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# Long-Term Effectiveness of Cardiac Resynchronization Therapy in Patients With Refractory Heart Failure and "Narrow" QRS

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**OBJECTIVES** The aim of the study was to evaluate the effectiveness of cardiac resynchronization therapy (CRT) in patients with refractory heart failure (HF) and incomplete left bundle branch block ("narrow" QRS), together with echocardiographic evidence of interventricular and intraventricular asynchrony.

**BACKGROUND** Cardiac resynchronization therapy has been proven effective in patients with HF and wide QRS by ameliorating contraction asynchrony.

**METHODS** Fifty-two patients with severe HF received biventricular pacing. The patients were eligible in the presence of echocardiographic evidence of interventricular and intraventricular asynchrony, regardless of QRS duration. The patient population was divided into group 1 ($n = 38$), with a QRS duration >120 ms, and group 2 ($n = 14$), with a QRS duration ≤120 ms.

**RESULTS** The baseline parameters considered in the study were similar in both groups. At follow-up, CRT determined narrowing of the QRS interval in the entire population and in group 1 ($p < 0.001$), whereas a small increase in QRS duration was observed in group 2 (p = NS); in all patients and within groups, we observed improvement of New York Heart Association functional class ($p < 0.001$ in all), left ventricular ejection fraction ($p < 0.001$ in all), left ventricular end-diastolic and end-systolic diameter ($p < 0.05$ within groups), mitral regurgitation area ($p < 0.001$ in all), interventricular delay ($p < 0.001$ in all), and deceleration time (group 1: $p < 0.001$, group 2: $p < 0.05$), with no significant difference between groups. The 6-min walking test improved in both groups (group 1: $p < 0.001$; group 2: $p < 0.01$).

**CONCLUSIONS** Cardiac resynchronization therapy determined clinical and functional benefit that was similar in patients with wide or "narrow" QRS. Cardiac resynchronization therapy may be helpful in patients with echocardiographic evidence of interventricular and intraventricular asynchrony and incomplete left bundle branch block. (J Am Coll Cardiol 2003;42:2117–24) © 2003 by the American College of Cardiology Foundation

Despite major therapeutic advances with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and spironolactone, the prognosis of patients with heart failure (HF) is substantially poor and disappointing. Additionally, the previous uncontrolled (1,2) and subsequent randomized (3–5) trials suggested that cardiac resynchronization therapy (CRT) determines a clinical and functional benefit by reducing ventricular asynchrony. To date, CRT has been a valid option for patients with dilated cardiomyopathy (DCM) in New York Heart Association (NYHA) functional class III to IV, together with severe ejection fraction (EF) depression and prolonged QRS duration (>120 to 150 ms) on surface electrocardiogram (ECG).

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The rationale for CRT is based on the assumption that the structural modifications of DCM are responsible for the development of cardiac asynchrony at various levels (atrioventricular [AV], interventricular and intraventricular), thus resulting in an abnormal coordination of contraction (6) and relaxation (7) and in poor hemodynamics, and that these pathophysiologic deteriorations may be corrected by CRT (8). Cardiac asynchrony is usually associated with the presence of an intraventricular conduction delay (i.e., left bundle branch block [LBBB]), and, for this reason, CRT has been proposed for patients with a relatively marked prolongation of the QRS interval on surface ECG. Indeed, this electrocardiographic aspect is a rather "coarse" and indirect index of asynchrony. A wide QRS may be helpful in identifying the presence of interventricular asynchrony (9), but it may not be related to intraventricular asynchrony or regional dyssynchronies and, therefore, should not be considered a specific marker of mechanical asynchrony.

These uncertainties have represented a major limitation in identifying the "ideal" QRS interval for the selection of candidates for CRT therapy, ranging from 120 ms (5) to 150 ms and beyond (3).

Our working hypothesis is based on the presence of contraction asynchrony patterns in patients with DCM and an incomplete LBBB ("narrow QRS"), even though this finding is not as frequent as in subjects with complete

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**Abbreviations and Acronyms**

ACE = angiotensin-converting enzyme
AV = atrioventricular
CRT = cardiac resynchronization therapy
DCM = dilated cardiomyopathy
DT = deceleration time
E-A = left ventricular filling time
ECG = electrocardiogram
EF = ejection fraction
HF = heart failure
IVD = interventricular delay
LBBB = left bundle branch block
LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter
MR = mitral regurgitation
NYHA = New York Heart Association
PM = pacemaker
SR = sinus rhythm
Q-E = Q-wave–transmitral filling E-wave interval
Q-LW = posterolateral left ventricular wall activation delay
6MWT = 6-min walking test

LBBB. Provided that asynchrony is documented, CRT may be effective in this particular subset of patients.

