Original articles

Evidence of reverse remodeling after long-term biventricular stimulation for resynchronization in patients with wide QRS selected on the basis of echocardiographic electromechanical delays

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Key words:
Heart failure; Imaging; Pacing; Remodeling.

Background. **There is increasing evidence that cardiac resynchronization therapy (CRT) may trigger an inverse remodeling process leading to decreased left ventricular (LV) volumes in patients with heart failure and wide QRS. However, it is still important to simplify patient selection and achieve a widely applicable parameter to better stratify patients who are candidates for CRT.**

Methods. **Eighteen patients (13 males, 5 females, mean age 67.5 ± 7.2 years) with advanced heart failure due to ischemic (n = 12) or idiopathic dilated cardiomyopathy (n = 6) and complete left bundle branch block received biventricular pacing. The patients were considered eligible in the presence of echocardiographic evidence of intra- and interventricular asynchrony, defined on the basis of LV electromechanical delay. Investigations were performed before pacemaker implantation (at baseline), the day after, and 3 and 6 months later.**

Results. **Two patients died before the first outpatient examination. There were 15 (83%) responders to reverse remodeling among the remainder. In the overall population, there was a significant and progressive improvement in LV sphericity indexes, ejection fraction, mitral regurgitation area and LV volumes ($p < 0.001$). The improvement in the interventricular mechanical delay after CRT was significantly correlated with the decrease in LV end-systolic volume ($r^2 = 0.2558$, $p = 0.04$).**

Conclusions. **CRT reduces LV volumes in patients with advanced heart failure, complete left bundle branch block and detailed documentation of ventricular asynchrony prior to therapeutic pacing. Broadly applicable Doppler echocardiographic measures may increase the specificity of the long-term response to CRT in terms of LV performance.**

(Ital Heart J 2004; 5 (11): 818-825)

Received March 23, 2004; revision received August 27, 2004; accepted August 30, 2004.

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Cardiac resynchronization therapy (CRT) in the form of biventricular pacing is a new non-pharmacological option for a subset of patients with advanced heart failure (HF) and ventricular conduction delay[1]. The long-term studies published to date have reported improved symptom class and exercise duration with CRT[2], and there is increasing evidence that CRT may trigger an inverse remodeling process leading to a decrease in ventricular volumes[3]. However, the optimal identification of candidates for CRT remains challenging. Although the QRS duration was the first variable considered and is the only parameter that has been validated in large-scale randomized clinical trials, QRS width is only an insensitive surrogate marker of electromechanical delay. Acute hemodynamic data showed an association between QRS width and the level of the acute hemodynamic response[4], but long-term results are lacking. Appropriate cardiac asynchrony assessment may be achievable through alternative methods, examined by means of tagged magnetic resonance, radionuclide angioscintigraphy and tissue Doppler imaging[1]. Such measures appear to provide the strongest correlation with the response to CRT, although none have yet been proven to be optimal or broadly applicable[5]. It is still important to simplify patient selection and achieve a widely acceptable parameter for a better stratification of patients who are candidates for CRT.

The echocardiographic determination of mechanical synchrony could be sufficient to prospectively identify potential CRT responders. In the InSync Italian Registry, an interventricular mechanical delay (IVD) ≥ 45 ms was proved to be the only

significant prognostic indicator[6]. The aortic pre-ejection period may identify patients in whom reverse remodeling is likely and whose symptoms may improve following CRT[7]. On the other hand, while CRT may improve the contractile function only in patients with sufficient baseline biventricular asynchrony, it may not be sufficient to assess this parameter using the "conventional" imaging modalities available to date and detailed documentation of ventricular asynchrony using more sophisticated technologies prior to therapeutic pacing may be necessary[8].

The aim of this study was to assess the effects of long-term CRT with biventricular stimulation on the echocardiographic surrogate parameters of reverse remodeling in patients with congestive HF, left bundle branch block (LBBB) and significant electromechanical delay as determined by means of broadly applicable Doppler echocardiographic measures.

Methods

Patient selection. The study was approved by the local ethics committee, and all patients gave written, informed consent.

