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Left Ventricular Architecture, Long-Term Reverse Remodeling, and Clinical Outcome in Mild Heart Failure With Cardiac Resynchronization

Results From the REVERSE Trial

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ABSTRACT

OBJECTIVES This study sought to determine the effects of abnormal left ventricular (LV) architecture on cardiac remodeling and clinical outcomes in mild heart failure (HF).

BACKGROUND Cardiac resynchronization therapy (CRT) is an established treatment for HF that improves survival in part by favorably remodeling LV architecture. LV shape is a dynamic component of LV architecture on which contractile function depends.

METHODS Transthoracic 2-dimensional echocardiography was used to quantify changes in LV architecture over 5 years of follow-up of patients with mild HF from the REVERSE study. REVERSE was a prospective study of patients with large hearts (LV end-diastolic dimension ≥55 mm), LV ejection fraction <40%, and QRS duration >120 ms randomly assigned to CRT-ON (n = 419) and CRT-OFF (n = 191). CRT-OFF patients were excluded from this analysis. LV dimensions, volumes, mass index, and LV ejection fraction were calculated. LV architecture was assessed using the sphericity index, as follows: (LV end-diastolic volume)/$(4/3 \times \pi \times r^3) \times 100\%$.

RESULTS LV architecture improved over time and demonstrated significant associations between LV shape, age, sex, and echocardiography metrics. Changes in LV architecture were strongly correlated with changes in LV end-systolic volume index and LV end-diastolic volume index (both $p < 0.0001$). Sphericity index emerged as a predictor of death and HF hospitalization in spite of the low adverse event rate. A decrease in LV end-systolic volume index >15% occurred in more than two-thirds of patients, which indicates considerable reverse remodeling.

CONCLUSIONS We demonstrated that change in LV architecture in patients with mild HF with CRT is associated with structural and functional remodeling. Mean LV filling pressure was elevated, and the inability to lower it was an additional predictor of HF hospitalization or death. (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction [REVERSE]; NCT00271154) (J Am Coll Cardiol HF 2017;5:169–78) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

HF = heart failure

IVMD = intraventricular mechanical delay

LBBB = left bundle branch block

LVEDV = left ventricular end-diastolic volume

LVEDVI = left ventricular end-diastolic volume index

LVESV = left ventricular end-systolic volume

LVESVI = left ventricular end-systolic volume index

MR = mitral regurgitation

NYHA = New York Heart Association

TTE = transthoracic echocardiogram

Cardiac resynchronization therapy (CRT) is an established treatment for patients with New York Heart Association (NYHA) symptom class I to IV heart failure (HF), reduced left ventricular ejection fraction (LVEF) (<40%), and prolonged QRS duration (>120 ms), as shown in several randomized trials (1-7). CRT prolongs survival, alleviates symptoms, and improves exercise capacity (1). These beneficial effects of CRT are mediated by attenuation of disease progression and by left ventricular (LV) reverse remodeling. LV remodeling results in progressive LV dilation, abnormal LV architecture, increased LV filling pressure, intraventricular mechanical delay (IVMD), and deterioration in LV function, all factors that portend a poor clinical outcome. By contrast, reverse LV remodeling is associated with decreased LV volume, restoration of near-normal LV shape, decreased LV filling pressures, decreased IVMD, increased LVEF, and a more favorable long-term outcome. Currently, there is a paucity of information regarding the effects of abnormal LV architecture and myocardial ischemia on LV remodeling, and there is controversy as to whether it is associated with abnormal hemodynamics (8,9) or with clinical endpoints in HF with reduced ejection fraction (HFrEF).

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We studied 419 patients with HFrEF from the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial (10), a large, randomized, prospective study of CRT in mild HFrEF (NYHA functional class I/II) designed to determine whether CRT limited disease progression in HFrEF compared with optimal medical therapy without CRT, as well as how long these beneficial effects lasted. This large dataset allowed exploration and serial measurements of pre-defined key echocardiographic parameters involved in the remodeling process.

Our specific aims were: 1) to test the hypothesis that abnormal LV architecture provides important new biological information regarding the timing and amplitude of LV structural and functional remodeling with long-term CRT (5 years); and 2) to determine whether abnormal LV architecture, LV filling pressure (E/e′), mitral regurgitation, or left atrial (LA) size predicts clinical outcomes in patients with HFrEF.

METHODS

STUDY POPULATION. Inclusion and exclusion criteria for patient recruitment in REVERSE have been published previously (10,11) but in brief were NYHA symptom class I/II (mild) HFrEF, QRS duration ≥120 ms, left ventricular end-diastolic diameter (LVEDD) ≥55 mm, and LVEF ≤40%. The ethics committee at each investigator site approved the protocol, and all patients provided written informed consent. Almost all patients (>95%) were receiving optimal medical therapy for HF (10). Patients were implanted with a CRT device with defibrillator capabilities (CRT-D), if interventional electrophysiological treatment was indicated, or without defibrillator capabilities (CRT-P). Patients were then randomized 2:1, CRT-ON to CRT-OFF.