To validate our hypothesis, a patient population with severe HF and echocardiographic evidence of interventricular and intraventricular asynchrony was treated by CRT regardless of the QRS interval on the baseline surface ECG.

## METHODS

**Patient selection.** Between February 2000 and March 2002, we prospectively evaluated 52 consecutive patients with an EF ≤35% and with echocardiographic evidence of interventricular and intraventricular asynchrony (see Echocardiographic section) who underwent biventricular pacemaker (PM) implantation. Our patient population was affected by chronic HF, in NYHA functional class III to IV, secondary to DCM of any etiology and refractory to optimal and maximally tolerated medical therapy (i.e., diuretics, ACE inhibitors, beta-blockers, and digoxin). All patients had to be in clinically stable condition at least 30 days preceding the enrollment. The patients had either a normal sinus rhythm (SR) or had a PM-induced rhythm. The patients with a prior PM implantation underwent the procedure for advanced or complete heart block and were totally PM-dependent. Clinical evaluation and serial echocardiographic examinations were carried out throughout the follow-up (at least six months). Exclusion criteria were permanent atrial fibrillation, inability to perform a technically acceptable echocardiogram, surgically correctable significant valvular disease, restrictive or hypertrophic cardiomyopathy, suspected acute myocarditis, acute coronary syndrome (<3 months) or correctable by revascularization, severe chronic obstructive pulmonary disease, and inability to walk.

All patients gave their written informed consent before study enrollment.

**Echocardiography.** The echocardiographic examination was performed with a commercially available imaging system (Hewlett Padkard Sonos 5500, Hewlett Packard Co., Andover, Massachusetts) equipped with an S4 multifrequency transducer. The recordings were always performed by the same physicians (S.F. and D.P.) who were unaware of the clinical status of the patients at the time of examination and reviewed in blind. The examinations were obtained from the parasternal and apical windows with the patient in the left lateral position. Complete M-mode, two-dimensional, pulse, continuous wave, and color-Doppler recordings were performed. M-mode echocardiography measurements were made according to the guidelines of the American Society of Echocardiography (10). Measurements of all indexes were carried out on a minimum of five consecutive cardiac cycles, and the average value was used in the analysis. The following parameters were evaluated: left ventricular end-diastolic diameter (LVEDD); left ventricular end-systolic diameter (LVESD); EF, assessed using the modified biplane Simpson's rule (11); severity of mitral regurgitation (MR), evaluated by measuring the maximum MR jet area by color-Doppler from the apical view; left ventricular electromechanical delay, as the time from QRS onset to systolic aortic flow onset; right ventricular electromechanical delay, as the time from QRS onset to systolic pulmonary flow onset; interventricular delay (IVD), as the difference between right and left ventricular electromechanical delay; QRS onset-beginning of transmitral filling interval (Q-E); posterolateral left ventricular wall activation delay (Q-LW), from QRS onset to the maximal left ventricular posterolateral wall inward movement, recorded from the apical four-chamber view with the M-mode cursor positioned 1 cm below the mitral annulus on the lateral wall of the left ventricle; deceleration time (DT) obtained by extrapolating the time of the decay of the E-wave velocity to baseline; left ventricular filling time (E-A), as the time from the beginning to the end of diastolic mitral flow.

**Evaluation of asynchrony.** The patients were considered eligible for CRT if interventricular and intraventricular asynchrony was echocardiographically documented. Interventricular asynchrony was defined as IVD >20 ms, whereas intraventricular asynchrony was identified when Q-LW >Q-E and Q-LW >9.9 corrected units (c. u. = measured interval in ms/$\sqrt{}$ R-R interval); this value represents the upper 95th percentile of normal values in healthy subjects (Appendix).

**Assessment of functional capacity.** The 6-min walking test (6MWT) was carried out according to the recommendations of Guyatt et al. (12) and Lipkin et al. (13). Patients used their usual aids and received standardized encouragement at regular intervals. Each visit included two tests performed after a time lapse of at least 3 h. The recorded value was the mean of the results of the two tests.

