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Presence of Extensive LV Remodeling Limits the Benefits of CRT in Patients With Intraventricular Dyssynchrony

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OBJECTIVES The aim of this study was to evaluate whether, in patients with evidence of both electrical and mechanical left ventricular (LV) dyssynchrony, extensive LV dilation would affect response to cardiac resynchronization therapy (CRT).

BACKGROUND Cardiac resynchronization therapy is effective in heart failure patients with LV dysfunction and wide QRS complex. However, many patients still fail to respond. We hypothesized that presence of extensive LV dilation might prevent response to CRT, despite LV mechanical dyssynchrony.

METHODS We studied 78 heart failure patients (68 ± 9 years of age, 77% men) with both electrical (QRS width >120 ms) and mechanical intraventricular dyssynchrony (by tissue Doppler imaging and/or left lateral wall post-systolic contraction). Echocardiographic evaluation was performed at baseline and 6 to 8 months after CRT. As an indication of LV remodeling, end-diastolic volume index and end-systolic volume index (ESVI) and sphericity index were measured. Long-term (40 ± 23 months) clinical follow-up (events: cardiac death and hospital admission for heart failure) was also obtained.

RESULTS At follow-up after CRT, in the overall population, ejection fraction increased from 26 ± 6% to 35 ± 11% ($p < 0.0001$), whereas end-diastolic volume index (from 144 ± 43 ml/m^2 to 119 ± 55 ml/m^2), ESVI (from 108 ± 37 ml/m^2 to 82 ± 49 ml/m^2, $p < 0.0001$ for both), and sphericity index (from 0.60 ± 0.22 to 0.53 ± 0.15, $p = 0.0036$) all significantly decreased. By multiple linear regression analysis, after controlling for confounding factors, change in LV ejection fraction at follow-up resulted independently and negatively associated with baseline ESVI ($p = 0.001$), with much lower improvement after implant in the highest tertile of baseline ESVI. During follow-up, 31 patients (39.7%) had a cardiac event. By Cox regression model, baseline ESVI was the most powerful predictor of events, with event-rate/year increasing with increasing tertiles of ESVI (6.3%, 10.1%, and 23.8%, respectively, $p < 0.05$).

CONCLUSIONS In this nonrandomized, open-label clinical study, despite intraventricular electrical and mechanical dyssynchrony, extensive LV remodeling at baseline negatively impacted CRT results in terms of LV function improvement and incidence of cardiac events at follow-up. (J Am Coll Cardiol Img 2011;4:1067–76) © 2011 by the American College of Cardiology Foundation

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In symptomatic, optimally treated heart failure (HF) patients with <35% left ventricular ejection fraction (LVEF) and wide QRS, cardiac resynchronization therapy (CRT) by biventricular pacing significantly reduces morbidity and mortality, and it improves quality of life, functional class, and exercise capacity (1,2). Therefore, CRT has become established treatment for patients with symptomatic HF and systolic dysfunction in whom dyssynchrony is present, as denoted by >120-ms QRS duration (3,4). However, response in terms of clinical benefits and left ventricular (LV) reverse remodeling is heterogeneous and often unpredictable, because many such patients fail to respond to CRT (1,2,4,5).

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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

EDVI = end-diastolic volume index

EF = ejection fraction

ESVI = end-systolic volume index

HF = heart failure

interVD = interventricular dyssynchrony

intraVD = intraventricular dyssynchrony

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

LWPSC = left wall post-systolic contraction

NYHA = New York Heart Association

TDI = tissue Doppler imaging

TsO = interval from the onset of QRS to the onset of systolic velocity

sumVD = sum dyssynchrony

Reasons for lack of response to CRT are not fully understood. For one thing, a wide QRS (i.e., electrical dyssynchrony) does not necessarily equate to mechanical dyssynchrony (6). Therefore, direct assessment of mechanical dyssynchrony by echocardiography has been proposed to select CRT candidates (6–9). However, even patients with ascertained mechanical dyssynchrony might fail to respond (10). Association between increased LV diameters at baseline and poor outcome after CRT implant has been described in some (11,12) but not all studies (13). Inherent limitations of LV diameters as a measure of LV remodeling might explain shortcomings of diameter measurements in predicting outcome after CRT (11–13). In fact, although LV diameter measurements by M-mode echocardiography allow acceptable estimation of LVEF and correlate with LV volumes, they are hindered by a wide margin of error when it comes to accurate LV size assessment, especially for enlarged ventricles (14). Therefore, little and conflicting information is currently available on this issue. In particular, the relationship between extent of baseline LV remodeling, degree of intraventricular mechanical dyssynchrony, and improvement of LV function at follow-up is not well-known.