There were a total of 610 subjects randomized, 419 of whom were assigned to CRT-ON. Only the CRT-ON subjects are included in this analysis, and almost all had 5 years of CRT-ON. We calculated the predictive values of abnormal LV architecture, left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), LVEF, and LA size for detecting adverse events and poor outcome.

FOLLOW-UP. All patients were evaluated at baseline and every 6 months during the randomization period. Patients had assessments of NYHA symptom class, 6-min hall walk, quality of life, and a transthoracic echocardiogram (TTE) at each clinic visit. Patients continued to have an annual clinical assessment with a TTE at each follow-up visit from 2 through 5 years (12).

DEFINITIONS AND CLINICAL ENDPOINTS. The primary endpoint in REVERSE was the HF clinical composite response (13), which included total mortality, and HF hospitalization, which were adjudicated by an independent endpoints committee unaware of CRT programming during the randomized phase of the study. The second powered endpoint was LV remodeling, assessed as change in LVESVI >15%.

TTEs were analyzed in an echocardiography core laboratory to obtain LVEDD, LV end-systolic dimension, and fractional LV shortening: LVEDD − LV end-systolic dimension / LVEDD × 100%. LV volume indices were calculated (LVEDVI and LVESVI) using Simpson's method of discs as recommended by the American Society of Echocardiography (14), and from these volumes, LVEF was calculated as follows:

$$\text{LVEF} = (\text{LVEDV} - \text{LVESV}) / \text{LVEDV} \times 100\%$$

where LVEDV is LV end-diastolic volume and LVESV is LV end-systolic volume. LV mass was estimated at end diastole and indexed to body surface area:

$$5/6 \times \text{LV short-axis muscle area} \times 0.5 \times \text{LV cavity length} \times 1.055$$

where 1.055 is the density of the myocardium (15).

Abnormal LV architecture was expressed as a sphericity index on the basis of LV shape at end diastole (9). The sphericity index was computed as LVEDV estimated from analysis of the 2-dimensional echocardiographic images, divided by the volume of a sphere with the LV long axis as its diameter.

Sphericity index was estimated as:

$$(\text{LVEDV}) / (4/3 \times \pi \times r^3) \times 100\%$$

where $r = 0.5 \times$ LV length at end diastole (9). There is also a simpler formulation for assessing LV architecture is the ratio of long axis diameter to short axis diameter, but the results are difficult to interpret in the presence of regional LV wall motion abnormalities (16).

The presence and severity of mitral regurgitation (MR) were assessed by visual estimation. MR severity was also semiquantified as the average of orthogonal regurgitant mitral valve jet areas indexed to LA size.

Mean LV filling pressures were estimated with the E/e′ ratio. We also assessed whether LV filling pressures interacted with LV reverse remodeling or predicted clinical outcomes, because E/e′ does not possess the discriminatory power to be used alone to assess LV diastolic function (17).

LA size was quantified as the average of the 2 areas of the LA from the apical 2- and 4-chamber views indexed to LA size. Increased LA size has been shown to predict adverse outcomes in patients with advanced HF.

STATISTICAL ANALYSIS. All patients randomized to CRT-ON with available echocardiographic values were included in the analyses. When single time points are reported, all patients with data at that time are included. All patients with paired data are reported in paired data analyses. Linear regression analysis was used to determine significant baseline factors (alpha = 0.10) for change in LV architecture. Although data were dichotomized and put into quartiles for reporting purposes, all p values are on the basis of continuous variables. Generalized linear models were used to test the effect of baseline sphericity index and left bundle branch block (LBBB) on changes in remodeling variables. In graphs showing changes in echocardiography variables over time, years with a significant change ($p < 0.05$) from one year to the next with a paired Student *t* test are denoted by arrows. Multivariable logistic regression was used to find potential baseline factors for predicting which patients would have significant improvements in LVESVI (by ≥15%) with CRT. Candidate variables initially chosen for multivariable analysis were on the basis of clinical knowledge of typical HF factors. Proportional hazards that treated univariate variables as continuous variables were used to test for relation of changes in echocardiography variables to HF hospitalization or death. Multivariable proportional hazards were used to assess independence of the factors found to be significant in univariate analysis. Kaplan-Meier methods were used to estimate rates. SAS software version 9.4 (SAS Institute, Cary, North Carolina) was used for analysis. The intraobserver reproducibility of repeated echocardiographic measurements of LV geometry and function was assessed as described previously (18).

TABLE 1 CONSORT Table Summarizing Randomization and Follow-Up in 419 CRT-ON Patients

Follow-Up	Paired Echo Data	Dead	Exited Study	Follow-Up, No Echo Data	Missing Follow-Up
6 months	353	8	0	55	3
1 yr	344	9	1	62	3
2 yrs	319	15	6	71	8
3 yrs	290	30	14	80	5
4 yrs	270	39	21	68	21
5 yrs	245	52	32	70	20

CONSORT = Consolidated Standards of Reporting Trials; CRT-ON = cardiac resynchronization therapy programmed "on"; Echo = echocardiography.

