Left Ventricular Reverse Remodeling in Recent Onset Idiopathic Dilated Cardiomyopathy Using Contemporary Echo Techniques

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ABSTRACT: **Background:** Early identification of patients with a likelihood of cardiac improvement has important implications for management strategies.

Objectives: To evaluate whether tissue Doppler imaging (TDI) and two-dimensional (2D) strain measures may predict left ventricular (LV) improvement in patients with recent onset dilated cardiomyopathy (ROCM).

Methods: Clinical and comprehensive echo were performed at baseline and at 6 months. Patients who achieved an increase of ≥ 10 LV ejection fraction (LVEF) units and LV reverse remodeling (LVRR) (group 1) and those who improved beyond the device threshold achieving LVEF of ≥ 0.40 (group 2) were compared to patients who did not improve to this level.

Results: Among 37 patients with ROCM (mean age 56.3 ± 12.9 years and LVEF 29.1 ± 7.0%), 48% achieved LVEF ≥ 0.40 and 37.8% demonstrated LVRR. Patients with LVEF improvement ≥ 40% presented at diagnosis with higher LVEF ($P = 0.006$), smaller LV end-diastolic diameter (LVEDd) ($P = 0.04$), higher E' septal ($P = 0.02$), lower E/E' ratio ($P = 0.02$), increased circumferential strain ($P = 0.04$), and apical rotation ($P = 0.009$). Apical rotation and LVEDd were found to be independent predictors of LVRR. End-systolic LV volume was a significant predictor of LVEF improvement (≥ 40%).

Conclusions: Nearly half of the patients with ROCM demonstrated cardiac function improvement beyond the device threshold by 6 months. Apical rotation was introduced in our study as 2D strain prognostic parameter and found to be an independent predictor of LVRR. LV size and volume were predictors of LV improvement.

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KEY WORDS: cardiomyopathy, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDd), left ventricular reverse remodeling (LVRR), recent onset nonischemic cardiomyopathy (ROCM)

Idiopathic dilated cardiomyopathy is a common cause of heart failure in young people [1] and remains the most widespread cause for heart transplantation [2,3]. Despite significant morbidity and mortality, current medical therapy has led to improvement in survival in this patient population [2]. Restoration of left ventricle (LV) function has been reported in a significant number of patients with recent onset nonischemic cardiomyopathy (ROCM), which is defined as development of symptoms within 6 months [4]. Although inflammatory pathogenesis of this disease was suspected, immune modulatory therapy has been introduced with no success [5]. In most studies, marked improvement of LV function has been observed. With the natural history of dilated cardiomyopathy with contemporary therapies, the so-called LV reverse remodeling (LVRR), and even recovery, may be anticipated in most cases. Early identification of patients with a high likelihood of LVRR may have important implications on the management strategies and can possibly alter prognosis by avoiding early unnecessary interventions (i.e., implantable cardioverter-defibrillator/cardiac resynchronization therapy or heart transplantation). Previous studies have found several clinical and echocardiographic predictors of LVRR in patients with ROCM [5-7]. Recently, tissue Doppler imaging (TDI) and two-dimensional (2D) strain were introduced as more sensitive techniques to assess changes in cardiac function [8,9]. In our study, we evaluated the prognostic value of clinical and echocardiographic measures using contemporary echo techniques such as TDI and 2D strain to predict LV function improvement in patients with ROCM.

PATIENTS AND METHODS

PATIENTS

Of 450 patients treated and followed in our outpatient heart failure clinic, 51 were defined as having ROCM, LVEF < 0.40 by echocardiography, and symptoms of < 6 months in duration. Patients were excluded if they presented with other coronary artery diseases (excluded by coronary angiography), valvular diseases, and/or disorders including suspected myocarditis, tachycardia, post-chemotherapy cardiac issues, peripartum cardiomyopathies, and other systemic disorders with associated dilated cardiomyopathy. In total, 37 patients with ROCM in sinus, on optimal medical treatment who did not receive CRT

and had optimal imaging quality underwent comprehensive echocardiographic assessment at presentation and at 6 months follow-up.

