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Tissue Doppler Imaging Predicts Improved Systolic Performance and Reversed Left Ventricular Remodeling During Long-Term Cardiac Resynchronization Therapy

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OBJECTIVES We sought to evaluate the long-term impact of cardiac resynchronization therapy (CRT) on left ventricular (LV) performance and remodeling using three-dimensional echocardiography and tissue Doppler imaging (TDI).

BACKGROUND Three-dimensional echocardiography and TDI allow rapid and accurate evaluation of LV volumes and performance.

METHODS Twenty-five consecutive patients with severe heart failure and bundle branch block who underwent biventricular pacemaker implantation were included. Before and after implantation of the pacemaker, three-dimensional echocardiography and TDI were performed. These examinations were repeated at outpatient visits every six months.

RESULTS Five patients (20%) died during one-year follow-up. In the remaining 20 patients, significant reductions in LV end-diastolic volume and LV end-systolic volume of 9.6 ± 14% and 16.5 ± 15%, respectively ($p < 0.01$), could be demonstrated during long-term follow-up. Accordingly, LV ejection fraction increased by 21.7 ± 18% ($p < 0.01$). According to a newly developed TDI technique—tissue tracking—all regional myocardial segments improved their longitudinal systolic shortening ($p < 0.01$). The extent of the LV base displaying delayed longitudinal contraction, as detected by TDI before pacemaker implantation, predicted long-term efficacy of CRT. The QRS duration failed to predict resynchronization efficacy.

CONCLUSIONS Cardiac resynchronization significantly improved LV function and reversed LV remodeling during long-term follow-up. Patients likely to benefit from CRT can be identified by TDI before implantation of a biventricular pacemaker. (J Am Coll Cardiol 2002;40:723–30)
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According to the findings at cardiac catheterization, cardiac resynchronization therapy (CRT) by biventricular pacing acutely improves left ventricular (LV) function in patients with severe heart failure and bundle branch block (1,2). Reports on the use of noninvasive techniques for the short- and long-term evaluation of CRT efficacy are limited thus far (3–5). However, radioisotope techniques have a low temporal and spatial resolution, making them less suitable to quantify regional LV synchrony. Recently introduced echocardiographic techniques, such as tissue Doppler imaging (TDI) and three-dimensional echocardiography, enable accurate quantification of regional and global LV function and volumes (6–10). From digitally recorded TDI loops of one or more heart beats containing velocity data from the entire myocardium, two new TDI modalities can be derived: tissue tracking (TT) and strain rate (SR) analysis (11). Tissue tracking visualizes the longitudinal motion amplitude in each myocardial segment during systole (Figs. 1 and 2), and SR analysis can be used to determine whether this motion represents contraction or is merely passive (Fig. 3). We found TT and SR useful for the evaluation of regional myocardial pathophysiology before and after cardiac resynchronization and, therefore included TT and SR analysis in our follow-up study.

Using TDI and three-dimensional echocardiography (5,6), we have recently reported on the immediate benefit of CRT in terms of myocardial synchrony and performance, resulting in the early reduction in operating LV volumes (5). We also quantitated the degree of LV mechanical asynchrony by the extent of myocardium at the LV base displaying delayed longitudinal contraction (DLC) (i.e., contraction after closure of the aortic valve). Using multivariate analysis, we found that the number of segments with DLC (at the LV base) was the only co-variate to predict short-term CRT efficacy (5).

At present, the long-term efficacy of CRT in terms of LV performance is poorly elucidated. Because of the observed short-term effect on LV function and volumes, we hypothesized that long-term therapy would further improve LV systolic performance and reverse LV remodeling. These aspects, as well as potential predictors of long-term CRT benefit, are addressed in the present report.

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Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
DLC = delayed longitudinal contraction
GSCA = global systolic contraction amplitude
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RV = right ventricle/ventricular
SR = strain rate
TDI = tissue Doppler imaging
TT = tissue tracking

METHODS

Patient group. The patient group comprised 25 consecutive patients included in a recently published study on the short-term effect of CRT (5). Despite receiving stable (>6 months), contemporary medication for heart failure, all patients were in New York Heart Association (NYHA) functional class III or IV. All were in sinus rhythm and had bundle branch block with a QRS width above 120 ms.