RESULTS

Of the 610 patients, 419 were randomized to CRT-ON. Average length of follow-up was 54.6 months, and 2.9% of patients terminated CRT permanently because of worsening HF, diaphragmatic pacing, or LV lead dislodgement (12). Follow-up data through

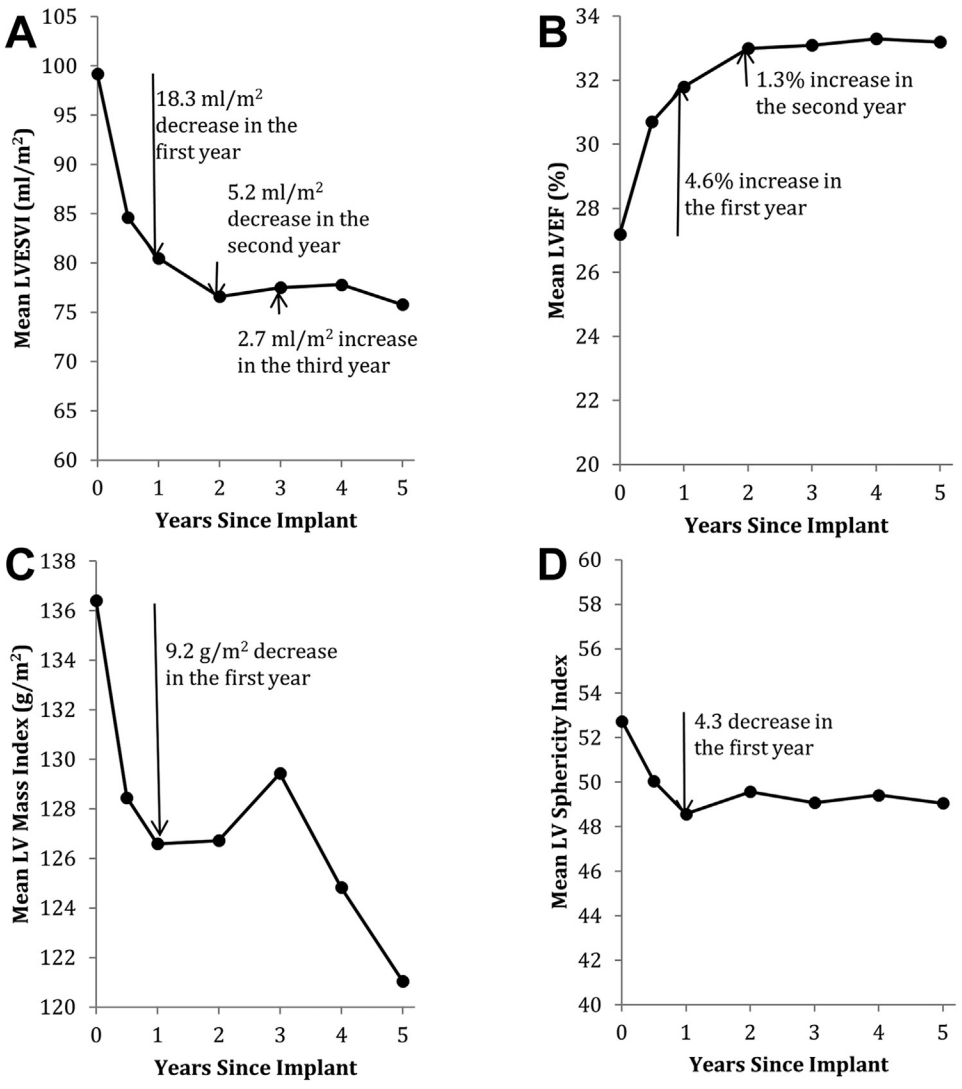
TABLE 2 Baseline Clinical and Echocardiography Characteristics

Age (yrs), n = 419	62.9 ± 10.6
Male, n = 419	78%
QRS duration (ms), n = 419	153 ± 21
Ischemic pathogenesis, n = 419	56%
NYHA functional class II, n = 419	82%
Diabetes, n = 419	22%
LVESD (cm) (M-mode), n = 271	5.7 ± 1.0
LVEDD (cm) (M-mode), n = 271	6.9 ± 0.9
LVEF (%), n = 386	27.2 ± 6.6
Sphericity index, n = 386	52.7 ± 11.7
LV 4-chamber length, diastole (cm), n = 386	9.8 ± 0.9
LV 4-chamber length, systole (cm), n = 386	9.1 ± 1.0
LVESVI (ml/m^2) (2D), n = 386	134.8 ± 40.8
LVEDVI (ml/m^2) (2D), n = 386	99.2 ± 35.0

Values are mean ± SD or %.

2D = 2-dimensional; LV = left ventricular; LVEDD = left ventricular diastolic diameter; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESVI = left ventricular end-systolic volume index; NYHA = New York Heart Association.

