)	41 (41%)	0.4
Alcohol abuse	1 (2%)	8 (6%)	0.3	2 (2%)	7 (7%)	0.1
History of chemotherapy	8 (16%)	10 (7%)	0.07	14 (16%)	4 (4%)	0.005
Pregnancy associated	8 (16%)	14 (10%)	0.3	17 (19%)	5 (5%)	0.002
Renal failure	11 (22%)	31 (22%)	0.9	23 (26%)	19 (19%)	0.2
Pulmonary disease	3 (6%)	17 (12%)	0.2	7 (8%)	13 (13%)	0.3
Liver disease	2 (4%)	10 (7%)	0.4	4 (5%)	8 (8%)	0.4
Possible TICM	6 (12%)	20 (14%)	0.7	16 (18%)	10 (10%)	0.1
Thyroid disease	7 (14%)	26 (19%)	0.1	16 (18%)	17(17%)	0.3
Iron deficiency	3 (13%)	8 (16%)	0.7	7 (19%)	4 (11%)	0.3
Anemia	7 (14%)	17 (12%)	0.8	12 (14%)	12 (12%)	0.7
Sleep apnea	4 (8%)	11 (8%)	0.995	6 (7%)	9 (9%)	0.6

*CAD/ischemia = coexistent coronary artery disease
TICM = tachycardia-induced cardiomyopathy

Table 2. Univariate predictors of reverse remodeling: clinical features, heart failure therapies and outcome