Implantation technique. Pacemaker leads were inserted by the transvenous route. Three pacing leads were implanted: one in the right atrium, another in the high septum or outflow tract of the right ventricle (RV) and one in the coronary sinus (Medtronic 2187 or 10512, Minneapolis, Minnesota); this last lead was positioned on the LV free wall through a coronary sinus tributary. The RV and LV pacing leads were positioned to ensure that the sensed local intracardiac activation during sinus rhythm was measured as early for the RV lead and as late for the LV lead as possible, according to the QRS complex on the surface electrocardiogram. The pacing leads were connected to a dual-chamber biventricular pacemaker (Medtronic, InSync), with nonprogrammable simultaneous pacing of the two ventricular leads. The biventricular pacemaker was programmed in DDD mode. Adjustment of the atrioventricular delay was performed to ensure the longest possible atrioventricular filling time evaluated from pulsed Doppler analysis of transmitral LV filling.

Echocardiographic protocol. We have previously reported in detail on the three-dimensional echocardiographic and TDI protocol (5–7). We have also established our coefficient of variation of TDI measures of velocities and asynchrony to be 4% to 6% (5), comparable to values reported by other investigators (9). Three-dimensional echocardio-

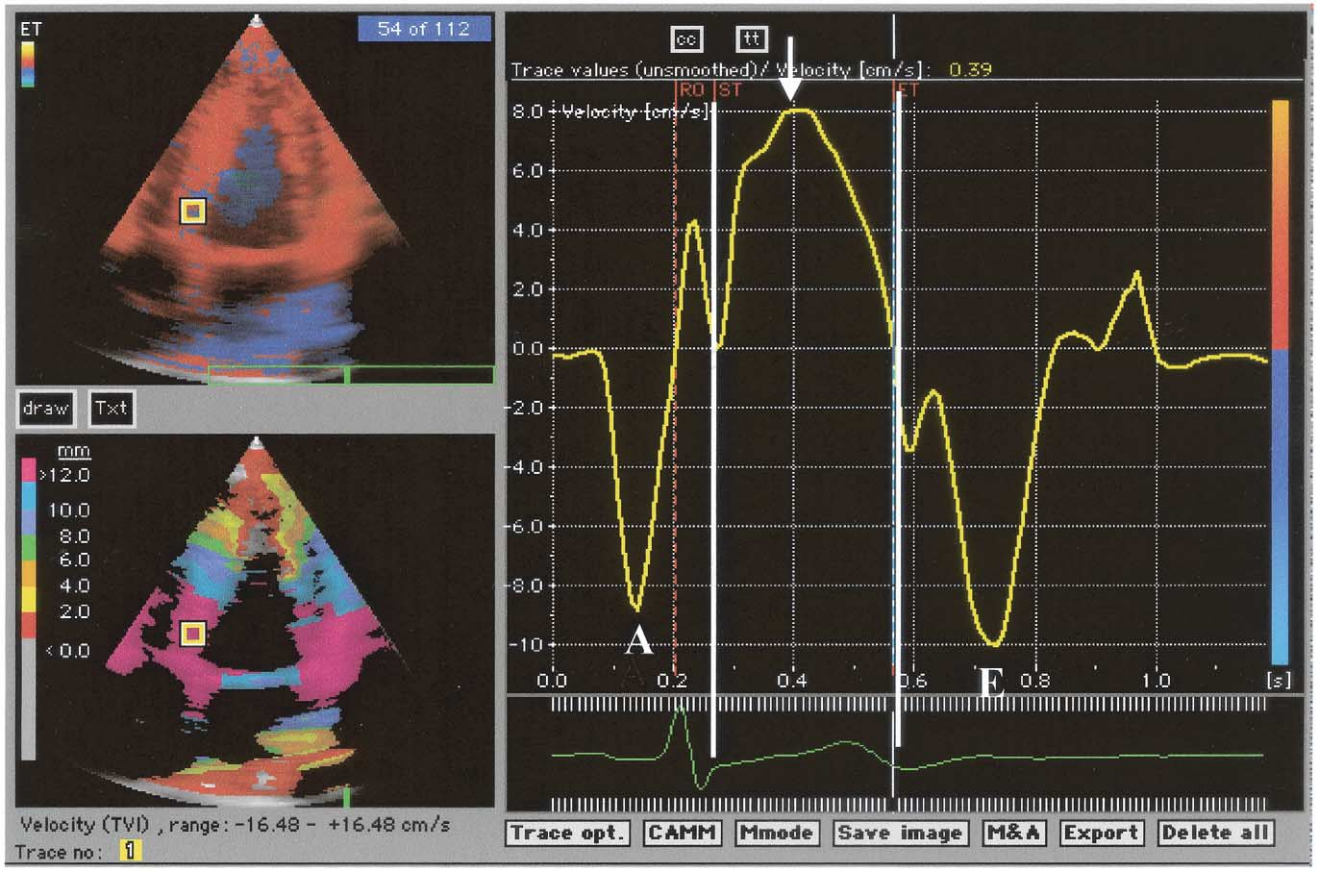

Figure 1. Tissue Doppler image in the apical four-chamber view of a normal subject **(upper left panel)**. **(Right panel)** The velocity profile during one cardiac cycle obtained at the base of the interventricular septum. The **solid lines** mark the duration of systole (310 ms), and the **arrow** indicates the peak systolic velocity (8 cm/s). The diastolic filling of the LV is reflected in the E-wave (E) and A-wave (A). **(Lower left panel)** Tissue tracking displays, in color-coded format, the regional myocardial shortening (mm) in each segment, calculated automatically as the integral of the digitally stored velocity tracing in systole in each segment.