FIGURE 1 Echocardiography Values Over Time



(A) Mean LVESVI (in ml/m^2) over time. Arrows show where there was a statistically significant change from one year to the next. **(B)** Mean LVEF (%) over time. Arrows show where there was a statistically significant change from one year to the next. **(C)** Mean LV mass index (in g/m^2) over time. Arrows show where there was a statistically significant change from one year to the next. **(D)** Mean LV architecture over time. Mean LV sphericity index values over time are graphed. Arrow shows where there was a statistically significant change from one year to the next. LV = left ventricular; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index.

5 years are summarized in Table 1, including deaths, exits from the study, and cases for which no follow-up echocardiography was obtained.

At baseline, TTE showed that LV dimensions and volumes were markedly increased (Table 2). The temporal changes in LV volumes, LVEF, and LV mass index for up to 5 years are shown in Figure 1. The greatest reduction in LVESVI with CRT occurred over the first 12 months (mean 18.3 ml/m^2 reduction, $p < 0.0001$). There were further significant reductions in LVESVI over the second year (mean 5.2 ml/m^2, $p < 0.0001$). There was a slight increase in LVESVI during the third year (mean 2.7 ml/m^2, $p = 0.01$), but no significant changes were seen in years 4 and 5. Overall, LVESVI declined by a mean difference of 22.8 ml/m^2 from baseline to 5 years of follow-up. There were similar significant reductions in LVEDVI at all time points (5-year reduction was 25.0 ml/m^2).

Changes in LV volumes induced by CRT were associated with progressive improvement in LV function. LVEF increased by 4.6 units in the first year ($p < 0.0001$), reaching a plateau after gaining 1.3 additional units in the second year ($p = 0.005$). The increases in LVEF were significant at every time point (all $p < 0.0001$) compared with baseline. Mean LVEF increased from 27.2 ± 6.6% to 33.2 ± 12.7% ($p < 0.0001$) over 5 years.

There was a significant reduction in LV mass indexed to body surface area over time, with most of the decrease occurring in the first 6 months.

ABNORMAL LV ARCHITECTURE. In our patients with HFrEF, the LV dilated by increasing its short-axis diameter more than by increasing its LV long-axis diameter. This resulted in the LV becoming progressively more spherical as it dilated. Abnormal LV architecture was associated with a progressive reduction in LVEF. In the present study, the LV sphericity index decreased to its nadir within 1 year of the onset of CRT and did not change thereafter (Figure 1D).

We performed regression analysis of the 5-year change in LV architecture with baseline factors including age, sex, ischemic cardiomyopathy, LVESVI, LVEF, presence of LBBB, QRS duration, and MR. After we eliminated nonsignificant ($p > 0.10$) factors, younger age, female sex, higher baseline LVESVI, and LBBB were associated with a better likelihood of lowering the LV sphericity index (Table 3). Although pathogenesis was not a significant factor in this multivariable analysis, it was a significant univariate predictor of change in LV architecture, with a mean change of −6.2 for patients without, versus −0.4 for patients with, ischemic cardiomyopathy ($p = 0.0006$).

Change in LV sphericity index ($p < 0.0001$) and LBBB ($p < 0.0001$) were associated with change in LVESVI over 5 years (Figure 2A). However, there was no significant interaction between LV sphericity index and LBBB ($p = 0.88$). Patients with a large positive change in LV sphericity index showed less remodeling than patients whose LV sphericity index was reduced. This was not the case for LV mass index (Figure 2B), for which there was no significant effect of change in sphericity index in either non-LBBB or LBBB patients. LVEF showed a trend ($p = 0.07$) toward an association with sphericity index only in non-LBBB patients (Figure 2C).

MITRAL REGURGITATION. Spherical LV cavity shape is frequent in HF and can disrupt the spatial relations of the mitral valve and subvalve apparatus that predisposes patients to developing MR. Thus, MR begets further LV dilation that in turn begets more MR. The severity of MR, assessed by visual inspection and by measuring the regurgitant mitral jet areas indexed to LA area, was small and infrequent at baseline and did not change during the 5-year follow-up (Figure 3A).

TABLE 3 Predictive Baseline Variables for Change in LV Architecture at 5 Years

	Related to Larger Reduction in LV Architecture	Parameter Estimate	SE	p Value
Intercept		4.30508	6.05317	0.48
Age (yrs)	Lower age	0.18767	0.07471	0.01
Sex	Female	−3.45253	1.80812	0.06
LVESVI (ml/m^2)	Higher LVESVI	−0.12984	0.02269	<0.0001
LBBB (yes)	Presence of LBBB	−3.40825	1.67699	0.04

Variables considered for the model were age, sex, pathogenesis, LVESVI, LVEF, LBBB, mitral regurgitation, and QRS duration.

LBBB = left bundle branch block; SE = standard error; other abbreviations as in Table 2.