ECHOCARDIOGRAPHY

Conventional echo and Doppler analysis

LV dimensions and LVEF by biplane (Simpson's rule) were measured according to the recent American Society of Echocardiography recommendations, including assessment by conventional and tissue Doppler imaging [10]. Raw data was stored digitally as DICOM cine loops and transferred for offline analysis to a workstation with the EchoPAC Clinical Workstation Software (PC dimension version 5.0.1, GE Vingmed Ultrasound, Horten, Norway).

Speckle-tracking strain analysis

For 2D speckle tracking, the LV myocardium was imaged with a frame rate > 50 Hz. Measurements of 2D strain (S) and strain rate (SR) were performed by offline semiautomatic analysis. The endocardial border was semi-manually traced, and a myocardial region of interest was then automatically identified by the software package. S and SR were measured in the parasternal short-axis views at the papillary muscle level to determine circumferential and radial S and SR, and in the three apical views (which were then averaged) to determine longitudinal S and SR. Myocardial rotation in the parasternal short-axis view was measured at the mitral valve and apical levels. The protocol was approved by the human research institutional review board.

STATISTICAL ANALYSIS

Univariate analysis compared patients who achieved an increase in LVEF of ≥ 40% to patients who did not improve to this magnitude. In addition, patients with LVRR (≥ 10 LVEF units) were compared to those without LVRR at 6 months follow-up. Chi-square tests for categorical variables and *t*-tests for continuous variables were used to evaluate associations between each variable and LVEF improvement. The following echo variables ($P < 0.05$) were retained for further examination in a multivariable model: LVEF, LV end-diastolic diameter (LVEDd), LV end-systolic volume (LVESV), E/E', apical rotation, and circumferential strain. A backward stepwise approach was used to identify the best predictive model of LVEF improvement. Logistic regression methods were used to model the outcome LV function improvement by the predictor variables. $P < 0.05$ was considered statistically significant.

Table 1. Comparison of baseline clinical characteristics between patients with and without left ventricular function improvement

	All	LVEF ≥ 40	LVEF < 40	*P* value	Change in LVEF ≥ 10	Change in LVEF < 10	*P* value
Age, years	56.3 ± 12.9	57.3 ± 11.7	55.3 ± 14.2	0.64	57.8 ± 11.4	54.9 ± 13.7	0.38
Female (%)	8 (21)	4 (22)	4 (21)	1.00	3 (21)	5 (21)	1.00
Smoking (%)	12 (32)	4 (22)	8 (42)	0.20	4 (29)	8 (35)	1.00
Hypertension (%)	17 (45.9)	10 (56)	7 (37)	0.25	8 (57)	9 (31)	0.29
Diabetes mellitus (%)	7 (18.9)	3 (17)	4 (21)	1.00	2 (14)	5 (22)	0.69
Hyperlipidemia (%)	22 (60)	11 (61)	11 (58)	0.84	9 (64)	13 (57)	0.64
NYHA 3–4 (%)	14 (37.8)	4 (22)	10 (53)	0.06	2 (14)	12 (52)	0.02
LBBB (%)	10 (27)	2 (11)	8 (42)	0.06	1 (7)	9 (39)	0.06
Mean blood pressure, mmHg	94 ± 16	100 ± 19	90 ± 14	0.08	98 ± 16	93 ± 16	0.34
Heart rate, beats per minute	82 ± 13	86 ± 14	79 ± 12	0.08	85 ± 15	81 ± 13	0.42

LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association functional class

RESULTS

This study was comprised of 37 patients with ROCM. The mean age was 56.3 ± 12.9 years, 8 (21.6%) were females, 17 (45.9%) had hypertension, and 7 (18.9%) were diagnosed with diabetes. Fourteen patients (37.8%) were in New York Heart Association (NYHA) class 3–4 at presentation and 10 (27%) had left bundle branch block (LBBB) on the electrocardiogram. All but two were in sinus rhythm. All patients received maximal treatment for heart failure: 94% were taking angiotensin-converting enzyme inhibitor/angiotensin receptor blockers ACEI/ARB, 100% received beta-blockers, 62% took spironolactone, and 81% were treated with furosemide. Eighteen patients (48%) achieved LVEF ≥ 40% and 52% remained with LVEF < 40% at 6 months follow-up. No significant differences were seen in the two groups in terms of age, gender, prevalence of hypertension, and diabetes diagnosis [Table 1].