All patients were recruited from our HF outpatient clinic and were considered eligible if they were in NYHA functional class III or IV despite optimized drug treatment including diuretics in all patients, ACE-inhibitors, angiotensin II receptor antagonists, beta-blockers at the maximal tolerated dosages, and aldosterone antagonists. The shortest duration of HF was set at 6 months. Patients had to be clinically stable at the time of implantation and without any modifications of their drug regimen for at least 1 month before enrolment except some adjustments in the dose of diuretics. Only patients with a left ventricular (LV) ejection fraction ≤ 35% and LBBB were enrolled. The QRS duration had to be > 120 ms. A His-ablation performed for atrial fibrillation < 3 months prior to enrolment was considered an exclusion criterion. All patients were submitted to coronary angiography to rule out any indication for revascularization. Other exclusion criteria were unstable angina, recent revascularization (< 6 months), recent myocardial infarction (< 3 months), and the traditional indications for pacemaker or an implantable cardioverter-defibrillator.

Protocol. Investigations were performed before pacemaker implantation (at baseline), the day after, and 3 and 6 months later. These evaluations included a 12-lead surface electrocardiogram, Doppler echocardiography, technical pacemaker follow-up, 6-min walk distance test, and quality of life assessment using the Minnesota Living With HF Questionnaire. During the study period, medical therapy for HF was maintained unchanged except for diuretics that were adjusted according to clinical demands. Any changes of other medications, the need of hospitalization, and the length of hospital stay were noted throughout the follow-up.

Pacemakers and leads. A permanent LV-based pacemaker was implanted in all patients along with three pacing leads. The LV pacing lead (one St. Jude Aescula, St. Jude Medical, Veddesta, Sweden; two Medtronic model 4189, Medtronic Inc., Minneapolis, MN, USA; one 15 Guidant model 4512, Easy/track over the wire, Guidant Inc., St. Paul, MN, USA) were positioned in the coronary veins in accordance with the technique described by Daubert et al.[9]. In the patients with atrial fibrillation the pacemaker was programmed in the DDDR mode with the shortest sensed and paced atrioventricular delay set at 20 ms which corresponds to the time between left and right ventricular activation. For patients in sinus rhythm the device was programmed to the DDD mode with simultaneous stimulation of both ventricles. The atrioventricular delay in patients with sinus rhythm was individually optimized as described by Ritter[10].

Two patients (10%) underwent a second procedure: in one case, owing to coronary sinus dissection the LV lead placement was delayed and performed successfully at a second moment, and in the second patient the impossibility of identifying the coronary sinus necessitated a second, coronary angiography-guided procedure.

Hospital days and hospitalizations. All-cause hospitalizations and the length of hospital stay during follow-up were compared with the same parameters during the same period of time for each individual patient prior to pacemaker implantation, for a maximum of 1 year. The hospital records were reviewed by one investigator (AB) to determine the exact cause and duration of the hospital stays. Pacemaker-related hospitalizations and the length of hospital stay following the primary implantation of the biventricular pacemaker were monitored separately.

Echocardiographic measurements. Standard echocardiography, including Doppler, was performed (Agilent Sonos 5500, Andover, MA, USA) during each of the follow-up visits. All echocardiographic data measured during follow-up were compared with those obtained at baseline by one skilled operator (AB) not involved in the clinical follow-up and blinded at all times to the clinical data.

The LV diameters were measured during two-dimensional M-mode echocardiography in the short-axis view. The LV end-diastolic diameter (LVEDD) was measured at the onset of the QRS complex[11]. The longitudinal and transverse LV diameters were measured in the apical 4-chamber view at end-diastole and end-systole, and the sphericity index was calculated as the LV transverse diameter/longitudinal diameter ratio[12]. The biplane LV end-systolic and end-diastolic volumes (LVESV and LVEDV, respectively) were determined using Simpson's equation[11].

Patients were classified as responders to reverse remodeling if LVESV decreased by > 15% with respect to baseline, and as non-responders if LVESV decreased by ≤ 15%. This classification was based on data showing a variability of ≤ 15% for repeated volume calculations made using two-dimensional echocardiographic measurements[13]. The diastolic function was assessed as recommended by the American Society of Echocardiography Committee[14]. Mitral regurgitation (MR) was quantified by calculating the area of the regurgitant jet at color Doppler[12].