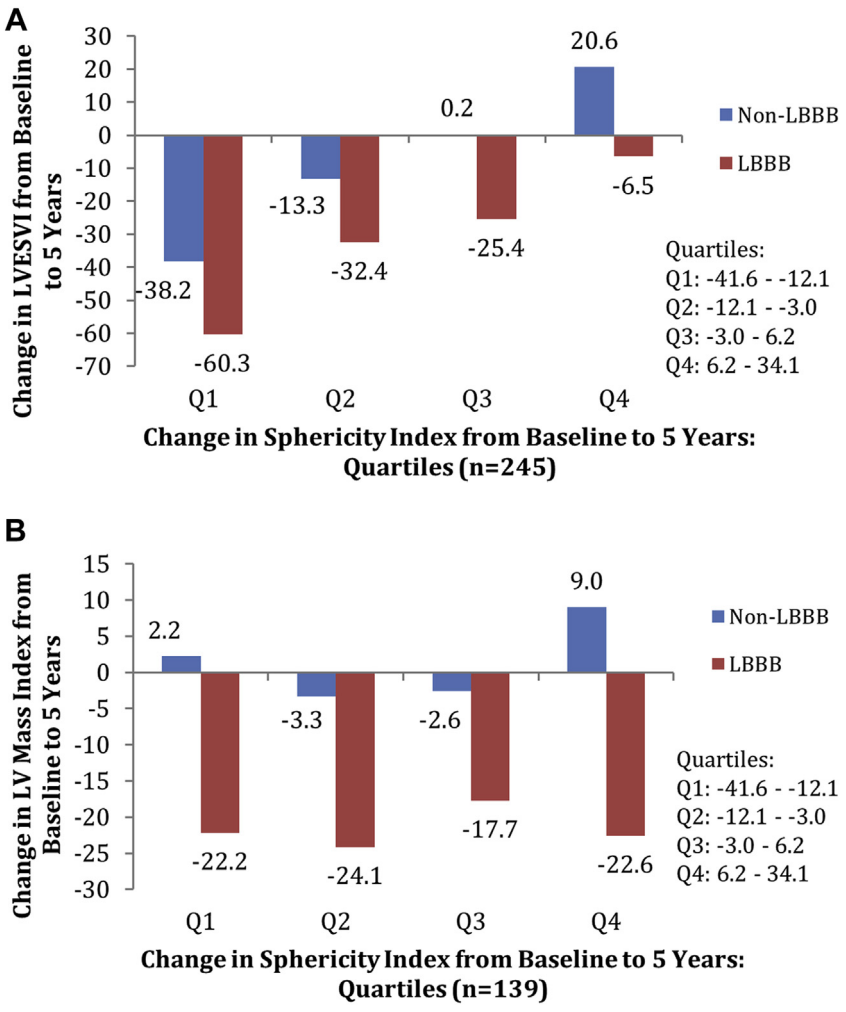
LA SIZE. LA size varied widely over time, although the overall change at 5 years was not significant ($p = 0.95$ in systole; $p = 0.08$ in diastole). Yearly changes were statistically significant in years 1 (decrease; $p < 0.0001$) and 4 (increase; $p = 0.0002$) for LA size in systole (Figure 3B) and in years 1 (decrease; $p < 0.0001$), 2 (increase; $p = 0.005$), 3 (decrease; $p < 0.0001$), and 4 (increase; $p = 0.001$) for LA size in diastole (not shown).

INTRAVENTRICULAR MECHANICAL DELAY. IVMD fell precipitously ($p < 0.0001$) from its baseline value of 33.8 ms once CRT commenced and remained steady over the following 4 years (Figure 3C). This change did not correlate with abnormal LV architecture either after 6 months ($p = 0.61$) or after 5 years ($p = 0.32$). Change in IVMD correlated modestly with change in LVESVI at 5 years ($r = 0.20$; $p = 0.005$) but not at 6 months ($p = 0.44$).

LV FILLING PRESSURES. The ratio of E/e′, which was used as a surrogate measure of mean LV filling pressures, was elevated but remained stable and unchanged over time (Figure 3D).

REGRESSION ANALYSIS. Of 369 patients with evaluable data, 263 (71%) had an improved (reduced) LVESVI by at least 15% from baseline at 1 or more yearly follow-up visits. Using logistic regression analysis, the baseline factors of abnormal LV architecture, age, sex, ischemic cardiomyopathy, LVESVI, LVEF, presence of LBBB, QRS duration, and MR were considered as factors to predict which patients would have significant improvement in LVESVI with CRT. Patients most likely to improve significantly ($p < 0.10$) were females, those without ischemic HF, those with LBBB, and those with less MR at baseline (Table 4).

FIGURE 2 Changes in Sphericity Index



(A) Change in sphericity index versus change in LVESVI. Quartiles of 5-year change in the sphericity index are shown across the x-axis. The y-axis shows the mean change in LVESVI over 5 years. In both patients with and without LBBB, those whose sphericity index was reduced the most had the best mean reductions in LVESVI. **(B)** Change in sphericity index versus change in LV mass index. Quartiles of 5-year change in the sphericity index are shown across the x-axis. The y-axis shows the mean change in LV mass index over 5 years. In both patients with and without LBBB, there was no significant effect of change in sphericity index. **(C)** Change in sphericity index versus change in LVEF. Quartiles of 5-year change in the sphericity index are shown across the x-axis. The y-axis shows the mean change in LVEF over 5 years. In non-LBBB patients, only the lowest quartile of patients (sphericity index ≥ 12.1) showed a mean improvement in LVEF over 5 years. LBBB patients' change in LVEF was similar over the quartiles. LBBB = left bundle branch block; other abbreviations as in Figure 1.