We sought to investigate whether, in patients with evidence of both electrical and mechanical LV dyssynchrony, extensive LV dilation would affect successful response to CRT in terms of improvement in LVEF and of occurrence of cardiac events at follow-up.

METHODS

Patient population. From August 2003 to June 2010, in 158 patients who underwent CRT at our institution according to guideline recommendations, complete echocardiographic evaluation was also performed before device implant. Of these, we enrolled patients who also met the following criteria: 1) chronic LV systolic dysfunction (ejection fraction [EF] ≤35%); 2) optimal medical treatment for HF since >2 months; 3) QRS duration >120 ms; and 4) mechanical dyssynchrony (see the Assessment of Intraventricular Dyssynchrony section). In addition, exclusion criteria were: atrial fibrillation, recent (<6 months) myocardial infarction and/or coronary revascularization, poor echocardiographic window, hemodynamic instability, and life expectancy of <1 year due to noncardiac diseases.

Study protocol. Baseline evaluation included clinical variables, New York Heart Association (NYHA) functional class, electrocardiogram, and 2-dimensional echocardiography. Implant of CRT device occurred within 1 month of baseline evaluation. Patients were then scheduled for follow-up (1 week, 1 and 6 months); at each follow-up visit, CRT device was interrogated to ensure that biventricular pacing was maintained. Within 1 month after CRT implant, LV diastolic filling time was optimized. Six to 8 months after CRT implant, 2-dimensional echocardiography was repeated to assess LVEF and volumes. Clinical follow-up was then continued for 40 ± 23 months after implant. An absolute LVEF improvement ≥5% was considered clinically significant (15). The protocol was approved by our ethics committee, and all patients gave written informed consent.

Device implantation. The LV pacing leads were implanted transvenously typically through a single left chest incision, left cephalic vein cutdown, and left subclavian puncture. Transvenous implantation of the device was successful in all patients but 1, who had the LV lead surgically implanted. The LV pacing lead was placed in a tributary of the coronary sinus. A posterolateral branch was used in 68% of patients; a lateral branch was used in the remainder. The LV lead position was assessed by chest x-ray in frontal and lateral views. Optimal atrioventricular delay was determined by pulsed-wave Doppler of LV inflow, selecting the optimal atrioventricular delay associated with the longest LV filling time without interrupting the A-wave (16).

Echocardiography. Echocardiographic examinations were performed with GE Vivid 7 (GE Healthcare, Chalfont St. Giles, United Kingdom), equipped with a transducer employing harmonic imaging. Exams were obtained in digital format and stored on compact disc/digital video disc for offline analysis. Patients were studied in left-lateral decubitus. The LV end-diastolic and end-systolic volumes, EF, and left atrial end-systolic volume were calculated by a modified Simpson biplane method from apical imaging planes (17). The LV mass was calculated by the area–length formula (17). The LV transverse diameter at end-systole was calculated from LV short-axis area at papillary muscle level as: LV diameter $= 2 \times 2 \times (\text{LV area}/3.14)^{0.5}$. Severity of mitral regurgitation (grades I to IV) was determined according to American Society of Echocardiography guidelines (17,18). All cardiac chamber volumes and mass measures were indexed to body surface area. Global geometry was evaluated by calculating the sphericity index (19,20).

Assessment of intraventricular dyssynchrony. Intraventricular dyssynchrony (intraVD) was assessed by the following:

1. Spectral displays with pulsed-wave tissue Doppler imaging (TDI), obtained by placing a 3-mm sample volume in the middle of each of the 6 basal LV segments in 4-, 3-, and 2-chamber apical views (21). Gain and filter settings were adjusted to minimize background noise and to allow for a clear spectral display. Care was taken to keep the incident angle between direction of Doppler beam and the analyzed vector of myocardial motion as small as possible. Measurements were performed at 100 mm/s sweep. Three end-expiratory beats were averaged. The interval from the onset of QRS to the onset of systolic velocity (TsO) in each explored segment, a surrogate for regional electromechanical coupling interval (Fig. 1A), was measured (21). Intraobserver and interobserver variabilities for TsO were 5.2 ± 2.4% and 6.4 ± 2.8%, respectively. IntraVD was considered in the presence of an absolute difference (Delta-TsO) ≥65 ms between the longest and the shortest TsO in the 6 LV basal segments (21).
2. Post-systolic contraction of left lateral wall (LWPSC), recorded in the 4-chamber apical view with color M-mode TDI after aortic valve closure. When LWPSC persisted beyond the onset of the next filling phase (measured from QRS onset to the beginning of E-wave at pulsed-wave Doppler of mitral inflow), the overlap of LWPSC contraction and ventricular filling was measured (22). Diastolic contraction and overlap identify presence of LV segments not temporally synchronized within the cardiac cycle. Any positive LWPSC was considered as a sign of dyssynchrony (22) (Fig. 1B).
3. Finally, interventricular dyssynchrony (interVD) was calculated as the difference between TsO in the basal lateral segment of right ventricle and in the most delayed LV segment. A sum dyssyn-

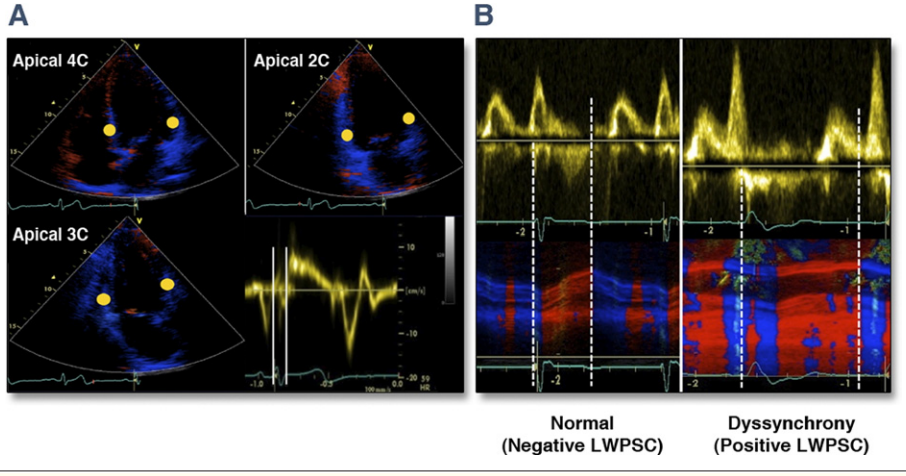

Figure 1. Measurement of Intraventricular Dyssynchrony and of Diastolic Overlap

Measurement of intraventricular dyssynchrony by tissue Doppler imaging (**A**), and of diastolic overlap (left wall post-systolic contraction [LWPSC], **B**). Simultaneous display of electrocardiogram, left ventricular filling and left lateral wall contraction is shown: LWPSC is the contraction of lateral wall after aortic valve closure, whereas diastolic overlap identifies persistence of contraction after mitral valve opening.

chrony (sumVD) was then calculated by adding intraVD and interVD, and a value ≥140 ms was considered significant.

Patients needed to fulfill ≥1 of the aforementioned criteria of mechanical dyssynchrony to be included in the study.

Long-term follow-up. Long-term follow-up was performed by chart review, clinical exam at our outpatient HF clinic, and telephone contacts. Events included death and hospital admission for HF.

Statistical analysis. Continuous data are presented as mean ± SD, and categorical data are presented as frequencies and percentages. The NYHA functional class is presented as median + interquartile range. Two-sided paired and unpaired Student *t* test were used for normally distributed variables, whereas Mann-Whitney *U* test or Wilcoxon signed-rank test were used for non-normally distributed variables. Pearson correlation coefficient was used when appropriate. Chi-square test (with Fisher exact test when appropriate) was used to compare categorical variables in 2 × 2 contingency tables. Linear regression analysis was performed to assess univariate relationships between change of LVEF at follow-up and continuous clinical and echocardiographic variables. Stepwise multivariable linear regression analysis was then used to determine which of the important univariate variables were significant independent predictors of LVEF improvement. Collinearity diagnostic procedure was performed first by examining the correlation between independent variables to detect a high level of association. If high bivariate correlation (>0.50) was present between 2 variables, the variable that was a stronger predictor in univariable unadjusted analysis was chosen and the other eliminated.