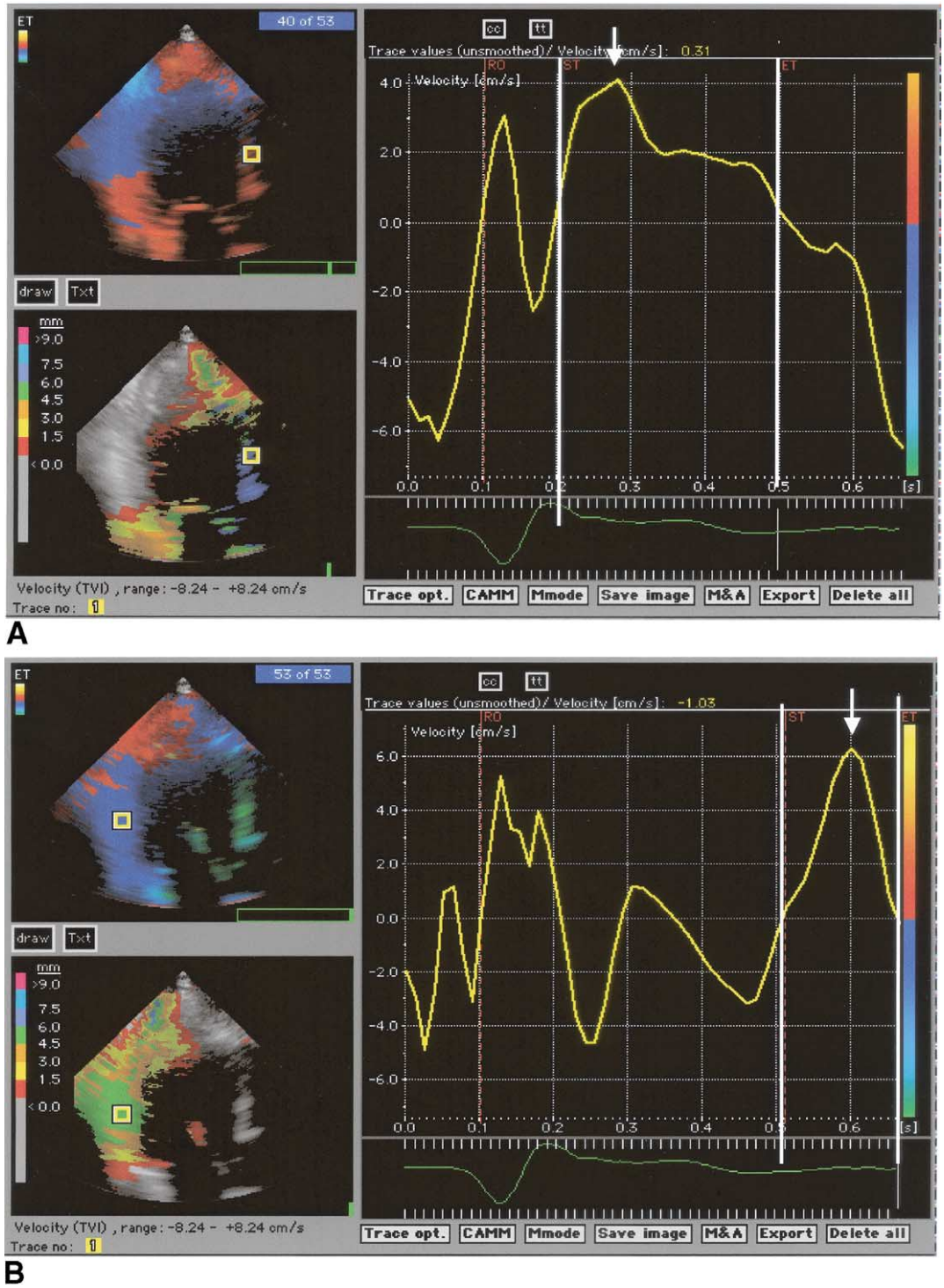

Figure 2. **(A)** Apical long-axis view in a patient with dilated cardiomyopathy and left bundle branch block. **Solid lines** mark the duration of systole (300 ms). The sample point is located at the base of the anteroseptal region. In this region, the peak velocity is 4 cm/s **(arrow)**. **(Lower left panel)** Tissue tracking. From the color coding, it appears that the majority of the posterior wall is gray, indicating either no or paradoxical motion (i.e., motion away from the apex during systole). **(B)** The same patient as in **part A**, with the cursor positioned in the basal segment of the posterior wall. The interval between the **solid