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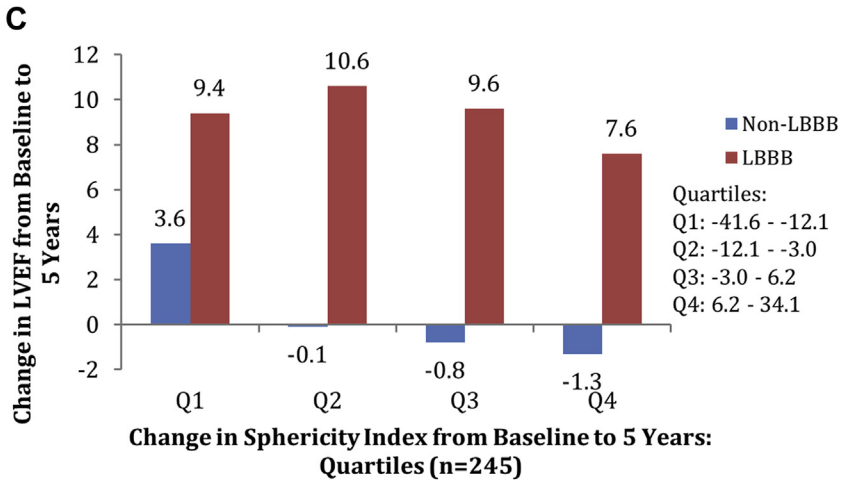
A univariate analysis of the effect of changes in echocardiography variables on the composite endpoint of HF hospitalization plus mortality showed (after CRT) that a decrease in LV sphericity index, a decrease in LVESVI, a decrease in LVEDVI, an increase in LVEF, and a decrease in E/e′ statistically significantly reduced patients' risk (Table 5). Reduction in E/e′ was a strong predictor, because 33.4% of patients whose E/e′ ratio did not decrease by at least 0.18 were hospitalized for HF or died compared with only 17.1% of those who did have a 0.18 or better reduction. In multivariable analysis, E/e′ ratio remained a strong predictor ($p = 0.05$) in a model with the other 4 significant factors.

FIGURE 2 Continued



DISCUSSION

The novel findings of this large echocardiographic study of the REVERSE trial include the definition of abnormal LV architecture as a discrete entity, which is a frequent finding in HF. We used a simple algorithm for computing LV architecture in terms of a sphericity index on the basis of end-diastolic volume that we also used to quantify changes in LV architecture and contractile function. We showed that this sphericity index was closely associated with LV volumes. In addition, increasingly abnormal LV architecture was associated with increasing LV dysfunction and a progressive reduction in LVEF. Although reverse remodeling has been shown to predict outcomes in patients with mild HF who are undergoing CRT (19–21), the impact of abnormal LV architecture on LV reverse remodeling and on pre-defined clinical outcomes is largely unknown but was quantified here over a 5-year follow-up. In our patient cohort, the characteristic progressive changes in LV volumes, LV mass index, and LVEF peaked at 2 years and reached a plateau between 3 and 5 years. In contrast, abnormal LV architecture decreased, with its peak effect occurring 1 year after device implantation. This difference in timing makes a direct cause and effect relationship unlikely. We speculate that the discordance in timing suggests an intermediate regulatory step(s) in the remodeling process. Importantly, when patients were dichotomized by the origin of HF into ischemic versus nonischemic, there was no difference between the 2 groups with regard to the extent of remodeling.