Differences in cardiac event rates over time were analyzed by the Kaplan-Meier method and log-rank test. The effect of different variables on event-free survival was investigated with Cox proportional hazards model. Variables that showed a significant effect on survival in univariable analyses ($p < 0.1$) were entered in a multivariable Cox proportional hazards model with backward stepwise selection to obtain the final model. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p value <0.10. The number of variables that could enter the multivariate was limited with the $p < m/10$ rule to prevent over-fitting the model. All p values were 2-sided; a p value <0.05 was considered statistically significant. Analyses were performed with STATA software version 9, (StataCorp, College Station, Texas) and SAS (Chicago, Illinois).

RESULTS

From an initial population of 95 patients fulfilling all enrolment criteria, 4 were subsequently excluded for failure of device implant, 4 patients died before echocardiographic follow-up, and 6 patients were lost to follow-up; whereas in 3 patients LV pacing was switched off due to phrenic nerve stimulation. Seventy-eight patients represent the final population. Of these, 44 (56%) received a CRT with biventricular pacing-only device, and 34 (44%) received a CRT with a biventricular implantable cardioverter defibrillator device. Table 1 summarizes baseline characteristics of the population; mean age was 69 ± 9 years; 67% of patients had nonischemic etiology of HF.

IntraVD by TDI was 77 ± 29 ms at baseline, and it was >65 ms in 54 (69%) patients. InterVD by TDI was 82 ± 50 ms at baseline, whereas a sumVD >140 ms was found in 47 (60%) patients (Table 2). A LWPSC >40 ms was found in 51 (65%) patients, and 52 (67%) patients showed a positivity of ≥2 dyssynchrony parameters.

Response to cardiac resynchronization. In the whole population, NYHA functional class improved at follow-up from a median 3 (interquartile range 2 to 4) to 1 (interquartile range: 1 to 2) ($p = 0.0001$), and prevalence of patients in NYHA functional class III/IV decreased from 72% to 21% ($p < 0.01$). The EF also significantly improved, from 26 ± 6% to 35 ± 11% ($p < 0.0001$); significant reduction in end-diastolic volume index (EDVI) (144 ± 43 ml/m^2 to 119 ± 55 ml/m^2; $p < 0.0001$), ESVI (108 ± 37 ml/m^2 to 82 ± 49 ml/m^2; $p < 0.0001$), and sphericity index (0.60 ± 0.22 to 0.53 ± 0.15, $p = 0.0036$) was also observed.

Parallel to improvement in LV remodeling parameters, mitral regurgitation severity also significantly improved at follow-up, because the proportion of patients with significant mitral regurgitation (defined as effective regurgitant orifice area ≥0.2 cm^2) decreased from 39% to 21% ($p < 0.05$).

LV remodeling and EF improvement after CRT. Linear regression analysis was performed to define the strength of association between EF improvement at follow-up and clinical and echocardiographic variables of LV remodeling and mechanical dyssynchrony (Table 2). Percentage increase in EF was associated with QRS duration ($p = 0.007$), LV diastolic and systolic diameters ($p = 0.004$ for

Table 1. Characteristics of Study Population (n = 78)

Age (yrs)	68 ± 8
Male	60 (77)
BSA (kg/m^2)	1.86 ± 0.21
Heart rate (beats/min)	70 ± 11
Systolic BP (mm Hg)	116 ± 13
Diastolic BP (mm Hg)	70 ± 9
NYHA functional class 3 to 4	56 (72)
QRS duration (ms)	165 ± 30
LBBB	57 (73)
Etiology of heart failure	
Ischemic	26 (33)
Nonischemic	52 (67)
Medications	
ACEI/ARB	66 (85)
Diuretics	69 (89)
Beta-blockers	59 (76)
Nitrates	35 (45)
Aldosterone antagonists	49 (63)
Echocardiography	
LV internal diastolic diameter (cm)	7.63 ± 0.88
EDVI (ml/m^2)	144 ± 43
ESVI (ml/m^2)	108 ± 37
Ejection fraction (%)	26 ± 6
Left atrial volume index (ml/m^2)	44 ± 20
Mitral regurgitation severity (EROA >0.2 cm^2)	31 (39)
Sphericity index	0.62 ± 0.23
IntraVD by TDI (ms)	77 ± 29
InterVD (ms)	82 ± 49
SumVD (ms)	159 ± 71
LWPSC (ms)	69 ± 87

Values are mean ± SD or n (%).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; BSA = body surface area; EDVI = end-diastolic volume index; EROA = effective regurgitant orifice area; ESVI = end-systolic volume index; interVD = interventricular dyssynchrony; intraVD = intraventricular dyssynchrony; IQR = interquartile range; LBBB = left bundle branch block; LV = left ventricular; LWPSC = left wall post-systolic contraction; NYHA = New York Heart Association; sumVD = sum dyssynchrony; TDI = tissue Doppler imaging.