lines in the right panel** represents the duration (180 ms) of delayed longitudinal contraction (DLC), with a peak velocity of 6 cm/s **(arrow)**. The onset of this DLC corresponds to the cessation of systole in the septum, as in **part A, right panel**. Tissue tracking **(lower left panel)** displays the extent of myocardium **(colored segments)** with DLC (diastole, open mitral valve). Note that the remaining part of the LV is **gray**, indicating either no motion or motion toward the base of the heart (relaxation). The strain rate is required to detect shortening or passive stretching.

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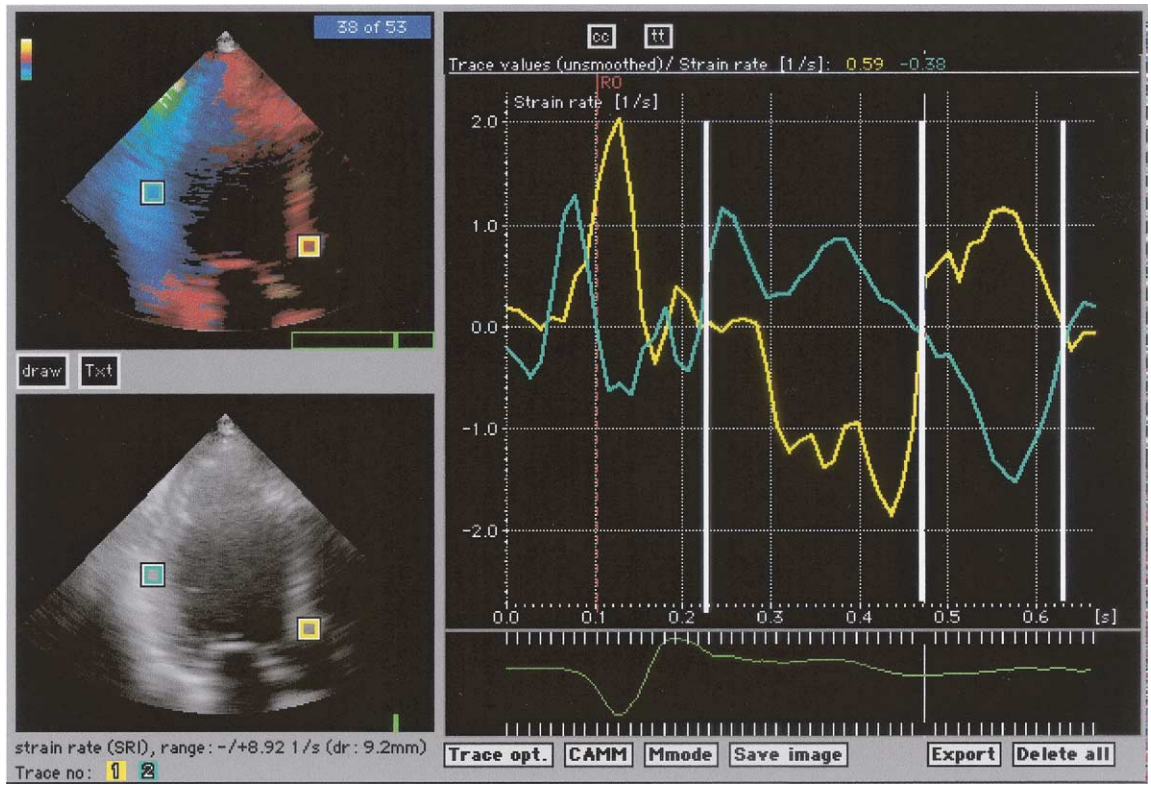