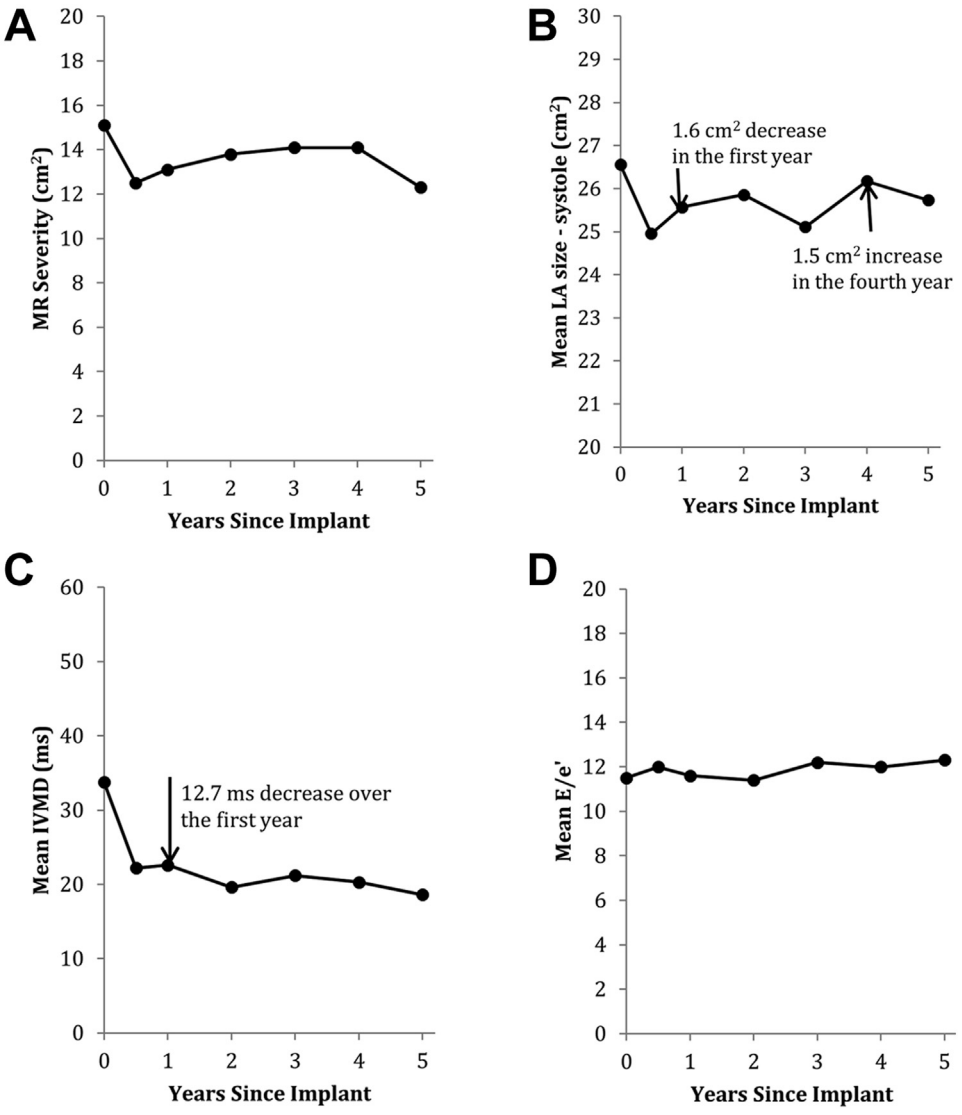
The mechanisms responsible for triggering and then driving LV remodeling in HFrEF are poorly understood. This was evaluated in more detail in the present study by use of a large cohort of patients with mild NYHA functional class I/II HFrEF from the REVERSE trial with pre-defined long-term follow-up. The majority of these patients (71%) benefited symptomatically from extensive LV reverse remodeling The average age of this cohort of patients was 62.9 ± 10.6 years, which implies some elderly patients were included. There was an independent effect of age on change in LV architecture, with older patients less likely to have remodeling.

LV dilation in patients with HFrEF decreased rapidly with the onset of CRT and remained unchanged from 2 to 5 years. Abnormal LV architecture was dependent on LV size and ejection fraction. In addition, abnormal LV architecture has been shown to predict clinical outcomes and correlates with appropriate implantable cardioverter-defibrillator therapy (22).

We also measured the changes in LV filling pressures using the E/e′ ratio (23) and LA size to determine whether these echocardiographic parameters were abnormal or implicated in LV remodeling in patients with HFrEF over the long term. The E/e′ ratio was elevated at baseline; despite the mean being unchanged from baseline, we did find that the change in the E/e′ ratio was associated with the endpoints of mortality and new or recurrent HF. In this study, mean LA size was enlarged at baseline and was similar at 5-year follow-up.

During LV remodeling, the initial fall in LV volume occurs before there is any detectable change in LV mass index, which typically decreases slowly between 3 to 6 months later. LV dilation, without a simultaneous increase in LV mass or change in blood

FIGURE 3 Changes in Echocardiographic Measurements Over Time



(A) Mitral regurgitation (MR) severity (expressed as cm^2) over time. There were no statistically significant changes from one year to the next. **(B)** Mean left atrial (LA) systolic size (cm^2) over time. Arrows show where there was a statistically significant change from one year to the next. **(C)** Mean intraventricular mechanical delay (IVMD) (in ms) over time. Arrow shows where there was a statistically significant change from one year to the next (only in the first year). **(D)** Left ventricular filling pressure over time. Mean ratio E/e′ over time is graphed. There were no statistically significant changes from one year to the next.

pressure, results in an obligatory increase in wall stress. This increase in wall stress activates a hypertrophic response to counterbalance the elevated loading conditions. Wall stress is the main determinant of myocardial oxygen consumption and decreases with reverse remodeling induced by CRT. Wall stress is also a key factor in remodeling LV architecture, LV hypertrophy, myocardial composition, and contractile function.

We did not attempt to estimate mid-wall stresses in this study because more than one-half the patients had an ischemic cause of HF. HF due to ischemic heart disease is characterized by regional variation of contraction and heterogeneity of the myocardial material properties, which precludes the use of stress equations because they assume that myocardial material properties are homogeneous. Down-regulation of wall stress by CRT could be an

TABLE 4 Predictive Baseline Variables for Reduction in LVESVI by ≥15%

	Higher Chance of 15% LVESVI Reduction	Estimate	SE	p Value
Intercept		1.5299	0.2688	<0.0001
Sex	Female	−0.5869	0.2138	0.006
Ischemic	Nonischemic	0.3985	0.1555	0.01
LBBB	Presence of LBBB	−0.6619	0.1372	<0.0001
Mitral regurgitation	Lower	−0.0654	0.0390	0.09

Variables considered for the model were LV sphericity index, age, sex, pathogenesis, LVESVI, LVEF, LBBB, mitral regurgitation, and QRS duration.
Abbreviations as in Tables 2 and 3.