	Reverse remodeling			Improved LVEF		
	Yes (n=50)	No (n=138)	*P*	Yes (n=87)	No (n=101)	*P*
Heart rate (bpm)	85 ± 21	80 ± 15	0.1	86 ± 19	77 ± 14	0.007
Systolic BP (mmHg)	124 ± 28	123 ± 23	0.9	126 ± 28	120 ± 20	0.1
Diastolic BP (mmHg)	77 ± 18	75 ± 14	0.5	78 ± 17	74 ± 14	0.2
Shortness of breath	39 (78%)	81 (59%)	0.02	64 (74%)	56 (55%)	0.01
Chest pain	8 (16%)	31 (22%)	0.3	17 (19%)	22 (22%)	0.7
Syncope	1 (2%)	7 (5%)	0.3	1 (1%)	7 (7%)	0.05
Thromboembolism	4 (8%)	14 (10%)	0.7	8 (9%)	10 (10%)	0.9
Fatigue	13 (26%)	26 (19%)	0.3	25 (29%)	14 (14%)	0.01
Edema	17 (34%)	43 (31%)	0.7	29 (33%)	31 (31%)	0.7
Gallop	16 (32%)	24 (17%)	0.03	27 (31%)	13 (13%)	0.002
Atrial fibrillation	18 (36%)	51 (37%)	0.9	34 (39%)	35 (35%)	0.5
Ventricular tachycardia	11 (22%)	39 (28%)	0.4	20 (23%)	30 (30%)	0.3
Functional class NYHA 1 NYHA 2 NYHA 3 NYHA 4	 7 (14%) 17 (34%) 19 (38%) 6 (12%)	 32 (23%) 37 (27%) 56 (41%) 9 (7%)	0.4	 15 (17%) 27 (31%) 35 (40%) 8 (9%)	 24 (24%) 27 (27%) 40 (40%) 7 (7%)	0.6
Sinus rhythm	42 (84%)	111 (80%)	0.6	69 (79%)	84 (83%)	0.5
Normal ECG	9 (18%)	12 (9%)	0.07	15 (17%)	6 (6%)	0.01
LVH (voltage criteria)	7 (14%)	6 (4%)	0.02	9 (10%)	4 (4%)	0.08
Low ECG voltage	3 (6%)	6 (4%)	0.6	6 (7%)	3 (3%)	0.2
LBBB	12 (24%)	34 (25%)	0.9	19 (22%)	27 (27%)	0.4
QRS duration (msec)	107 ± 36	113 ± 30	0.3	107 ± 33	116 ± 31	0.08
Max LVWT (mm)	10.8 ± 1.7	10.4 ± 1.7	0.2	10.7 ± 1.8	10.4 ± 1.5	0.2
LAD (mm)	43 ± 6	43 ± 8	1	42 ± 7	43 ± 8	0.2
LVEDD (mm)	60 ± 7	59 ± 8	0.4	58 ± 8	61 ± 8	0.056
LVESD (mm)	49 ± 9	47 ± 9	0.1	47 ± 9	48 ± 9	0.3
LVEF (%)	24 ± 7	29 ± 9	0.001	26 ± 7	30 ± 9	0.001
Estimated PAP (mmHg)	39 ± 10	38 ± 12	0.5	38 ± 10	38 ± 13	1
Diastolic dysfunction grade 2-3	24 (69%)	50 (53%)	0.03	40 (68%)	34 (49%)	0.05
Significant MR	20 (40%)	33 (25%)	0.2	30 (34%)	23 (23%)	0.08
Significant TR	6 (12%)	15 (11%)	0.6	9 (10%)	12 (12%)	0.3
RA enlargement	8 (17%)	20 (16%)	0.8	13 (16%)	15 (16%)	0.989
RV enlargement	6 (13%)	15 (11%)	0.8	12 (15%)	9 (9%)	0.3
RV dysfunction	14 (29%)	27 (20%)	0.5	20 (22%)	21 (21%)	0.7
Heart failure therapies						
Diuretics	32 (64%)	94 (68%)	0.6	55 (62%)	71 (70%)	0.2
Mineralocorticoid antagonist	24 (48%)	66 (48%)	0.983	39 (45%)	51 (50%)	0.4
ACEI or ARB	42 (84%)	121 (88%)	0.5	74 (85%)	89 (88%)	0.5
Dose (% of maximal)	48 ± 35	54 ± 40	0.3	54 ± 41	51 ± 37	0.5
Beta-blocker	42 (84%)	114 (83%)	0.8	75 (86%)	81 (80%)	0.3
Dose (% of maximal)	57 ± 8	52 ± 37	0.4	62 ± 38	46 ± 35	0.004
Statin	18 (36%)	51 (37%)	0.9	33 (38%)	36 (36%)	0.7
Beta-blocker	2 (4%)	5 (4%)	0.9	4 (5%)	3 (3%)	0.5
Dihydropyridine CCB	9 (18%)	11 (8%)	0.05	14 (16%)	6 (6%)	0.02
Anti-arrhythmic	7 (14%)	22 (16%)	0.7	11 (13%)	18 (18%)	0.3
Digoxin	11 (22%)	35 (25%)	0.6	20 (23%)	26 (26%)	0.7
Nitrate	1 (2%)	13 (9%)	0.09	4 (5%)	10 (10%)	0.2
Anti-platelets	19 (38%)	42 (30%)	0.3	26 (30%)	35 (35%)	0.5
Anticoagulant	10 (20%)	41 (30%)	0.2	25 (29%)	26 (26%)	0.6
Insulin	2 (4%)	14 (10%)	0.2	6 (7%)	10 (10%)	0.5
Thyroid replacement	8 (16%)	12 (9%)	0.1	13 (15%)	7 (7%)	0.08
Vitamin supplements	17 (34%)	40 (29%)	0.5	31 (36%)	26 (26%)	0.1
Iron	5 (10%)	9 (6%)	0.4	7 (8%)	7 (7%)	0.8
Oral anti-diabetic	6 (12%)	19 (14%)	0.7	8 (9%)	17 (17%)	0.1
Allopurinol	0 (0%)	12 (9%)	0.03	3 (3%)	9 (9%)	0.1
ICD	7 (14%)	22 (16%)	0.7	11 (13%)	18 (18%)	0.3
CRT	8 (16%)	12 (9%)	0.1	9 (10%)	11 (11%)	0.9
Cardiac rehabilitation	23 (46%)	44 (32%)	0.07	34 (39%)	33 (33%)	0.4