**Biventricular pacing system.** A permanent left ventricular-based PM, along with three pacing leads, was implanted in all patients. The left ventricular pacing lead (Guidant

Model 4512, Easy/trak over the wire [Guidant Inc., St. Paul, Minnesota], or Medtronic Model 2187 or 4191 [Medtronic Inc., Minneapolis, Minnesota]) was advanced transvenously into a tributary vein of the coronary sinus in 49 patients. Only when this transvenous technique resulted in failure (three patients) was the pacing lead (Medtronic Model 4965) positioned epicardially by a small thoracotomy. The target pacing position for the left ventricle was the midportion of the left free wall, which was reached in 49 patients; in 2 patients, the lead was positioned toward the anterior wall, and, in the remaining 1 patient, the lead was placed in a basal position.

**Optimiziation of the AV delay.** Atrioventricular delay optimization was performed using Doppler echocardiography, interrogating transmitral flow with the sample volume at the tip of the mitral valve leaflets to obtain the best flow profile. First, the device was programmed to DDD mode with a lower rate of 40 beats/min to ensure the patient's intrinsic rhythm. Subsequently, the sensed AV delay was programmed to 200 ms. In this setting, mitral valve closure is delayed to the end of the A wave. The sensed AV interval was decreased in steps of 20 ms until the mitral valve Doppler signal caused truncation of the A wave. Finally, the sensed AV interval was increased in steps of 10 ms to ensure that the mitral valve closure Doppler signal was synchronous with, or occurred shortly after, the end of the A-wave; AV optimization was performed at every follow-up visit.

**Data collection.** Clinical status, echocardiographic data, 6MWT, and surface ECG were prospectively evaluated in all patients at baseline, within the week preceding device implantation, before hospital discharge (day 4), after one, three, and six months, and then every six months. Standard 12-lead ECGs were recorded at a paper speed of 50 mm/s and a scale of 10 mm/mV on a Model Landscape instrument (Mortara Instruments Inc., Milwaukee, Wisconsin). Computed values of PR, RR interval, and QRS duration were recorded. The QRS width was evaluated as the mean of two values determined by automatic analysis of two successive ECGs. A control of the pacing system and of effective biventricular capture was also performed during each visit.

The mean follow-up duration was 546 ± 277 days, while clinical and echocardiographic data were collected after 6 months of follow-up for all patients.

The investigators involved in the clinical follow-up visits, in echocardiographic examinations, and in the outcome analysis were unaware of each other's findings.

**Statistical analysis.** All statistical analyses were performed using a software program (SPSS for Windows, version 11.0, SPSS Inc., Chicago, Illinois). To initially evaluate the net effect or interference of CRT on every single parameter considered in the study, we performed an analysis on the entire patient population (follow-up vs. baseline). Moreover, the net effect of QRS duration was evaluated with a data analysis within (follow-up vs. baseline) and between the groups at baseline and after CRT. Summary data are expressed as mean ± SD or percentage of patients. Differences in quantitative variables in all patients and in each group were validated using a single or a two-way repeated measure of variance, as appropriate. Differences in proportions were compared by a chi-square analysis or Fisher exact test, as appropriate. Linear regression analysis was performed to show the relationship between echocardiographic and mechanical indexes of synchrony, using QRS duration as a categorical variable, and differences between regression lines were performed using analysis of covariance. Bonferroni correction for multiple tests was used for post-hoc comparisons. A threshold value of $p < 0.05$ was considered significant.

## RESULTS

**Patient characteristics.** Table 1 illustrates the baseline data of our patient population. Mean age was 69.6 ± 9 years, and HF was ischemic in 21 (40%) patients and idiopathic in 31 (60%) patients. Our population was divided into two groups on the basis of the QRS interval at the time of enrollment: group 1, consisting of 38 patients with a QRS duration >120 (range 128 to 227 ms), and group 2, consisting of 14 patients with a QRS ≤120 ms (range 80 to 120 ms). The only baseline difference between the groups was QRS duration ($p < 0.0001$).

**Clinical and electrocardiographic outcome.** The main features are depicted in Table 2. The only baseline difference between the two groups was the QRS duration, which was obviously significantly higher in group 1. After CRT, QRS duration decreased significantly in the entire population and in group 1, whereas a small increase in QRS duration was observed in group 2. Cardiac resynchronization therapy was effective in reducing NYHA functional class and 6MWT duration in all patients and within the groups. The improvement in the 6MWT was significantly greater in group 1 than in group 2 (138.2 ± 68.9 m vs. 93.6 ± 65.7 m, $p < 0.01$). A total of 10 deaths (19.2%) occurred during the follow-up: 7 (18.4%) in group 1 (4 sudden deaths, 2 due to progressive HF, and 1 noncardiac death), and 3 (21.4%) in group 2 (1 sudden death, 2 due to progressive HF), with no difference between the groups.