both), EDVI ($p < 0.0001$), ESVI ($p = 0.003$), left atrial volume index ($p = 0.037$), intraVD by TDI ($p < 0.001$), and sumVD by TDI ($p = 0.027$). Furthermore, patients with ≥2 dyssynchrony parameters at baseline showed greater increase in LVEF (10 ± 9% vs. 6 ± 9%, $p < 0.05$) than patients in whom only 1 parameter of mechanical dyssynchrony was altered. Age and blood pressure showed no correlation with LVEF improvement.

A multivariable linear regression analysis was then constructed specifically to determine which of these variables were independent predictors of LVEF improvement. Baseline EDVI and LV systolic diameter showed high collinearity and therefore were not included in the final model. Both baseline ESVI and intraVD by TDI were found to be significant and independent predictors of EF improvement ($p = 0.001$ and $p < 0.0001$, respectively), whereas the association of LV diastolic diameter with EF improvement became insignificant (p = NS). Improvement in EF was lowest in the highest tertile of baseline ESVI and greatest in the lowest tertile (i.e., smaller LV volume) (Fig. 2). Figure 3 shows the interrelations between baseline ESVI, intraVD, and improvement in EF after CRT; patients with low ESVI (<103 ml/m^2, median value) and ≥2 parameters of IntraVD at baseline had the greatest increase in EF at follow-up, whereas patients with high ESVI (>103 ml/m^2) and only 1 parameter of intraVD at baseline showed no significant improvement in EF after CRT.

LV dyssynchrony, remodeling, and prognosis. During a mean follow-up of 40 ± 23 months, an event of the composite endpoint (death/hospital admission for HF) occurred in 31 (40%) patients. At the end of follow-up, 16 patients (21%) had died, and there had been 25 (32%) repeat hospital admissions for HF. Table 3 shows clinical and echocardiographic characteristics of patients according to whether or not they developed an event during follow-up.

Table 2. Univariate Correlates of EF Improvement

	Univariate Analysis	
	Beta	p Value
Age (yrs)	−0.15	0.194
BSA (kg/m^2)	−0.06	0.557
Heart rate (beats/min)	0.20	0.075
Systolic BP (mm Hg)	0.10	0.335
Diastolic BP (mm Hg)	0.14	0.223
QRS duration (ms)	0.30	0.007
LV internal diastolic diameter (cm)	−0.32	0.004
LV internal systolic diameter (cm)	−0.32	0.004
EDVI (ml/m^2)	−0.41	<0.0001
ESVI (ml/m^2)	−0.34	0.003
Ejection fraction (%)	−0.07	0.514
Left atrial volume index (ml/m^2)	−0.24	0.037
Mitral regurgitation severity (grade)	−0.11	0.336
LV mass index (g/m^2)	0.16	0.148
Sphericity index	−0.09	0.392
InterVD by TDI (ms)	0.14	0.218
IntraVD by TDI (ms)	0.37	0.001
SumVD (ms)	0.25	0.027
LWPSC (ms)	−0.07	0.536
Combined IntraVD (≥2 parameters)	0.23	0.042
LV lead position	0.05	0.680

EF = ejection fraction; other abbreviations as in Table 1.

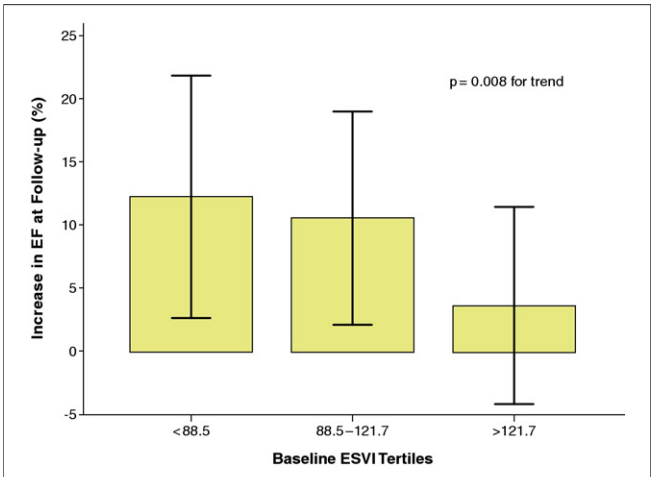

Figure 2. Relationship Between Baseline ESVI and Changes in EF After CRT Implant

Likelihood of improvement in ejection fraction (EF) was lowest in the highest tertile of baseline end-systolic volume index (ESVI) and highest in the lowest tertile. CRT = cardiac resynchronization therapy.