Atrial fibrillation includes paroxysmal or chronic flutter or fibrillation, ventricular tachycardia includes non-sustained and sustained VT
NYHA FC = New York Heart Association functional class, LVH = left ventricular hypertrophy, LBBB = left bundle branch block, Max LVWT = maximal LV wall thickness, LAD = left atrial dimension, LVEDD = LV end-diastolic diameter, LVESD = LV end-systolic diameter, LVEF = LV ejection fraction, PAP = pulmonary artery pressure, significant MR = mitral regurgitation of moderate or severe grade, significant TR = tricuspid regurgitation of moderate or severe grade, RA = right atrium, RV = right ventricle, diuretics = furosemide and/or thiazide, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, CCB = calcium-channel blocker, ICD = implantable cardiac defibrillator, CRT = cardiac resynchronization therapy

The parameters that showed a significant univariate association with outcome measures [Tables 1 and 2] were studied with multivariate logistic regression. Only variables with a prevalence of ≥ 20% in the study population were introduced into the multivariate model. Normal ECG, lower initial EF and shorter disease duration were independent predictors of RR or improving LVEF [Table 3]. A higher beta-blocker dose independently predicted improving LVEF but not RR. Because disease duration was not documented and could not even be estimated in 31 patients (16%), we repeated the multivariate analysis without this parameter. After excluding 'disease duration', familial cardiomyopathy became an independent adverse

predictor of RR with an odds ratio of 0.32 and 95% confidence interval of 0.1–1.

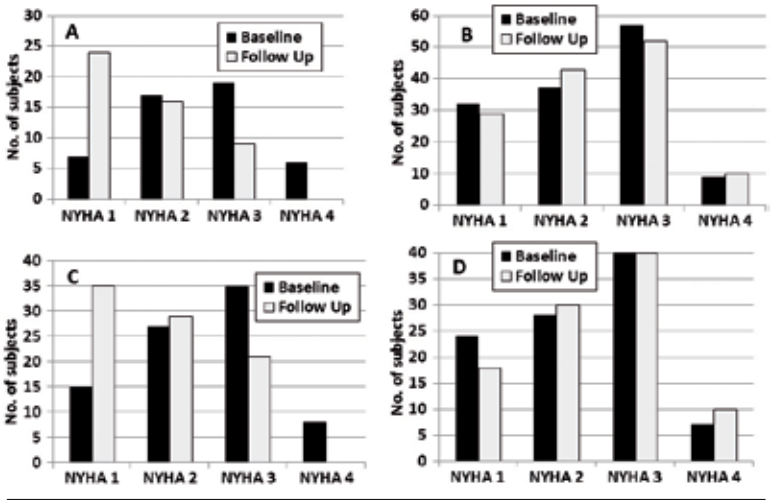
RR was associated with a significant improvement in NYHA functional class. A similar result was apparent in those who improved their LVEF [Figure 1]. The follow-up time after Echo2 averaged 22–23 months and did not differ between the groups. Within this short period 12 (9%) from the no-RR group died and 4 (3%) underwent assist device or heart transplantation vs. none in the RR group ($P = 0.006$). Only one case of death occurred in those who had 'improved EF' but did not qualify as RR.