**Echocardiographic outcome.** Data are summarized in Table 3. The baseline characteristics were similar in the two groups. The EF, LVEDD, LVESD, and MR improved significantly in all patients after CRT and, to a similar extent, in both groups. As regards diastole, the E-A interval did not vary after CRT, whereas DT had increased significantly at follow-up.

**Asynchrony patterns.** The baseline interventricular and intraventricular asynchrony patterns of both groups are depicted in Figure 1; moreover, in group 1 we analyzed the patients with (PM) or without (SR) a prior PM implantation. A comparison between these subgroups did not reveal any difference regarding IVD (SR: 57.0 ± 32.4 ms, PM: 53.0 ± 24.6 ms; $p = 0.388$), or Q-LW (SR: 416.2 ± 73.9

**Table 1.** Baseline Characteristics of the Patient Population

| Characteristics | All Patients (n = 52) | Group 1 (n = 38) | Group 2 (n = 14) | 1 vs. 2 p Value* |
|---|---|---|---|---|
| Age (yrs) | 69.6 ± 9 | 70.1 ± 9 | 68.3 ± 8 | 0.515 |
| Male gender | 60% | 55% | 71% | 0.292† |
| Ischemic DCM | 40% | 45% | 29% | 0.353‡ |
| NYHA functional class | 3.5 ± 0.5 | 3.6 ± 0.4 | 3.4 ± 0.5 | 0.242 |
| ECG measurements | | | | |
| QRS duration (ms) | 152.6 ± 32.1 | 168.2 ± 21.4 | 110.0 ± 10.9 | <0.0001 |
| RR interval (ms) | 819.7 ± 127.4 | 819.1 ± 102.5 | 821.4 ± 183.6 | 0.845 |
| PR interval (ms) | 158.1 ± 47.7 | 153.5 ± 47.0 | 170.7 ± 49.1 | 0.225 |
| Echo measurements | | | | |
| EF (%) | 23.2 ± 4.7 | 22.6 ± 4.6 | 24.6 ± 5.0 | 0.272 |
| LVEDD (mm) | 75.9 ± 10.4 | 77.4 ± 10.6 | 71.8 ± 9.2 | 0.077 |
| LVESD (mm) | 63.9 ± 9.7 | 64.8 ± 10.2 | 61.4 ± 8.4 | 0.252 |
| MR ($cm^2$) | 7.0 ± 4.2 | 6.9 ± 4.1 | 7.5 ± 4.7 | 0.820 |
| 6MWT (m) | 261.5 ± 85.8 | 256.0 ± 65.4 | 276.4 ± 88.9 | 0.099 |
| Previous pacemaker | 11.5% | 15.7% | 0 | 0.174‡ |
| Follow-up duration (days) | 546 ± 277 | 565 ± 282 | 493 ± 264 | 0.417 |

*p value based on: analysis of variance, chi-square test, † or Fisher exact test. ‡Data are presented as the mean value ± SD, or percentage of patients.

DCM = dilated cardiomyopathy; ECG = electrocardiogram; EF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation area; NYHA = New York Heart Association; 6MWT = 6-min walking test.

ms; PM: 451.7 ± 62.7 ms; p = 0.139), or as regards the other major clinical and functional parameters, therefore highlighting a substantial homogeneity of the subgroups.

Pacing therapy was effective in the significant reduction of IVD and Q-LW in the entire patient population. The QRS duration does not alter the impact of CRT on the IVD. In fact, IVD significantly improved in all groups after CRT with no statistically significant difference between the groups. Moreover, whereas a significant reduction in the Q-LW interval was observed after CRT only in group 1, the difference between groups 1 and 2 was not statistically significant.

A regression analysis of the asynchrony patterns and the echocardiographic outcome in both groups showed a significant inverse correlation between ΔIVD and ΔEF in group 1 ($r^2 = 0.2386$; $p < 0.002$) and a direct correlation between ΔIVD and ΔLVESD in group 1 ($r^2 = 0.2229$, $p < 0.003$). On the contrary, we did not observe any correlation between ΔQ-LW and the echocardiographic outcome (Fig. 2).