Intraventricular and interventricular systolic echocardiographic asynchrony was defined on the basis of LV electromechanical delay (LVEMD) (i.e., the time interval from QRS onset to the onset of aortic flow as determined using pulsed wave Doppler) ≥ 140 ms and of IVD (i.e., the time interval between the onset of pulmonary ejection and aortic ejection as determined using the same technique) ≥ 40 ms, respectively. Moreover, the combined index of intraventricular and interventricular mechanical asynchronies was calculated by adding both numbers: asynchrony = LV asynchrony (LVEMD) + LV-right ventricular asynchrony (IVD).

Since the intraobserver reproducibility of LVEMD and IVD has been shown to be very high, a 10% variation of either of these two parameters was considered significant[15].

All M-mode, two-dimensional and Doppler measurements were calculated as the average of at least three consecutive cardiac cycles (five consecutive cardiac cycles in patients with atrial fibrillation).

Statistical analysis. All numerical data are expressed as mean ± SD unless otherwise specified. Within group comparisons were made using the one-way ANOVA test for repeated measures or paired Student's t-tests with the Bonferroni correction for multiple comparisons. Univariate linear regression analysis was used to correlate the decrease in the electromechanical delay with the long-term improvement in LV volumes. In addition, linear regression analysis was used for the evaluation of changes in the MR area, LV volumes, and sphericity indexes. The Wilcoxon signed rank test was used to compare all-cause hospitalization and the length of hospital stay before implantation and during follow-up.

A two-tailed p value < 0.05 was considered as statistically significant.

Results

Patient characteristics. Between November 2001 and April 2003, 18 patients were enrolled in the study after obtaining informed consent and following the successful implantation of a biventricular pacemaker. No patient was lost to follow-up. The mean duration of HF before inclusion in the study was 40.5 ± 25 months. Table I illustrates the baseline data of our patient population. Of the 12 patients with ischemic heart disease, 7 had previous myocardial infarction and 4 had undergone coronary artery bypass surgery. Apart from 6 patients with atrial fibrillation who had previously been submitted to radiofrequency ablation of the atrioventricular node, none had a conventional indication for pacing. Thirteen patients were on treatment with ACE-inhibitors or angiotensin II receptor blockers (for enalapril the mean dose was 20.0 ± 5 mg); 10 patients were on beta-blockers (the mean dose of carvedilol was 12.5 ± 0.5 mg), and 11 on aldosterone antagonists. The mean dose of furosemide was 52.2 ± 20.2 mg. Two patients died of progressive HF before the first outpatient examination (22 and 46 days after biventricular pacemaker implantation). Their baseline characteristics were comparable to those of the remaining study group. All the remaining 16 patients completed 6 months of follow-up.

Table I. Baseline clinical characteristics.

No. patients	18
Age (years)	67.5 ± 7.2
Male gender	13 (72%)
Body mass index (kg/m^2)	25 ± 4.0
Ischemic etiology	12 (67%)
NYHA class III	14 (77%)
NYHA class IV	4 (22%)
Left ventricular ejection fraction (%)	23.2 ± 5.7
Baseline QRS length (ms)	157.9 ± 14.4
Atrial fibrillation	6 (33%)
Concomitant therapy (%)	
ACE-inhibitors	61
AT_1 receptor antagonists	11
Beta-blockers	55
Aldosterone antagonists	61

Pacemaker implantation. The mean operative time was 65.4 ± 28.2 min and the mean fluoroscopy time 33.6 ± 21.3 min. The mean length of hospital stay for pacemaker implantation was 2.3 ± 0.7 days. Follow-up evaluation revealed stable LV stimulation thresholds over time. The LV lead threshold increased in 2 cases that were treated via telemetry.

Reverse remodeling. Data regarding reverse remodeling are summarized in table II. LVESV and LVEDV decreased early after pacing ($p < 0.0001$) and improved further during follow-up ($p < 0.0001$ at 3 months, $p < 0.0001$ at 6 months). LVEDD was also significantly decreased 3 and 6 months after pacing therapy ($p < 0.0001$, $p < 0.0001$ respectively).