However, patients who achieved LVEF ≥ 40% had a trend toward lower prevalence of LBBB (11% vs. 42%, $P = 0.06$) and lower prevalence of NYHA class 3–4 (22% vs. 53%, $P = 0.06$). In addition, they had significantly smaller LV end-diastolic diameter (LVEDd) (52.3 ± 6.9 mm vs. 59 ± 8 mm, $P = 00.4$), smaller LVED (148.6 ± 44.2 vs. 194.2 ± 57.7, $P = 0.01$), and lower LVES volumes (105.1 ± 32.2 vs. 152.1 ± 50.5, $P = 0.003$) [Table 2].

On TDI, the patients with LVEF ≥ 40% had higher early velocities E' septal ratio (7.5 ± 2.2 vs. 5.6 ± 1.2, $P = 0.02$), with significantly lower E/E' septal ratio (11.0 ± 4.7 vs. 15.6 ± 9.7, $P = 0.02$) representing higher LV filling pressures. When analyzing 2D strain parameters [Table 3] there were no significant differences in global LV longitudinal strain, but better early diastolic SR (0.8 ± 0.3 vs. 0.6 ± 0.2 1/sec, $P = 0.03$) was obtained in patients who achieved LVEF of ≥ 40%. There was a trend toward better circumferential strain at papillary muscle level (-9.3 ± 3.8 vs. -6.9 ± 2.7%, $P = 0.04$) and radial strain (22.9 ± 12.1 vs. 14.2 ± 8.9, $P = 0.05$) [Figure 1], in addition to significantly higher systolic SR (-0.6 ± 0.2 vs. -0.4 ± 0.2, $P = 0.003$). Moreover, differences in early diastolic SR (0.7 ± 0.4 vs. 0.5 ± 0.2, $P = 0.02$) and apical rotation (0.2 ± 3.3 vs. -2.0 ± 2.9, $P = 0.01$)

were shown in the two groups. On multivariate analysis LVES volumes were found to be predictors of LV improvement for LVEF ≥ 40% (odds ratio [OR] 0.88, 95% confidence interval [95%CI] 0.80–0.98, $P = 0.02$).

Fourteen patients (37.8%) showed LVRR. There was a lower prevalence of patients with NYHA 3–4) (14% vs. 52%, $P = 0.02$) and a trend for lower prevalence of LBBB (7% vs. 9%, $P = 0.06$). On echo significantly smaller LVEDd (50.9 ± 7.3 vs. 59.4 ± 7.3 mm, $P = 0.001$) was obtained in patients with LVRR [Table 2]. The longitudinal strain was low in all patients, but there was a significant difference in mean rotation at the apical level (3.4 ± 2.8 vs. -0.2 ± 3.9, $P = 0.009$) in the two groups by 2D strain [Table 3]; 79% of patients with LVRR showed counter-clockwise rotation compared to 56% of those without LVRR. On multivariate analysis LVEDd (OR 0.9, 95%CI 0.76–0.96, $P = 0.007$) and apical rotation (OR 1.47, 95%CI 1.08–2.00, $P = 0.01$) were significant predictors for LVRR. The determined cutoff value by ROC curve analysis was LVEDd of 59 mm with an area under curve of 0.8.

DISCUSSION

We evaluated the prognostic value of clinical and echocardiographic measures using, for the first time (to the best of our knowledge), TDI and 2D strain techniques to predict LV function improvement in patients with ROCM. Our main study findings were: reverse remodeling was obtained in 38% of patients with ROCM, and almost half of the patients achieved LVEF of ≥ 40%. Patients with LV improvement had lower prevalence of LBBB and better function class at presentation as well as smaller LV size and volume. Lower LV filling pressures by TDI and better circumferential and apical rotation by 2D strain were associated with LV function improvement in patients with ROCM at 6 months follow-up.