## DISCUSSION

The major finding of our paper is that CRT provides a significant clinical and functional benefit in patients with incomplete LBBB (QRS ≤120 ms) and DCM of various etiologies, selected on the basis of the presence of interventricular and intraventricular asynchrony. This amelioration is comparable to that obtained in patients who are currently selected by means of current indications for CRT (QRS duration >120 to 150 ms) (1–5).

**Current study rationale.** To date, CRT has been reserved for patients with refractory HF and a consistent prolongation of the QRS (>120 to 150 ms), as suggested by previous studies (1–5). This assumption is based on epidemiologic (14,15), clinical, and experimental data (16–18).

With respect to experimental data, the effectiveness of CRT is greater in patients with substantial QRS prolongation (>150 ms); this has usually been shown in acute hemodynamic studies (16,17) and, recently, in the Pacing

**Table 2.** Clinical and Electrocardiographic Characteristics Before and After CRT

| Characteristics | All Patients | Group 1 | Group 2 | 1 vs. 2 p Value* |
|---|---|---|---|---|
| QRS duration baseline (ms) | 151.3 ± 30.9 | 168.2 ± 21.4 | 110.4 ± 10.9 | <0.001 |
| QRS duration follow-up (ms) | 123.5 ± 9.7‡ | 125.2 ± 9.1‡ | 120.5 ± 13.1 | 0.453 |
| NYHA baseline | 3.4 ± 0.5 | 3.5 ± 0.5 | 3.3 ± 0.5 | 0.695 |
| NYHA functional class follow-up | 1.8 ± 0.5‡ | 1.8 ± 0.5‡ | 1.7 ± 0.6‡ | 1.000 |
| 6MWT baseline (m) | 258.1 ± 76.3 | 256.0 ± 65.4 | 276.4 ± 88.9 | 1.000 |
| 6MWT follow-up (m) | 389.8 ± 52.0‡ | 394.2 ± 38.4‡ | 369.9 ± 70.2§ | 0.362 |
| RR interval baseline (ms) | 824.8 ± 127.5 | 819.1 ± 102.5 | 821.4 ± 183.6 | 1.000 |
| RR interval follow-up (ms) | 800.1 ± 143.2 | 795.8 ± 149.7 | 810.7 ± 97.5 | 1.000 |
| Death (n) | 10 (19.2%) | 7 (18.4%) | 3 (21.4%) | 1.000† |

*p value based on: analysis of variance or †Fisher exact test; ‡$p < 0.001$ and §$p < 0.01$ vs. baseline. Data are presented as the mean value ± SD or percentage of patients.

CRT = cardiac resynchronization therapy; NYHA = New York Heart Association; 6MWT = 6-min walking test.

**Table 3.** Echocardiographic Data Before and After Cardiac Resynchronization Therapy

| Characteristics | All Patients | Group 1 | Group 2 | 1 vs. 2 p Value* |
|---|---|---|---|---|
| EF baseline (%) | 23.0 ± 4.6 | 22.6 ± 4.6 | 24.6 ± 5.0 | 0.591 |
| EF follow-up (%) | 33.4 ± 5.1† | 33.2 ± 5.4† | 33.6 ± 5.9† | 1.000 |
| LVEDD baseline (mm) | 76.8 ± 10.3 | 77.4 ± 10.6 | 71.8 ± 9.2 | 0.490 |
| LVEDD follow-up (mm) | 70.6 ± 10.4† | 71.6 ± 10.7‡ | 65.6 ± 8.5‡ | 0.380 |
| LVESD baseline (mm) | 64.7 ± 9.9 | 64.8 ± 10.2 | 61.4 ± 8.4 | 0.839 |
| LVESD follow-up (mm) | 57.9 ± 10.3† | 57.9 ± 11.0‡ | 55.6 ± 8.2‡ | 1.000 |
| MR baseline ($cm^2$) | 6.9 ± 4.2 | 6.9 ± 4.1 | 7.5 ± 4.7 | 1.000 |
| MR follow-up ($cm^2$) | 4.0 ± 3.2† | 3.8 ± 2.9† | 4.5 ± 3.5† | 1.000 |
| IVD baseline (ms) | 54.1 ± 29.7 | 56.4 ± 31.1 | 42.5 ± 16.6 | 0.320 |
| IVD follow-up (ms) | 14.2 ± 16.9† | 15.9 ± 15.2† | 6.4 ± 16.8† | 0.178 |
| Q-LW baseline (ms) | 418.8 ± 71.0 | 421.8 ± 72.6 | 395.0 ± 53.9 | 0.987 |
| Q-LW follow-up (ms) | 386.9 ± 55.3‡ | 389.7 ± 55.3‡ | 363.2 ± 47.3 | 0.472 |
| E-A baseline (ms) | 436.8 ± 124.1 | 425.3 ± 102.1 | 471.8 ± 166.3 | 0.687 |
| E-A follow-up (ms) | 455.0 ± 113.7 | 442.0 ± 120.8 | 437.5 ± 54.7 | 1.000 |
| DT baseline (ms) | 120.4 ± 29.6 | 121.5 ± 31.3 | 117.7 ± 25.8 | 1.000 |
| DT follow-up (ms) | 258.1 ± 76.3† | 157.2 ± 29.8† | 148.5 ± 17.4‡ | 0.223 |