TABLE 5 Effect of Echocardiography Variables on Morbidity/Mortality

Change From Baseline to 6 Months	Median Change	% With HF Hospitalization or Death From 6 Months to 5 Years		p Value
		< Median Change	≥ Median Change	
LV sphericity index	−3.25	21.6	32.2	0.01
MR 4 ch area	−0.6	28.2	31.4	0.20
LVESVI	−13.5	21.2	32.1	0.002
LVEDVI	−15.1	20.0	33.3	0.003
LVEF	2.8	31.2	22.5	0.01
LV mass	−14.5	18.8	38.2	0.23
Tei index	−2.96	30.3	22.1	0.35
LA size, systole	−1.30	27.7	28.8	0.35
LA size, diastole	−2.03	29.1	26.9	0.46
E/e′	−0.18	17.1	33.4	0.005
IVMD	−10.0	25.8	26.8	0.68

IVMD = intraventricular mechanical delay; LA = left atrial; MR 4 ch area = mitral regurgitation was assessed from the apical 4-chamber view; other abbreviations as in Table 2.

important mechanism that drives LV reverse remodeling and abnormal LV architecture once remodeling is triggered. Wall stress also modulates a portfolio of stretch-activated matrix metalloproteinases that simultaneously stabilize the extracellular collagen matrix, which facilitates changes in LV size and mass during remodeling (24).

Using logistic regression analysis, the baseline factors most likely to improve LVESVI by at least 15% were female sex, nonischemic HF, lower baseline MR, and LBBB. In addition, a univariate analysis showed that improvements in LV sphericity index, LVESVI, LVEDVI, LVEF, and E/e′ after CRT reduced patients risk of HF hospitalization and mortality.

STUDY LIMITATIONS. A potential shortcoming of this study is that it enrolled only patients with HFrEF with mild HF (NYHA functional class I/II), and these findings cannot be extrapolated to patients with more severe or end-stage HF (NYHA functional class III/IV). Furthermore, in this study, the mortality was low, and there were few adverse events due to HF. Our patient cohort included only patients who were randomized to CRT-ON for 5 years, which might have introduced an unfavorable bias in our patient cohort. However, objective endpoints showed stable equivalent event rates during the randomized and the nonrandomized periods. Although the method of assessing MR is far from reliable, we hoped that the vagaries of estimating MR would be outweighed by the large number of patients studied, and that if the MR was hemodynamically important, an MR signal would emerge. This is a post hoc analysis, involving multiple testing of hypotheses, for which there was no p-value multiplicity adjustment. Lastly, another potential weakness of the study relates to the degree of missing echocardiograms in the patients HFrEF, mostly because of poor image quality. The important impact of missing imaging data was minimized by the inclusion of all of the available echocardiography analyses.

CONCLUSIONS

We have described the effects of abnormal LV architecture on structural and functional LV remodeling and on clinical outcomes in a large cohort of patients with mild HFrEF treated with CRT. Pre-defined key echocardiographic metrics showed that abnormal LV architecture accompanied LV dilation, and the greater the LV size, the worse the LV function (LVEF). In addition, CRT attenuated abnormal LV architecture, reduced LV size, and improved LVEF by reverse LV remodeling. Although adverse events were scarce, abnormal LV architecture correlated significantly with clinical outcomes, adding incremental prognostic value to that of LV size and LVEF. Change in LV filling was a strong predictor of hospitalization for HF or death. Our findings have potential therapeutic implications for reducing abnormal LV architecture by modulating LV load, inducing LV reverse remodeling and improving LVEF in HFrEF. Finally, a significant interaction was observed between LV architecture and clinical outcomes in HFrEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE I: The effects of abnormal LV architecture on ventricular remodeling and clinical outcome in HF are not well known. Within a randomized clinical trial (REVERSE), we demonstrate that approximately two-thirds of patients with mild HF treated with CRT experience a significant reduction in LV volumes and improvement in LVEF. In addition, change in abnormal LV architecture is associated with both structural remodeling and future clinical outcomes. Baseline factors most likely to improve LVESVI by at least 15% include sex, nonischemic origin of HF, LBBB, and less MR.

COMPETENCY IN MEDICAL KNOWLEDGE II: Reduction in filling pressures was a strong predictor of clinical outcome, because 33.4% of patients whose E/e′ ratio was not reduced by at least 0.18 were hospitalized for HF or died compared with only 17.1% of those who had a 0.18 or better reduction.

TRANSLATIONAL OUTLOOK: The findings in this study, conducted on the framework of a randomized clinical trial, are directly applicable to optimizing the treatment of mild HF.

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