At 6 months 15 of 16 survivors (83%) were considered as responders to reverse remodeling with a > 15% decrease in LVESV compared to baseline. The average decrease in LVESV at 6 months was 28.6 ± 8.7% while the average decrease in LVEDV was 18.3 ± 7.2%. The sphericity indexes, both the end-systolic and end-diastolic, increased early after pacemaker implantation fur-

Table II. Echocardiographic indices of left ventricular remodeling.

Variables	Baseline (n=18)	After CRT (n=16)	3 months (n=16)	6 months (n=16)	p
LVEF (%)	23.2 ± 5.7	27.9 ± 5.9	33.5 ± 7.9	34.4 ± 4.4*	< 0.001
LVEDV (ml)	321.1 ± 30.0	301.9 ± 32.0	275.7 ± 34.0	258.1 ± 32.7	< 0.001
LVESV (ml)	256.4 ± 25.8	234.2 ± 26.4	201.9 ± 36.4	179.4 ± 30.2	< 0.001
LVEDD (mm)	84.1 ± 6.1	81.3 ± 5.9	75.9 ± 5.6	69.8 ± 6.0	< 0.001
MR (cm^2)	8.6 ± 4.1	6.5 ± 3.8	4.9 ± 3.6	3.4 ± 3.2**	< 0.001
E/A ratio	1.2 ± 0.8	1.1 ± 0.7	0.8 ± 0.6	0.7 ± 0.6	< 0.001
Diastolic SI	1.14 ± 0.05	1.23 ± 0.06	1.29 ± 0.06	1.38 ± 0.07	< 0.001
Systolic SI	1.27 ± 0.08	1.32 ± 0.08	1.47 ± 0.09	1.48 ± 0.103§	< 0.001
Heart rate (b/min)	70 ± 12	69 ± 12	67 ± 12	66 ± 11	NS

CRT = cardiac resynchronization therapy; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = area of mitral regurgitation; SI = sphericity index. All comparisons within subjects were found to be significant with $p < 0.0001$, apart from * $p = 0.08$ vs 3 months, ** p = NS vs 3 months, § $p = 0.01$ vs 3 months.

ther improving after 3 and 6 months (all $p < 0.0001$). The mean ejection fraction and mean MR area improved in survivors ($p < 0.001$). With regard to diastole, the deceleration time increased significantly at follow-up ($p < 0.003$). The duration of the QRS complex decreased significantly from 157.9 ± 14.4 ms at baseline to 134.5 ± 9.0 ms during pacing ($p < 0.0001$). In the 11 patients who were followed up until 12 months a further improvement in the echocardiographic indices of reverse remodeling (mean decrease in LVESV 35.8 ± 12.6%, mean decrease in LVEDV 20.2 ± 7.6%, $p < 0.0001$) was observed.

Clinical assessment. The main features are depicted in table III. The NYHA functional class improved by at least one class in all surviving patients. At follow-up CRT progressively improved the quality of life score ($p < 0.001$) and the 6-min walk distance test ($p < 0.001$). The systolic and diastolic blood pressure, resting heart rate and body weight at baseline and during follow-up were similar.

Asynchrony patterns. The baseline and follow-up asynchrony patterns are depicted in table III. CRT induced interventricular resynchronization, as shown by a significant reduction of the systolic IVD ($p < 0.001$) and LVEMD ($p < 0.001$) during follow-up.

Hospital days and hospitalizations. There was a significant reduction in the frequency and duration of hospitalization (Table IV).

Predictors of long-term efficacy. Regression analysis of the asynchrony patterns and the echocardiographic outcome showed a significant positive linear correlation between ΔIVD (Δ = baseline – the day after CRT absolute differences) and the decrease in LVESV ($r^2 = 0.26$, $p = 0.04$) (Fig. 1) and MR ($r^2 = 0.33$, $p = 0.01$) at follow-up, and an inverse correlation between ΔIVD and the increase in the systolic sphericity index at follow-up ($r^2 = 0.30$, $p = 0.02$). On the contrary, we did not observe any correlation between baseline IVD, ΔLVEMD or QRS width and the echocardiographic outcome. No associations were found between the QRS

Table IV. Hospitalizations during the 6 months before and the 6 months after biventricular pacing implantation.