LV IMPROVEMENT AND REVERSE REMODELING RATES

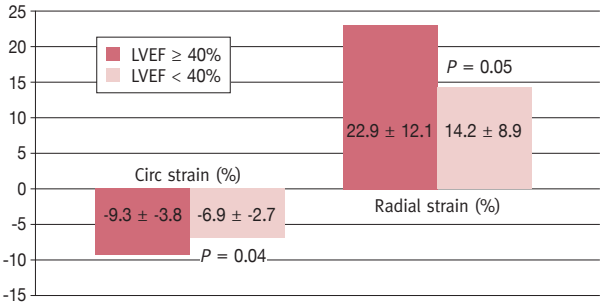
In our study LVRR was defined as LVEF increase of ≥ 10 units. LVRR was obtained in 37.8% patients and almost half of all patients achieved LVEF of ≥ 40%, namely recovered beyond

Table 2. Comparison of baseline echocardiographic measures between patients with and without left ventricular function improvement

	All	LVEF ≥ 40	LVEF < 40	*P* value	Change in LVEF ≥ 10	Change in LVEF < 10	*P* value
EF (%)	29.1 ± 7	32.2 ± 6.0	26.1 ± 6.7	0.006	29.3 ± 7.1	29.0 ± 7.1	0.89
LVEDd, mm	56.2 ± 8.3	52.3 ± 6.9	59 ± 8	0.004	50.9 ± 7.3	59.4 ± 7.3	0.001
IVS, mm	10.3 ± 3.7	11.4 ± 4.5	9.3 ± 2.6	0.09	11.9 ± 4.5	9.4 ± 2.9	0.05
LVED volume, ml	172.0 ± 55.9	148.6 ± 44.2	194.2 ± 57.7	0.01	152 ± 46.8	184.2 ± 58.4	0.09
LVES volume, ml	129.3 ± 48.2	105.1 ± 32.2	152.1 ± 50.5	0.003	114.1 ± 35.7	138.3 ± 53.1	0.15
LA area, cm^2	41.2 ± 7.9	39.8 ± 7.7	42.7 ± 8.1	0.28	40.9 ± 7.8	41.4 ± 8.2	0.86
PHT, mmHg	37.2 ± 14	40 ± 15	34.6 ± 13	0.25	41.1 ± 12.4	34.9 ± 14.8	0.20
E', cm/sec	77.5 ± 3.3	77.4 ± 22.7	77.5 ± 36.5	0.99	77.6 ± 20.5	77.4 ± 35.1	0.99
A, cm/sec	54.9 ± 21.9	54.4 ± 21.5	55.2 ± 22.8	0.93	49.0 ± 20.8	57.6 ± 22.4	0.34
E/A	1.7 ± 0.9	1.53 ± 0.9	1.8 ± 0.95	0.52	1.8 ± 1.1	1.6 ± 0.8	0.53
DT, sec	161.8 ± 56.7	174.9 ± 51.6	151.8 ± 59.8	0.27	168.4. ± 51.0	159.0 ± 59.9	0.68
E' septal (cm/sec)	6.4 ± 1.9	7.5 ± 2.2	5.6 ± 1.2	0.02	6.6 ± 2.4	6.3 ± 1.8	0.67
E/E' septal ratio	13.5 ± 7.7	11.0 ± 4.7	15.6 ± 9.7	0.02	13.7 ± 9.8	13.9 ± 7.9	0.96

LV = left ventricular, LVEDd = LV end-diastolic diameter, IVS = interventricular septum, LA = left atrium, LVEF = left ventricular ejection fraction, PHT = pulmonary hypertension, E = early transmitral flow velocity, A = late transmitral flow velocity, E' = early diastolic tissue Doppler velocity of septal corner of mitral annulus

Figure 1. Differences in baseline circumferential and radial strain between patients with LVEF improvement beyond 40% and those who did not improve to this magnitude



Circ Strain = circumferential strain, LVEF= left ventricular ejection fraction

Table 3. Comparison of baseline two-dimensional strain indexes between patients with and without left ventricular function improvement