Figure 3. The same patient as in Figure 2. One sample **(yellow)** is positioned at the base of the septum and another **(green)** is located in the posterior wall. In each point, strain rate (SR) analysis is carried out in a range of 10 mm. The **first solid line (right panel)** represents the onset of a negative SR in the septum **(yellow line)**, indicating the onset of systolic shortening. The **second solid line** indicates cessation of systole, where the SR in the septum becomes positive. At the same time, a negative SR is observed in the posterior wall **(green line)**, and this persists between the **second and third lines**, documenting shortening in early diastole (i.e., delayed longitudinal contraction).

graphic reproducibility was previously reported in depth (6,7). In brief, three-dimensional echocardiography and TDI were performed before implantation of the pacemaker, immediately after implantation and every six months after implantation. One observer, who had no knowledge of the clinical data of the patients, performed all three-dimensional echocardiographic and TDI analyses.

Three-dimensional echocardiography was performed during end-expiratory apnea within one breath hold, using electrocardiogram-triggered co-axial rotation from the apical window with 30° intervals between the scanning planes. The resulting six digital cine loops were transferred to a computer for off-line analysis (Echo-Pac Software, GE-Vingmed Ultrasound, Horten, Norway). In each view, the endocardial borders were drawn manually in end diastole and end systole for LV volume measurement.

Tissue Doppler imaging was acquired as digital loops during one heart beat in the apical four-chamber, two-chamber and long-axis views (5). Analysis of regional peak contraction velocities toward the apex and the duration of contraction (Fig. 1, showing a normal subject) was performed in each of 16 segments of the LV model of the American Society of Echocardiography (12).

A TT image in systole was derived from the TDI loop in each of the apical views (Fig. 1, lower left panel; Fig. 2A, lower left panel). If DLC was present, another TT image was recorded in diastole to visualize the extent of myocardium with DLC (Fig. 2B, lower left panel). The number of segments displaying DLC at the base of the LV (5) was recorded and expressed as the percentage of the total circumference of the LV base. Myocardial segments showing motion toward the apex were explored with SR analysis. Motion toward the apex after closure of the aortic valve was only registered as DLC if negative SR documented that the motion reflected true shortening. Figure 3 shows the SR analysis.

Figure 4 shows the development in myocardial performance, displayed as TT images obtained during long-term follow-up in one patient. Again using the 16-segment LV model, the average motion amplitude toward the apex in systole was estimated for each segment, and averages were calculated for the six segments at the LV base, six mid-ventricular segments and four apical segments. The global systolic contraction amplitude (GSCA) index was calculated as the average amplitude of all 16 segments.

Statistical analysis. The paired Student *t* test was used for comparison of three-dimensional echocardiographic and TDI measurements at baseline and during CRT. The QRS width and DLC extent were correlated to long-term improvement in LV performance by univariate linear regression analysis. In addition, linear regression analysis was used for the evaluation of changes in GSCA and percent LV