Variables	6 months before (n=16)	6 months after (n=16)	p
No. hospitalizations	1.5 (1-2)	0 (0-1)	0.008
Hospital stay (days)	8 (3-21)	0 (0-3)	0.06

Data are expressed as median and first and third quartile.

Table III. Functional and echocardiographic asynchrony parameters.

	Baseline (n=18)	After CRT (n=16)	3 months (n=16)	6 months (n=16)	p
Quality of life	60.4 ± 14	52.7 ± 13§	48.2 ± 15	30.6 ± 11	< 0.001
6MWD (m)	367.7 ± 94	401.0 ± 82	416.6 ± 73*	503.6 ± 64	< 0.001
LVEMD	164.9 ± 23.0	160.0 ± 21.0	150.4 ± 19.7**	149.9 ± 19.8§§	< 0.001
IVD	58.7 ± 11.7	43.5 ± 8.2	34.5 ± 5.8	27.4 ± 4.0§§§	< 0.001

CRT = cardiac resynchronization therapy; IVD = interventricular mechanical delay; LVEMD = left ventricular electromechanical delay; 6MWD = 6-min walk distance. All comparisons within subjects were found to be significant with $p < 0.0001$, apart from * $p = 0.017$ vs after CRT, ** $p = 0.001$ vs after CRT, § $p = 0.006$ vs baseline, §§ p = NS vs 3 months, §§§ $p = 0.01$ vs 3 months.

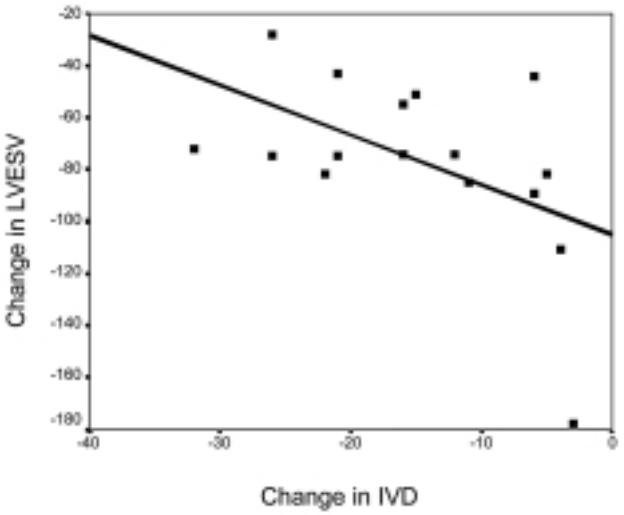

Figure 1. *The regression line shows a fairly good correlation between the magnitude of the interventricular mechanical delay (IVD) decrease (baseline – the day after cardiac resynchronization therapy absolute differences) and the magnitude of the left ventricular end-systolic volume (LVESV) decrease (follow-up – baseline absolute differences) ($p = 0.046$, $r^2 = 0.2558$).*

reduction after CRT and the echocardiographic indices of LV remodeling and the baseline measures of asynchrony. Moreover, no associations were found between the combined index of asynchrony and the variation in LVESV after CRT ($r^2 = 0.009$, $p = 0.22$).

The percentage LVESV decrease was inversely correlated with the diastolic sphericity index ($r^2 = 0.59$, $p = 0.025$). Improvement in MR area was slightly correlated with the systolic sphericity index ($r^2 = 0.52$, $p = 0.058$).

Reproducibility. In 6 study patients and 4 non-study subjects with LBBB and a QRS duration > 120 ms, the intraobserver variability was 7.8% for the measurement of LV ejection fraction, 4.4% for LVEDD, 8.6% for LVEDV, 9.1% for LVESV, 3.0% for IVD, and 4.0% for LVEMD.

Discussion

The main finding of our study is that CRT in the form of biventricular pacing provides a significant clinical and functional benefit in patients with complete LBBB (QRS ≥ 120 ms) and dilated cardiomyopathy of various etiologies, selected on the basis of simple and broadly applicable measures of interventricular and intraventricular asynchrony.

Previous studies have suggested, on the basis of the QRS duration, that despite careful patient selection, some did not respond to CRT[2]. In addition, many chronic studies have shown that the QRS duration is a poor predictor of the clinical CRT response, assessed largely by echo-Doppler-derived objective measures of chamber function or reverse remodeling[13,15-19] rather than by clinical symptoms.