	All	LVEF ≥ 40	LVEF < 40	*P* value	Change in LVEF ≥ 10	Change in LVEF < 10	*P* value
Longitudinal strain							
LGS%	-9.4 ± 3.5	-9.7 ± 3.9	-9.1 ± 3.2	0.59	-9.1 ± 3.4	-9.6 ± 3.6	0.68
Circumferential strain							
Circ GS% (apex)	-8.9 ± 4.1	-10.0 ± 4.2	-7.8 ± 3.8	0.14	-8.9 ± 4.9	-8.8 ± 3.6	0.95
Rotation (apex) (degree)	1.2 ± 3.9	2.9 ± 3.0	-0.4 ± 4.0	0.01	3.4 ± 2.8	-0.2 ± 3.9	0.009
CircGS% (PM)	-8.2 ± 3.5	-9.3 ± 3.8	-6.9 ± 2.7	0.04	-8.8 ± 4.0	-7.8 ± 3.2	0.44
CircGS% (base)	-8.2 ± 3.5	-7.3 ± 3.7	-6.7 ± 2.1	0.56	-6.0 ± 3.5	-7.3 ± 2.8	0.52
Rotation (base) (degree)	-0.9 ± 3.3	-2.3 ± 3.2	-2.9 ± 2.6	0.60	-1.8 ± 2.9	-3.1 ± 2.9	0.17
Radial strain (%)	18.9 ± 11.4	22.9 ± 12.1	14.2 ± 8.9	0.05	19.8 ± 10.9	18.1 ± 12.1	0.71

GS = global strain, SR = strain rate, LGS = longitudinal GS, CircGS = circumferential global strain, PM = papillary muscle level

the device threshold at 6 months follow-up. This high rate of cardiac function improvement is consistent with previously published data. In the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC-1) study [4], high LVRR rates (50%) were described. The IMAC-2 trial [5] reported even higher LVRR rates of up to 70% at 6 months follow-up, while 40% of all patients achieved LVEF ≥ 45%. In the IMAC-1 and IMAC-2 trials, the definitions of LVRR and patient treatment were similar to those in our study. However McNamara and colleagues [4] did not exclude women with postpartum cardiomyopathy, which are known for their relatively higher likelihood for improvement [11]. In fact these patients comprised 10% of that study population (IMAC-2) and the group of patients showed significantly higher recovery rates and magnitude compared to women with non-peripartum cardiomyopathy and men with ROCM [12]. This may explain the higher rates of LVRR reported compared to those reported in our results. Recently, Kubanek and co-authors [6] described LVRR rates of 45%, similar to those reported in our study, but at longer a follow-up of 12 months. It is important to note that the reports that were published before the use of beta-blockers, ACEI/ARB, and spironolactone mentioned lower rates of myocardial recovery, suggesting that that reversibility of myocardial dysfunction in this entity at least partially relies on pharmacological therapy [13].

CLINICAL PREDICTORS OF LVEF IMPROVEMENTS

Patients who experienced LV improvement (LVEF ≥ 40%) and LVRR in our study had lower prevalence of LBBB and a clear trend toward lower prevalence of NYHA class 3–4. Supporting our findings, Merlo et al. [2] showed that absence of LBBB is an independent predictor of LVRR. They also found that NYHA class 4 was associated with poorer survival. Furthermore, McNamara's group [4] showed that NYHA functional class 3–4 was associated with lower LVEF at 6 months and with a significantly higher risk of death or heart transplantation at 4 years of follow-up [4].

ECHOCARDIOGRAPHIC PREDICTORS OF LV FUNCTION IMPROVEMENT

Previous studies mentioned smaller LVEDd, higher baseline LVEF, less severe MR, and smaller left atrial dimensions as predictors of the LVRR [4,6,7]. Other studies demonstrated an association between greater LVEDd and lower rates of LVRR [7,14]. In the IMAC-2 study, smaller LVEDd at baseline was associated with higher LVEF at 6 months follow-up [4]. In patients on left-ventricular assist-device (LVAD), LV recovery occurred in 33% among patients with LVEDd < 6 cm versus 12% overall recovery rate [7]. Other studies showed lower LVEDd in patients with successful weaning from LVAD compared to those who failed to be weaned [14]. Consistent with previous studies, our patients who achieved LVEF > 40% tended to have smaller LV size and both LV end systolic and diastolic volumes. On multivariate analysis the LV size was found to be the independent predictor for LVRR and LVES volume for achieving of LVEF > 40%.