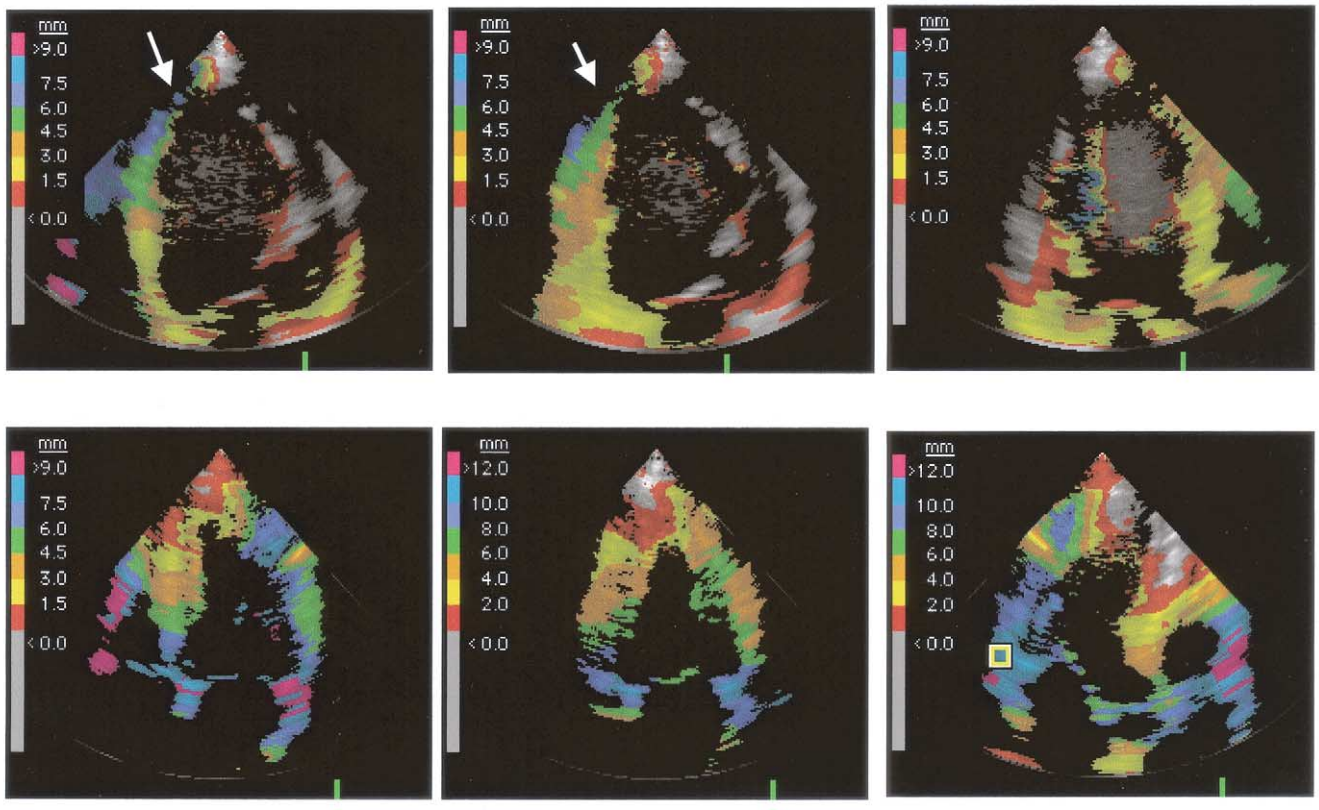

Figure 4. The **upper panels** represent the three apical views in systole in a patient with idiopathic dilated cardiomyopathy before implantation of a biventricular pacemaker. The majority of the lateral wall, anterior wall and posterior wall are **gray**, indicating a lack of systolic motion toward the apex. The mechanical function of the interventricular septum and inferior walls is abnormal, with a higher motion amplitude in the segment adjacent to the apex **(arrows)**. The **lower panels** show corresponding views after one year of cardiac resynchronization therapy. At this time, systolic motion toward the apex is present in the entire left ventricle. In addition, the reverse distribution of motion amplitude in the septum and inferior wall has been normalized, with greater systolic performance at the base of the left ventricle.

ejection fraction (LVEF) during follow-up. A value of $p < 0.05$ was considered statistically significant. Data are presented as the mean value ± SD.

RESULTS

Five (20%) of the 25 patients died during follow-up, before the first outpatient examination. All of the patients who died had ischemic heart disease. The QRS duration (179 ± 23 ms) was comparable to that of the remaining study group. However, these patients displayed only limited DLC at the LV base (20 ± 12% of the LV base circumference), and their immediate response to CRT, in terms of improvement in LVEF, was minor (20.1 ± 6% to 21.9 ± 7%). The remaining 20 patients were followed for a mean period of 12.6 months (range 6 to 18 months). The pre-implantation demographic and clinical variables of these patients are given in Table 1.

Long-term follow-up. At the end of follow-up, significant reductions in the LV end-diastolic volume and LV end-systolic volume of 9.6 ± 14% and 16.9 ± 15%, respectively, as compared with hospital discharge, were demonstrated ($p < 0.01$). This was associated with a significant increase in LVEF of 21.7 ± 18% ($p < 0.01$) (Table 2).