Compared with patients without events, patients with events showed lower systolic and diastolic blood pressure ($p < 0.05$ for both) and significantly higher EDVI, ESVI ($p < 0.05$ for both), and sphericity index ($p = 0.013$). Age, sex, dyssynchrony indexes, and QRS width did not significantly differ between the 2 groups.

By Cox proportional hazard model, after correcting for these confounding factors (Table 2), ESVI >103 ml/m^2 (median value) (hazard ratio: 2.53, 95% confidence interval: 1.17 to 5.44, $p = 0.017$) and low systolic blood pressure (hazard ratio: 0.95, 95% confidence interval: 0.93 to 0.99, $p = 0.006$) were the most powerful predictors of cardiac events. Figure 4A shows that incidence of events/year increased with increasing tertiles of baseline ESVI ($p < 0.01$) and that event-free survival was markedly lower in the higher tertile of baseline ESVI (Fig. 4B).

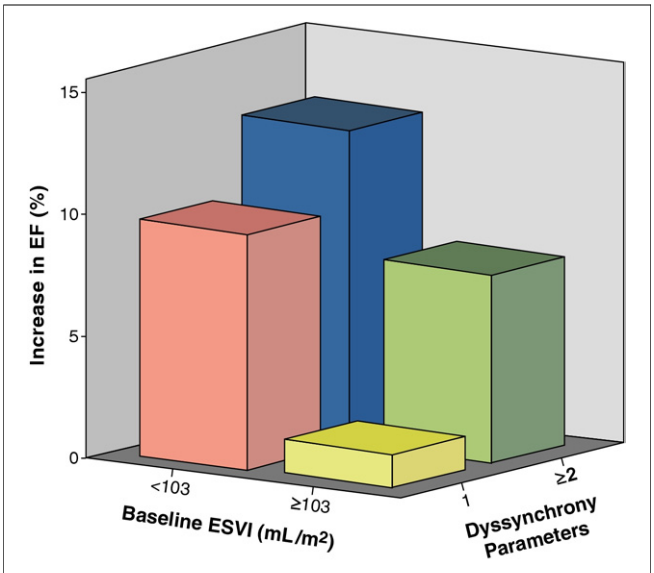

Figure 3. Relationship Between Baseline ESVI, intraVD, and Improvement in EF After CRT

Increase in EF at follow-up was greater in patients with lower ESVI (<103 ml/m^2) and >2 positive parameters of intraventricular dyssynchrony (intraVD) at baseline, whereas patients with higher ESVI (>103 ml/m^2) and only 1 parameter of intraVD at baseline showed no significant improvement in EF after CRT. Intermediate levels of improvement in EF were observed in patients with higher ESVI at baseline but combined intraVD as well as in patients with lower ESVI and only 1 parameter of intraVD. Abbreviations as in Figure 2.

DISCUSSION

The present study shows that, in HF patients with dyssynchrony documented by both electrical and mechanical criteria, resynchronization therapy might not be effective if extensive LV remodeling is present at the time of implant. Specifically, improvement in EF was inversely related to baseline ESVI. Moreover, long-term survival free of cardiac death/repeat hospital admission for HF was significantly better in the presence of smaller ESVI.

Although precise definition of what constitutes good CRT response is still controversial (10,23), failure of dyssynchronous myocardium to improve after CRT in many patients is a major limitation of this therapy. To increase the sensitivity, a composite definition of response has been proposed, which includes both clinical and functional measures (10). Because agreement between different methods to define response to CRT is poor (23), we avoided categorizing patients into responders or nonresponders. Therefore, we explored the relationship between degree of baseline LV remodeling and increase in EF at follow-up as a continuous variable. Furthermore, to circumvent limitations of NYHA functional class and/or quality of life measurement to assess the clinical benefit of CRT, we reported the incidence of hard endpoints, namely death and repeat hospital admission for HF.