*p value based on analysis of variance; †$p < 0.001$; ‡$p < 0.05$ vs. baseline. Data are presented as the mean value ± SD.
DT = deceleration time; E-A = left ventricular filling time; EF = left ventricular ejection fraction; IVD = interventricular delay; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation area; Q-LW = posterolateral left ventricular wall activation delay.

Therapies in Congestive Heart Failure II (PATH-CHF II) trial (18). However, in these studies, patients were considered eligible in the presence of QRS prolongation on surface ECG as the only marker of asynchrony, and with no demonstration of ventricular dyssynchrony using imaging techniques. Even though the available data in literature highlights a positive correlation between QRS duration and interventricular asynchrony (9), the correlation between QRS duration and intraventricular asynchrony is not straightforward. Actually, an echocardiographic study on patients with DCM by Blazek et al. (19) confirmed the presence of intraventricular asynchrony in 46% and 36% of patients with LBBB or QRS duration <120 ms, respectively. No correlation was found between the QRS duration and the degree of mechanical asynchrony. These data are also confirmed by a more recent observation by Yu et al. (20), documenting intraventricular systolic asynchrony in 73% of patients with HF and a QRS duration >120 ms and in 51% of patients with a QRS duration ≤120 ms, respectively. Again, this study did not show any correlation between QRS duration and systolic asynchrony. Moreover, Breithard et al. (21) have demonstrated that patients with a QRS duration >120 ms may show many different patterns of baseline intraventricular asynchrony, ranging from an almost complete contraction synchrony between the lateral wall and the interventricular septum, to a very delayed lateral wall displacement, and to a paradoxical septal motion. Søgaard et al. (22) have pointed out that the degree of intraventricular asynchrony, evaluated with tissue Doppler imaging, and not the baseline QRS duration, is predictive of the effectiveness of CRT.

These data stress the concept that, first, interventricular asynchrony may be perhaps grossly identified by the presence of a wide QRS (better so if LBBB is present) on surface ECG (9,17,18), but that, nevertheless, more sophisticated imaging techniques are needed to disclose intraventricular asynchrony; second, that a wide QRS cannot identify responders to CRT.

**Comparison between groups.** We are of the opinion that the strength of our patient selection criteria is supported by

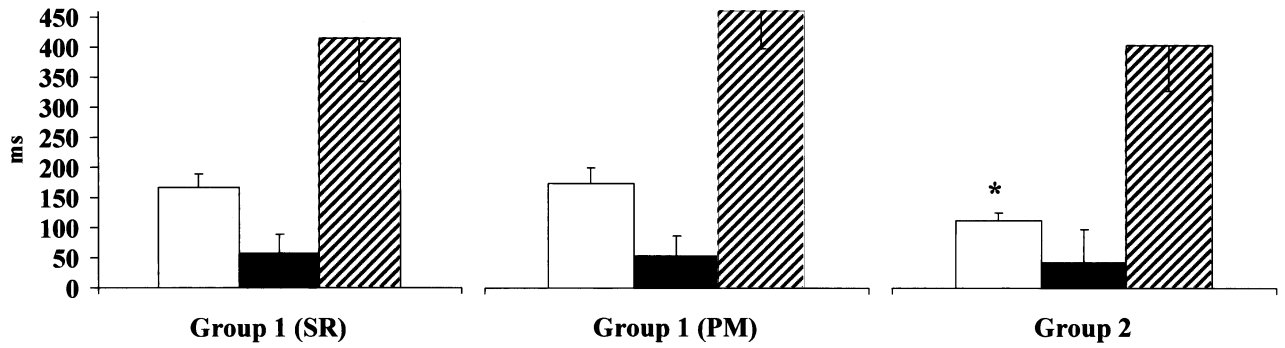


**Figure 1.** Baseline duration of QRS **(white bars)**, interventricular delay **(black bars)**, and posterolateral left ventricular wall activation delay **(striped bars)** in patients in group 1 with sinus rhythm (SR) at enrollment, with prior pacemaker implantation (PM), and in group 2. The only difference between the groups is represented by QRS duration (*$p < 0.001$ group 2 vs. RS and vs. PM).