By means of TT, it was documented that the average motion amplitude toward the apex during systole improved significantly throughout the entire LV (Table 2). Figure 4 demonstrates the use of TT to visualize changes in motion amplitude toward the apex in systole. The calculated improvement in GSCA from hospital discharge to the latest follow-up visit for each patient was significantly correlated to the improvement in LVEF ($r = 0.83$, $p < 0.01$). The

Table 1. Baseline Clinical and Demographic Variables in Survivors (n = 20)

NYHA functional class (III/IV)	11/9
Etiology (IHD/IDC)	11/9
LBBB/RBBB	18/2
Pre-implantation QRS duration (ms)	189 ± 23
Pre-implantation LVEF (%)	23.8 ± 6
Pre-implantation LVEDV (ml/m^2)	318 ± 89
Pre-implantation LVESV (ml/m^2)	246 ± 80
Pre-implantation MS (LV base) (mm)	2.4 ± 0.8
Pre-implantation MS (mid-ventricular LV) (mm)	1.0 ± 0.8
Pre-implantation MS (apical LV) (mm)	0.4 ± 0.5
DLC at LV base circumference (%)	51.4 ± 19

Data are presented as the number of patients or mean value ± SD.

DLC = delayed longitudinal contraction; IDC = idiopatic dilated cardiomyopathy; IHD = ischemic heart disease; LBBB = left bundle branch block; LV = left ventricle or ventricular; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MS = myocardial shortening toward the apex during systole; NYHA = New York Heart Association; RBBB = right bundle branch block.

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Table 2. Left Ventricular Volumes and Regional Myocardial Shortening During Long-Term Follow-Up in Survivors (n = 20)

	CRT Results at Hospital Discharge	CRT Results at Follow-Up
LVEDV (ml)	289 ± 92	261 ± 94*
LVESV (ml)	206 ± 74	171 ± 75*
LVEF (%)	28.7 ± 7	34.9 ± 8*
MS at LV base (mm)	3.4 ± 0.8	5.4 ± 0.9*
MS at mid-ventricular LV (mm)	1.4 ± 0.7	2.6 ± 1.0*
MS at apical LV (mm)	0.5 ± 0.6	1.0 ± 0.8†

*$p < 0.01$; †$p < 0.05$. Data are presented as the mean value ± SD.
CRT = cardiac resynchronization therapy; other abbreviations as in Table 1.

percentage of the LV base circumference displaying DLC was reduced from 18.7 ± 7% at discharge to 8.1 ± 8% at one year ($p < 0.05$).

There was improvement in NYHA functional class, from 3.5 ± 0.4 at baseline to 2.2 ± 0.5 at the completion of follow-up ($p < 0.01$). No significant change in medication, such as angiotensin-converting enzyme inhibitors, diuretics, or beta-blockers, was performed during follow-up.

Predictors of long-term efficacy. The percentage of the LV base circumference exhibiting DLC, as measured at baseline, predicted long-term improvement in LVEF and GSCA ($t = 3.1$, $p < 0.01$ and $t = 3.3$, $p < 0.01$, respectively) (Fig. 5). The QRS width did not predict long-term CRT improvement in LVEF and GSCA ($t = 1.0$, $p = NS$ and $t = 1.7$, $p = NS$, respectively).

DISCUSSION

Cardiac resynchronization therapy appears to be a promising therapeutic option in patients with bundle branch block and severe heart failure. In this study, we documented long-term improvement in LV systolic performance and a parallel reduction in LV volumes (i.e., reversed LV remodeling). The latter effect may be of particular interest, as it might be associated with an improved prognosis in patients with ischemic cardiomyopathy, where LV dilation has emerged as a powerful predictor of mortality (13). In patients with idiopathic dilated cardiomyopathy, however, the prognostic determinants may seem more complex, but the presence of a recruitable LV contractile reserve seems to predict a more favorable outcome (14). However, the potential impact of CRT on mortality awaits larger randomized trials.