Table 3. Multivariate predictors of reverse remodeling

	Reverse remodeling			Improved LVEF		
		95% CI for OR			95% CI for OR	
	OR	Lower	Upper	OR	Lower	Upper
Normal ECG	4.078	1.281	12.983	7.348	2.077	25.995
LVEF (per 1% unit)	0.891	0.841	0.944	0.915	0.871	0.961
Disease duration (per 1 month	0.875	0.795	0.963	0.889	0.823	0.961
Beta-blocker dose (per 1% of the maximal recommended dose)	–	–	–	1.013	1.004	1.023

OR = odds ratio, CI = confidence interval, ECG = electrocardiogram, LVEF = LV ejection fraction

Figure 1. NYHA functional class on baseline and during follow-up. **[A]** An improvement occurred in the reverse remodeling (RR) group ($P = 0.003$), but there was no change in the 'no-RR' group **[B]**. **[C]** An improvement occurred in the group with improved LVEF ($P = 0.003$), but no significant change was seen in the control group **[D]**. NYHA class was available in 183 patients on baseline and 182 patients on follow-up



DISCUSSION

Heart failure guidelines recommend postponing the decision on primary prevention implantable cardioverter defibrillators for DCM by at least 3 months, allowing the process of RR to take place [16]. The prevalence and predictors of RR among DCM patients are more controversial and may depend on the definition of RR. While improvement in LVEF may be the simplest and most effective way to risk-stratify the DCM population, decreasing the LV diastolic dimension is the most relevant physiological indicator of beneficial remodeling. The LV systolic dimension is an integrative parameter representing both the ventricular size and systolic function.

Our definition of a ≥ 10% decrease in the end-diastolic dimension with a ≥ 10% increase in LVEF [12,13,17] is easily applicable in a clinical setup that does not have a core echo lab. According to this definition, RR occurred in 26% of the non-selected DCM population and 46% improved their LVEF. Improvement mainly occurred within 2–3 years but some patients underwent RR many years after being diagnosed with DCM. The prevalence of improvement is somewhat lower than the 33–38% in recent studies of RR that combined measurement of LVEDD and systolic function [6,12,17] and 70% who improved LVEF in the IMAC registry [11].

Disease duration appears to be a major factor determining reversibility. While IMAC exclusively studied patients with recent-onset DCM, many of our patients had established disease [11]. In our study, shorter disease duration was an independent predictor of improvement [Table 1]. There was a series of signals associating recent onset in contrast to chronicity with the potential of undergoing RR. Shortness of breath, gallop, severe diastolic dysfunction (demarcating increased filling pressures) and lower LVEF were associated with RR. Of those parameters, lower LVEF at presentation emerged as an independent positive predictor of RR [Tables 2 and 3]. This finding appears to conflict with other studies associating low ejection fraction with poor prognosis, but we contend it reflects recent disease, sub-acute presentation, earlier intervention, and better chance to respond to therapy. The natural history of myocarditis shows that presentation with acute heart failure may be followed by complete recovery while chronic/persistent myocarditis has the worst outcome [18,19]. We suggest that NYHA class and LVEF after treatment be used to determine long-term prognosis, thereby allowing the heart to stabilize and recover [6,11].

ECG emerged as another important predictor of prognosis. Normal ECG and LV hypertrophy, while uncommon in DCM, emerged as powerful predictors of RR [Table 2]. LBBB was present in ~ 25% of the cohort but neither LBBB nor QRS duration was significantly associated with prognosis. These parameters were previously associated with adverse prognosis [12,17], but this negative effect is attenuated by resynchronization therapy. Since implantation of pacemakers was driven by clinical indications, this study was not able to assess the effect of resynchronization therapy on RR.

As indicated by other investigators, the definition of etiology is important because of its effect on therapy and prognosis. Due

LBBB = left bundle branch block

to multiple possible etiologies and the small number of patients, most items could be studied only with an explorative univariate analysis [Table 1]. Familial/genetic cardiomyopathy constitutes about 30% of unselected DCM. In our study ~ 20% had familial DCM based on clinical criteria and limited representation of only one person per family. Familial DCM, a chronic deleterious process, caused by an encoded defect in a protein function, was associated with a low likelihood of recovering function. 'Familial cardiomyopathy' emerged as a significant univariate predictor and could replace 'Disease duration' in multivariate analysis. Since familial DCM presents earlier than non-familial cases, admixture of familial cases possibly accounts for the absence of a beneficial effect of young age on RR. However, even among familial DCM, drugs are effective and some patients improve. A recent study examined the efficacy of the drug carvedilol on early familial DCM. While no difference was found after 6 months, there was a trend towards a decrease in the LV dimensions after 40 months of therapy [20].