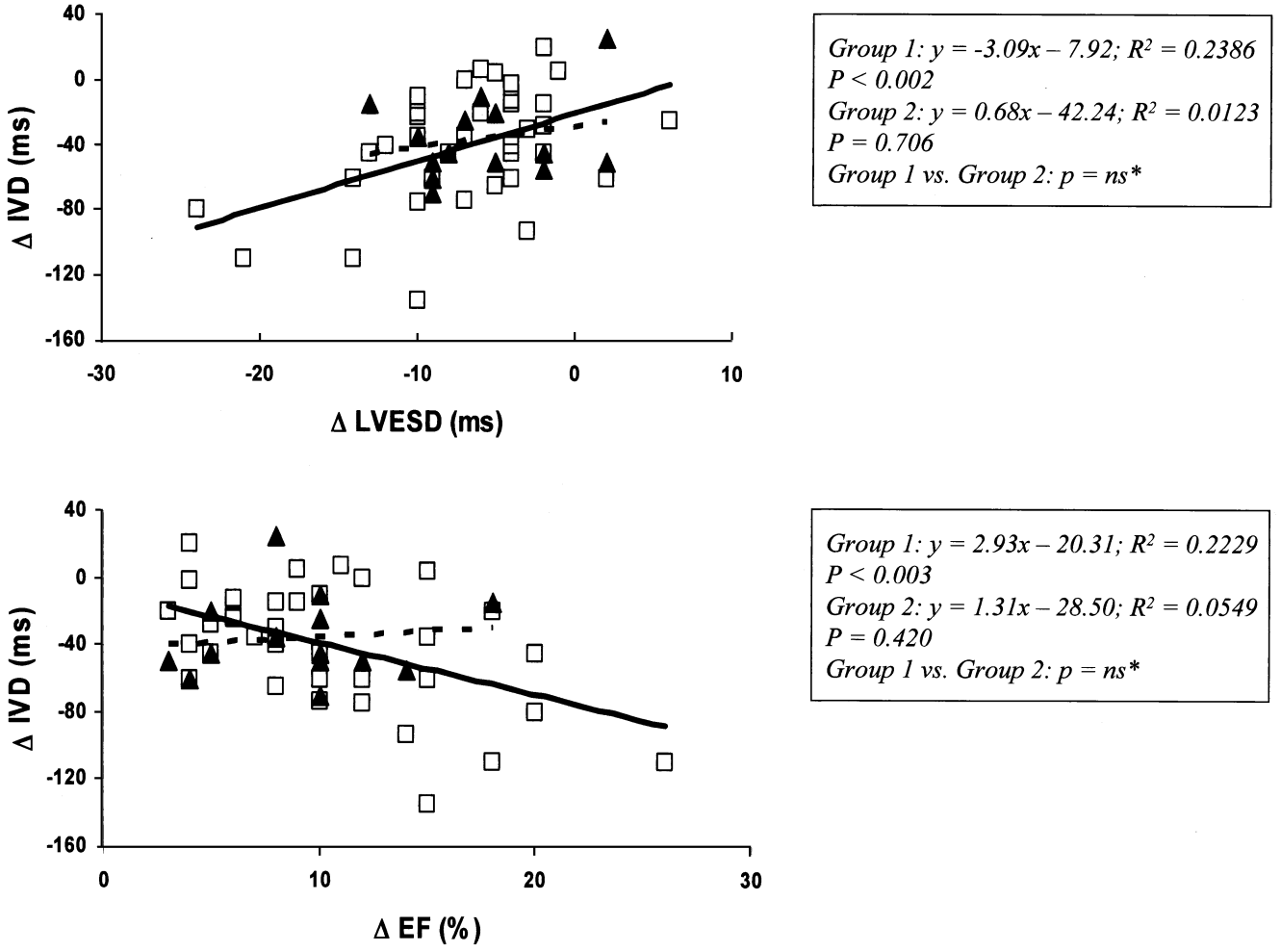


**Figure 2.** Regression lines (**solid line** = group 1; **dashed line** = group 2) show a fairly good correlation between the magnitude of interventricular delay decrease (ΔIVD) and magnitude of ejection fraction increase (ΔEF) **(top)** and left ventricular end-systolic diameter decrease (ΔLVESD) **(bottom)** in group 1 **(open squares)** but not in group 2 **(solid triangles)** after cardiac resynchronization therapy. Δ = follow-up − baseline absolute difference. *p value based on analysis of covariance.