Failure to improve after CRT has been related to various issues, including baseline altered LV dimensions. However, with respect to this latter mechanism, data are not conclusive. In 1 study (13), baseline LV end-diastolic diameter showed a positive correlation with echocardiographic endpoints at follow-up. Conversely, Diaz-Infante et al. (11) reported that large LV end-diastolic diameter (>75 mm) was an independent predictor of lack of

response to CRT; in that study, however, neither LV volumes nor mechanical dyssynchrony were assessed at baseline. More recently, in patients with chronic HF in whom CRT was performed only if mechanical dyssynchrony was documented, Gradaus et al. (12) found that increased LV end-systolic diameter and concomitant diastolic dysfunction were associated with significantly worse outcome. However, both latter studies employed LV diameters as an estimate of LV remodeling; as already mentioned, LV diameters might have substantial shortcomings as a measure of LV remodeling (11–13).

In the present study we performed a comprehensive assessment of LV remodeling, including measurements of baseline end-diastolic and end-systolic volumes, LV mass, and sphericity index (24,25). Thus, our study provides new information showing that extensive LV remodeling at baseline is associated with poor functional improvement at follow-up, with minimal changes in EF in the higher tertile of baseline ESVI. When we evaluated the relationship between intraVD, LV systolic dysfunction, baseline LV remodeling, and extent of functional improvement after CRT, severity of intraVD and low ESVI significantly predicted improvement in EF after CRT (Table 3), whereas LV diameters did not enter the equation. Interestingly, the greatest improvement in EF was seen in patients with the most dyssynchronous myocardium (≥2 parameters of intraVD) and smaller LV (ESVI <103 ml/m^2), whereas patients with extensive remodeling (ESVI >103 ml/m^2) and only 1 parameter of intraVD at baseline showed no significant changes in EF after CRT (Fig. 4). Therefore, patients with low likelihood to improve in LV function after CRT were more likely to be those with larger LVs.

Another finding of our study is that large ESVI at the time of implant was also an independent and strong predictor of poor outcome during long-term follow-up. Rate of cardiac events significantly increased with increasing tertiles of baseline ESVI; Kaplan-Meier analysis showed significantly lowest event-free survival in the highest tertile of ESVI. These findings are consistent with earlier observations that LV end-systolic volume is an independent strong predictor of long-term prognosis in the general population of HF patients (26) and in patients undergoing CRT (27). In a single-center registry of HF patients treated with CRT, assessment of the influence of pre-implant characteristics on long-term outcome has shown that large LV end-systolic volume was significantly and independently associated with poor prognosis after implant (27). Furthermore, increased end-systolic volume limits improvement in LVEF after revascularization in patients with chronic ischemic cardiomyopathy, despite presence of viability (28). Overall, these observations lend credence to the hypothesis that extensively remodeled ventricles might be beyond recovery (29), even in the presence of an amendable substrate, such as asynchrony (as in the present study) or myocardial hibernation (28).

Table 3. Characteristics of Study Population Grouped According to Presence or Absence of Cardiac Events

	Events (n = 31)	No Events (n = 47)	p Value
Age (yrs)	70 ± 7	67 ± 9	0.145
Male (%)	25 (81)	35 (74)	0.526
Heart rate (beats/min)	70 ± 10	70 ± 11	0.893
Systolic BP (mm Hg)	110 ± 12	119 ± 12	0.001
Diastolic BP (mm Hg)	68 ± 9	72 ± 8	0.039
NYHA functional class	3.0 ± 0.8	2.7 ± 0.5	0.090
QRS duration (ms)	163 ± 28	167 ± 31	0.217
Ischemic etiology (%)	11 (46)	13 (28)	0.558
LVIDd (cm)	7.74 ± 0.90	7.56 ± 0.87	0.382
EDVI (ml/m^2)	161 ± 47	133 ± 37	0.004
ESVI (ml/m^2)	120 ± 38	99 ± 34	0.015
Ejection fraction	25 ± 6	26 ± 6	0.974
Sphericity index	0.68 ± 0.23	0.58 ± 0.23	0.013
Delta EF after CRT	5.8 ± 9.5	10.7 ± 8.8	0.022
IntraVD by TDI (ms)	73 ± 33	80 ± 26	0.252
InterVD by TDI (ms)	83 ± 52	81 ± 47	0.514
SumVD (ms)	156 ± 79	161 ± 67	0.687
LWPSC (ms)	64 ± 74	73 ± 95	0.412

CRT = cardiac resynchronization therapy; LVIDd = left ventricular diameter at end diastole; other abbreviations as in Table 1.