DCM defined as peripartum cardiomyopathy or in association with pregnancy is associated with better prognosis [10] [Table 1]. This finding was true even though we excluded those women who experienced acute peripartum stress (hypertensive crisis, sepsis, etc.) which led to acute heart failure associated with a transient decrease in cardiac function [10]. Historically, chemotherapy-induced cardiomyopathy is associated with poor prognosis [8]. In our study, a considerable proportion of these patients improved their LVEF and some even underwent reverse remodeling. Most of our patients had a late-onset variant, which was precipitated by comorbidity, e.g., hypertension. These findings concur with other reports suggesting that early diagnosis and contemporary treatments may change the natural history of chemotherapy-induced cardiomyopathy [21,22].

Coronary artery disease was ruled out as a primary cause of cardiomyopathy by catheterization or non-invasive imaging. Some patients in this cohort (which included many aged individuals) had a coexistent CAD that complicated a non-ischemic DCM. Univariate analysis clearly indicated that a coexistent CAD impairs the capacity of DCM therapy to improve function.

This study was not designed to compare the pharmacological therapies as all patients were treated according to the guidelines. Therefore, about 80–86% were treated with a beta-blocker and 84–90% with an ACE inhibitor or ARB. Yet, we found that a higher beta-blocker dose predicted improvement of LVEF. The dose of renin-angiotensin-aldosterone system inhibitors appeared to be unrelated to outcome [Table 2]. These findings are in agreement with the literature and reinforce the recommendation to seek the maximal tolerated dose of beta-blockers [23].

An exploratory analysis of various drug therapies led to two significant observations [Table 2]. Dihydropyridine calcium-channel blockers were positively associated, while allopurinol was negatively associated with RR. The use of calcium-channel blockers may indicate treatment for hypertension – a potentially reversible aggravating factor in DCM. In contrast, allopurinol is usually given to patients with high uric acid levels, known to be an adverse prognostic factor in heart failure [24].

Our results reiterate the functional and prognostic importance of achieving RR in DCM [11,12,17]. Figure 1 depicts the improvement of NYHA class in patients with RR as compared with a neutral effect of time in 'no-RR'. The short-term outcome data over a follow-up of approximately 2 years also support a dramatic advantage in the RR group. Interestingly, the survival and functional benefits were as pronounced even when using a less stringent criterion for remodeling, i.e., ≥ 10% improvement in LVEF. The rather low mortality in stable DCM patients and the remarkably good short-term prognosis in those with improved LVEF strongly support the policy to delay invasive interventions in order to give the heart an opportunity to recover [25].

STUDY LIMITATIONS

This was an observational clinical study that lacked stringent inclusion and follow-up criteria and an echocardiographic core lab. There is an inherent difficulty to define the disease duration in DCM. Levels of brain natriuretic peptide, magnetic resonance data and LV volumes were not available in most of the patients. Genetic diagnosis was established only in a few, and endomyocardial biopsies are not routinely performed in our institution. Nearly 20% of the original cohort had to be excluded because they discontinued follow-up; their outcome could be worse because of non-compliance or progressive disease. We believe that our results need to be validated in a prospective study with a long-term follow-up since the phenomenon of fluctuations in LV function is well known in DCM. A set of criteria to predict reverse remodeling needs to be established and is expected to have an immense clinical and economic impact in this disease.

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Correspondence

Dr. M. Arad

Heart Institute & Heart Failure Service, Sheba Medical Center, Tel Hashomer, 52621, Israel

Phone: (972-3) 530-4560

Fax: (972-3) 530-4540

email: michael.arad@sheba.health.gov.il

CAD = coronary artery disease

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