In our observational series, we used imaging modalities to detect baseline evidence of systolic asynchrony in an effort to increase the specificity of the long-term response to CRT in terms of LV performance. We found a short-term effect of CRT on the systolic function, MR area, and LV volumes. However, the gain was even greater in the long-term (6 months), when the improvement was also confirmed by a reversal of LV remodeling, a major phenotypic component of the pathophysiologic mechanisms of HF[20].

It has been suggested that these long-term effects are similar in magnitude to the acute changes observed after 1 month of CRT[21], hypothesizing that Doppler echocardiography early after device implantation may predict a beneficial long-term response[22]. However, resynchronization is only one of the improvement mechanisms of CRT. Recently, in a randomized controlled study St. John Sutton et al.[23] have shown a reverse remodeling effect of CRT and confirmed earlier reports from smaller trials[13,15-19]. This chronic effect of CRT might be the result of an unloading process secondary to the decrease in mitral valve regurgitation, sympathetic/parasympathetic balance and the reduction in the total work performed by the late activated region[3], combined with progressive normalization, at a cellular level, in the concentrations of stress-sensitive kinases and calcium handling proteins[24].

Stellbrink et al.[13] evaluated non-responders to LV reverse remodeling after CRT using a cut-off > 15% for the decrease in LVESV; a lack of response was present in 9 out of 25 patients (36%). Yu et al.[19] found that 43% of their patients were volumetric non-responders. These included those patients (13%) who presented with a further increase in LVESV > 10%. Direct assessment of systolic asynchrony by noninvasive echocardiography was the only independent predictor of reverse remodeling. Unfortunately, these baseline parameters were identified only retrospectively.

In the present study, 15 of 18 patients (83%) were classified as long-term volumetric responders to CRT. At 28.6 ± 8.7%, the degree of improvement corresponds with that found in previous studies reporting a decreased LVESV at 6 months and is substantially greater than that achieved with pharmacological intervention alone[20]. LV reverse remodeling occurred in parallel with the improvement in symptoms, quality of life, and exercise tolerance. There was a strong trend toward a decreased hospitalization, as one would expect from a therapy that improves symptoms without major adverse effects.

Several studies have reported improved quality of life and functional parameters after CRT[2]. However, clinical endpoints are limited by the subjective nature of the patients' own evaluation (especially NYHA class and quality-of-life score). Besides, placebo effects may also contribute to the perceived improvement. Caution is warranted, however, when interpreting parameters of remodeling measured by those surrogates that do not

carry intrinsic value for survival or function, particularly with a novel type of therapy[25]. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, determination of the LV size and function was found to correlate only weakly with the clinical improvement and exercise capacity, although both measurements are predictive of the clinical outcome[23].

A dose-related "reverse remodeling effect" in HF has been described for beta-blocker treatment[20]. In our study, an addictive effect of beta-blockers on LV volumes cannot be completely ruled out. Since CRT may modify other aspects of the management of the patient, as would occur in clinical practice, it should be considered as a therapeutic strategy complementary to beta-blocker treatment rather than simply a device. However, the patients were receiving stable drug therapy before enrolment, and only minor dose adjustments were implemented during the study.

Importantly, in our study no relation was found between the extent of baseline intraventricular asynchrony and the magnitude of LV reverse remodeling. This is apparently in contrast with the results of the main studies on this topic. However, when LVEMD was investigated as a surrogate of global electromechanical coupling, our data were found to be similar to those of Pitzalis et al.[15]. Mechanical asynchrony, as assessed using echo-markers alone, may not be sufficiently precise to disclose the presence of this correlation. In fact, this technique does not allow simultaneous comparison of the regional timing in different cardiac segments during one beat. As described by Sogaard et al.[18], patients with greater systolic asynchrony (responders) have a significant amount of myocardium that exhibits post-systolic shortening, but the amount of myocardium with delayed contraction cannot be evaluated using conventional Doppler indices. However, what degree of mechanical asynchrony should be treated and what abnormalities may be reversible are still subjects of debate. In contrast, tissue Doppler imaging was demonstrated to be a better predictor of the improvement in LVEF and of the decrease in LV volumes after CRT than the QRS duration[26,27]. Other authors highlighted the potential of tissue Doppler imaging in the evaluation of the regional LV delay and its implications in the selection of the pacing site, as greater improvements in LVESV and ejection fraction were observed in patients paced specifically at sites of greatest contraction delay[28].