the evidence of similar baseline characteristics in both groups with the exception of QRS duration. Moreover, the effectiveness of CRT on the clinical and functional status of our patients is similar in the entire population and in both groups and in agreement with the current data in literature (1–5,23,24). As a result, EF, NYHA functional class, LVEDD, LVESD, and MR all improved after CRT without a substantial difference between the groups. The 6MWT did improve in both groups, but the magnitude of improvement was higher in group 1 than in group 2. With respect to diastole, CRT determined a significant increase in DT in both groups at follow-up, and these data are in agreement with previous studies (24). This amelioration was observed in the presence of a constant E-A filling interval throughout the study, thus indicating a shift from a restrictive toward a pseudonormal diastolic pattern. This improvement may contribute to the optimization of global ventricular performance.

When considering the asynchrony indexes, Q-LW indicates the total duration of left ventricular systole, whereas (Q-LW) − (Q-E) is the expression of the potential overlap of ventricular contraction and filling (25). We noted a trend toward the reduction of the Q-LW interval (i.e., intraventricular resynchronization) that was statistically significant only in group 1. Nonetheless, CRT induced interventricular resynchronization, as testified to by a significant reduction of IVD in both groups. Our data are in accordance with previous studies (26–28) performed with Doppler echocardiography that utilized asynchrony measurements similar to those obtained in our study (26) or tissue Doppler imaging (27).

Again, we observed an unimpressive, but significant, inverse correlation between ΔIVD and ΔEF and a direct correlation between ΔIVD and ΔLVESD only in group 1. Our study was not specifically conceived to identify the most powerful outcome predictor after CRT, which has been identified in recent studies as the pre-pacing intraventricular delay (21,29), but these observations suggest that the degree of IVD reduction can predict a favorable outcome in the long term.

As regards the correlation between QRS narrowing after CRT and functional enhancement, acute studies have clearly shown a lack of correlation between these variables (30), whereas there is controversial data in literature regarding the correlation between narrowing of the QRS interval after chronic CRT and clinical improvement (31–33). Even though chronic CRT usually shortens the QRS interval, in our series we observed a significant reduction of the QRS interval in group 1 and an increase in group 2; nevertheless, the clinical and functional benefit of CRT was present and significant in both groups, suggesting that the effectiveness of biventricular pacing may be independent of the evidence of QRS narrowing. In summary, even though a wide QRS interval may be associated with the presence of mechanical asynchrony, it is not to be considered an absolute marker of this condition, as already underscored by other authors (34).

**Study limitations.** The major limitation of our study is the lack of randomization. Nevertheless, our results appear to be substantiated by the similar baseline characteristics of the groups and the significant effectiveness of CRT in both groups, which represent the general population with HF. Ultimately, the evaluation of intraventricular asynchrony was obtained with a rather simple and non-sophisticated M-mode measurement, and a similar method has indeed been adopted for patient selection in the Cardiac Resynchronization in Heart Failure (CARE-HF) trial (35). Bearing this in mind, we could argue that, if CRT has been proven to be effective in this patient population that was selected using such a "simple and reproducible" measurement, we should expect even better clinical outcomes in the event of patients being selected with more sophisticated imaging techniques.

**Conclusions.** Our paper, in agreement with previous studies (1–5), confirms the effectiveness of CRT in moderate-severe HF patients refractory to optimal medical therapy. To our knowledge, it is the first time that such a clinical benefit has been demonstrated, not only in patients with major intraventricular conduction delay on surface ECG, but even in subjects with a QRS interval ≤120 ms, provided that echocardiographic evidence of interventricular and intraventricular asynchrony is present. Moreover, this study stresses the concept that the selection of patients for CRT should be performed using a mechanical evaluation of left ventricular contraction, rather than electrical criteria adopted so far. Further studies on larger patient populations are obviously needed to confirm our initial results.

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## APPENDIX

For the complete Appendix, please see the December 17, 2003, issue of *JACC* at www.cardiosource.com/jacc.html.