Having selected patients on the basis of the presence of intraVD, we obviously did not find differences in each single parameter of asynchrony between patients who developed events compared with those who did not develop events during long-term follow-up. However, patients who had a combination of ≥2 dyssynchrony parameters showed a greater increase in EF at follow-up than patients with just 1 parameter of dyssynchrony. Because no single parameter will completely dictate CRT response (23), this might highlight the concept that combining different methods or using scoring systems might be a better approach to select responders. In the study by Gorcsan et al. (30), combination of longitudinal and radial measures by speckle tracking predicted EF response significantly better than either technique alone. Recently, Lafitte et al. (31) demonstrated that use of a multiparametric approach that focused on criteria combination

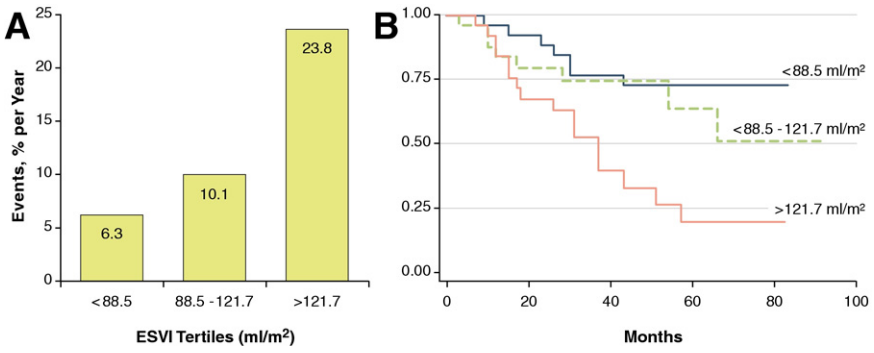

Figure 4. Extent of Remodeling and Cardiac Events After CRT

(A) Incidence of cardiac events increased with increasing tertiles of baseline ESVI. **(B)** Event-free survival was significantly lower in the highest tertile of baseline ESVI. Abbreviation as in Figure 2.

significantly decreased the rate of false-positive results. Thus, combining various echocardiographic parameters might be a better approach for predicting response to CRT; physicians should integrate more than just evidence of dyssynchrony in their management algorithm, taking into account degree of LV remodeling as well as clinical factors, to predict improvement of function.

Finally, although patients with ischemic heart disease tend to have a lower probability of response to CRT (32), we found only a trend toward a less beneficial effect of CRT in patients with ischemic versus nonischemic etiology of HF, both in terms of increase in EF (7 ± 9% vs. 10 ± 9%, p = NS) and in terms of events at follow-up (50% vs. 35%, p = 0.191). However, the relatively low prevalence of patients with ischemic disease in the present study might have contributed to reduce the statistical power.

Study limitations. This is a nonrandomized study; sample size is relatively small, due to stringent selection criteria. Furthermore, 4 patients died before echocardiographic follow-up, and 6 were lost to follow-up, which could be important with a small sample size. The LV volumes were not assessed by magnetic resonance or 3-dimensional echocardiography, and this might have introduced errors in the estimation of LV volumes. All patients had mechanical dyssynchrony; because this is not a mandatory requisite by current clinical guidelines, whether similar results can be obtained in patients without mechanical dyssynchrony remains to be demonstrated. Although concordance between LV lead position and LV segment with maximal mechanical delay before CRT resulted in significantly greater effectiveness of CRT in some studies (33), we did not assess optimal lead position at the time of implant, and only 68% of patients of our population received the LV lead in a posterolateral vein. However, significant improvement in cardiac function and exercise capacity has been shown, regardless of LV stimulation site, either considered singly or grouped as lateral versus septal sites (34). Furthermore, in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy) trial the extent of CRT benefit in term of decreased risk for HF/death was similar for leads in the anterior, lateral, or posterior position (35). Finally, it is also possible that our echocardiographic follow-up was not sufficiently long to catch further improvement in LV function.

CONCLUSIONS

This study demonstrates that, in a HF population with severely reduced EF and evidence of both electrical and mechanical dyssynchrony, measures of LV remodeling might have incremental prognostic value over dyssynchrony indexes alone in predicting response to CRT. Despite the presence of intraVD, patients with more dilated LV enjoy no or limited benefit after implant. A multiparametric echocardiographic strategy based on the combination of dyssynchrony measures and assessment of severity and pattern of baseline LV remodeling might help refine identification of patients scheduled for CRT.

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