In the present study, the magnitude of improvement in the interventricular synchrony after CRT correlated significantly with the improvements in echocardiographic outcome. This is in accordance with what observed in previous studies performed with Doppler echocardiography[16,29] or nuclear phase imaging[30]. These data suggest that interventricular asynchrony is a correctable parameter contributing to LV dysfunction. Although interventricular asynchrony did not prove to be of prognostic importance in idiopathic dilated cardiomyopathy[31], its correction may all the same constitute a therapeutic target and may still lead to hemodynamic improvement[32].

The results from this study show that pacing therapy is effective mainly in the reduction of IVD rather than of LVEMD. Our population was heterogeneous, including many patients with ischemic heart disease (67%) and previous myocardial infarction (38%). Myocardial scarring has a significant impact on LV synchronization even in the absence of bundle branch block. This is especially true in case of an anterior myocardial infarction[33]. The larger the myocardial infarct area, the more severe the LV asynchrony and the lower the probability that it reverses after CRT. Biventricular pacing, although changing the orientation of the activation/contraction wave-front, may not be sufficient to overcome the conduction delay related to a fixed scar in the myopathic ventricle. Moreover, biventricular pacing may improve LV synchronicity by shortening the total isovolumic time[17] or by redistributing the longitudinal myocardial deformation, indicating a more energy-efficient contraction[34]. Sogaard et al.[18] have pointed out that after CRT the improvement in systolic function appeared to be confined to the base of the left ventricle, whereas the mid-ventricular and apical areas of the ventricle did not seem to be resynchronized. These data stress the concept that left intraventricular asynchrony may still persist after biventricular pacing, notwithstanding right and left interventricular resynchronization.

Finally, in our series 2 patients died of progressive HF. In these patients, right ventricular HF was more pronounced than LV failure. Overriding comorbidities may attenuate the response to CRT and the long-term impact of CRT on hospitalization and mortality[28]. However, questions remain as to whether CRT stimulation is needed, whether multisite left-heart stimulation would enhance its efficacy and as to which is the best time delay between right ventricular and LV stimulation[8].

Study limitations. The main limitation of this study is the lack of a control group; i.e., patients with HF and LBBB but no echocardiographic asynchrony at baseline.

The site of LV pacing and the tailored sequential CRT were not individually optimized, but to date there is no agreement on how this is best accomplished. However, we selected patients with complete LBBB in whom it is mainly the lateral LV wall which is activated last[35].

Due to the small sample size, this study is not sufficiently powered to identify the baseline predictors of positive ventricular remodeling. The small number of non-responders does not justify a more extensive analysis, in particular of LV predictors, by means of univariate and multivariate models. However, in previous reports[19,26] the patient and disease characteristics were

not found to be predictive of the LV volumetric changes, highlighting the limitations of selecting patients on the basis of their clinical characteristics.

Six patients (33%) were in chronic atrial fibrillation and had been previously subjected to radiofrequency ablation of the atrioventricular node. This must be taken into consideration when interpreting results because the heart rate control benefit probably adds up to that of ventricular resynchronization. All the same, in acute and chronic hemodynamic studies the benefit was observed for both patients in sinus rhythm as well as for those with atrial fibrillation, stressing the importance of ventricular resynchronization, regardless of the atrioventricular synchrony[36].

Finally, the cardiac asynchrony was evaluated using a rather simple and non-sophisticated Doppler measurement. As previously suggested[29], we should expect even better clinical outcomes in the event of patients being selected with more sophisticated imaging techniques, but it is still important to simplify the selection process in candidates for CRT using widely acceptable parameters[5].

In conclusion, this study suggests that CRT in patients with stable severe HF (in spite of optimal therapy), LBBB and detailed documentation of ventricular asynchrony prior to therapeutic pacing is a useful clinical strategy, with benefit persisting for more than a few months. Whether reverse remodeling induced by CRT will improve the patient outcome, as observed with pharmacological therapy, needs to be addressed by large-scale, multicenter studies.

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