TDI AND 2 DIMENSIONAL STRAIN ECHOCARDIOGRAPHIC FINDINGS AS PREDICTORS

During the last decade, tissue Doppler imaging parameters of diastolic function have been shown to be relatively independent of changes in ventricular loading conditions and to have a good correlation with invasive hemodynamic measurements [8,15]. The recently developed 2D strain technique, which is based on speckle tracking, also provides information on multidimensional myocardial mechanics including data on longitudinal, circumferential myocardial deformation [9]. Such indexes, known as deformation indexes, are now recognized to be much more sensitive to assess changes in LV function, which cannot be detected by standard echocardiography. Using TDI, we found that patients with higher early velocities (E' septal) and lower E/E' ratio at baseline, which represented higher LV filling pressures, had higher likelihood of achieving LVEF > 40% at 6 months.

Implementation of 2D strain technique was used in our study to evaluate LV improvement in patients with ROCM. Longitudinal strain was uniformly low in all patients, but better longitudinal early and late strain rates were obtained in those with cardiac function improvement. Moreover, higher circumferential strain at papillary muscle level, and especially apical rotation as a compensatory mechanism in patients with ROCM, were associated with the ability to improve the LVEF > 40%. The normal function of the LV apex contributes to cardiac performance. The 2D strain technique has recently been proposed as a validated method for measuring rotation. Recently, good correlation of LVEF with apical, but not basal rotation, has been demonstrated in normal patients [16]. Augmentation of apical strain and rotation has been recently shown to be correlated with lack of symptoms in hypertrophic cardiomyopathy, as well as with better LV functional reserve in normal subjects [17]. Recently, increased apical rotation as a compensatory mechanism was observed in patients with severe aortic stenosis and LV dysfunction, who showed increased LVEF after aortic valve replacement [18].

CONCLUSIONS

In this study we found apical rotation to be a significant prognostic parameter of LVRR suggesting that not only LV dimensions and volumes are associated with improvement of LV performance.

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Capsule

Dendritic cells give mast cells a nudge

Anaphylaxis is a life-threatening allergic reaction triggered after antigen-specific immunoglobulin E (IgE) antibodies bind to target allergens. These antibodies then cross-link IgE-specific Fc receptors on the surface of mast cells. The mast cells rapidly release inflammatory mediators, including histamine, resulting in smooth muscle contraction, vasodilation, and blood vessel leakage. Because mast cells are usually found in the perivascular abluminal surface of blood vessels, it has been unclear how blood-borne allergens can interact with them. **Choi** et al. used live intravital imaging of the mouse vasculature to show that a specialized subset of dendritic cells sample blood-borne antigens and relay them to mast cells on the surface of microvesicles. IgE-bound mast cells then vigorously degranulate after contact with these microvesicles.

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Capsule

Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys

The latent viral reservoir is the critical barrier for the development of a cure for HIV-1 infection. Previous studies have shown direct antiviral activity of potent HIV-1 Env-specific broadly neutralizing antibodies (bNAbs) administered when antiretroviral therapy (ART) was discontinued, but it remains unclear whether bNAbs can target the viral reservoir during ART. **Borducci** and colleagues showed that administration of the V3 glycan-dependent bNAb PGT121 together with the Toll-like receptor 7 (TLR7) agonist vesatolimod (GS-9620) during ART delayed viral rebound following discontinuation of ART in simian–human immunodeficiency virus (SHIV)-SF162P3-infected rhesus monkeys in which ART was initiated during early acute infection. Moreover, in the subset of monkeys that were treated with both PGT121 and GS-9620 and that did not show viral rebound after discontinuation of ART, adoptive transfer studies and CD8-depletion studies also did not reveal the virus. These data demonstrate the potential of bNAb administration together with innate immune stimulation as a possible strategy for targeting the viral reservoir.

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