Potential mechanisms underlying CRT benefit. Several mechanisms could underlie the benefit of CRT on LV function and remodeling. If LV wall stress fails to decline during systole due to ailing LV systolic function, overall LV wall stress will be persistently elevated, causing progressive remodeling of the LV with continuous dilation. Therefore, by improving global systolic LV function, long-term CRT may reduce LV wall stress, a reduction that may, in turn, contribute to reversed LV remodeling. In addition, DLC (i.e., contraction during diastole representing mechanical LV asynchrony) not only reflects a loss of systolic force, it also causes inappropriate energy consumption and increased LV wall stress in early diastole. This would presumably interfere with regional myocardial perfusion that could, in turn, further reduce LV systolic performance and aggravate remodeling. Moreover, because CRT reduces the number of segments displaying DLC, pacing not only improves systolic function by recruiting this contractile reserve, it also facilitates diastolic filling of the LV. Interestingly, the improvement in LV systolic performance during CRT is not accompanied by an increase in myocardial oxygen consump-

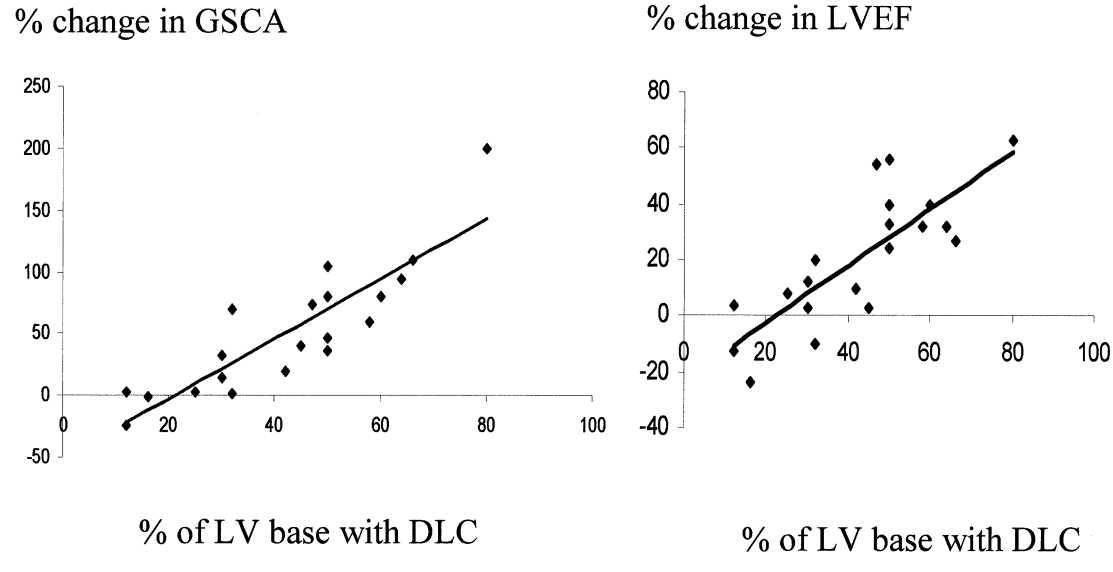

Figure 5. (Left) Scatterplot showing the relationship between the percentage of the left ventricular (LV) base circumference exhibiting delayed longitudinal contraction (DLC) (*x* axis) and the percent change in global systolic contraction amplitude (GSCA) during follow-up. **(Right)** Scatterplot showing the relationship between the percentage of the LV base circumference exhibiting DLC (*x* axis) and the percent change in left ventricular ejection fraction (LVEF) during follow-up.

tion (15), presumably because the reversion of LV remodeling, as documented in the present study, reduces myocardial oxygen demand. Finally, the majority of patients with end-stage heart failure and bundle branch block have secondary mitral valve regurgitation. Thus, reduced mitral regurgitation during CRT (16) could also contribute to the observed reversed LV remodeling.

During short-term CRT, both LV volumes and systolic function improve acutely (5,16). In our study of the immediate-term effect of CRT, the improvement in systolic function appeared to be confined to the base of the LV, whereas the mid-ventricular and apical areas of the ventricle did not seem to be resynchronized (5). We therefore proposed the hypothesis that multiple LV leads might be required to obtain resynchronization of more extended regions of the LV (5). However, during long-term CRT, both the mid-ventricular and the more distal part of the LV eventually showed improved systolic performance (Table 2). The absolute improvement in LVEF from baseline of the 20 patients was 11% (23.8% to 34.9%) before implantation to one-year follow-up. The long-term effect of CRT after hospital discharge was responsible for more than 50% of the total increase in LVEF (Tables 1 and 2). Thus far, two ventricular leads appear to be sufficient, although resynchronization of the mid and apical parts of the LV seems to be a delayed phenomenon.

Selection of responders to CRT. Our observation of improvement in LV performance corresponds with the recently published Multisite Stimulation in Cardiomyopathies trial (MUSIC) showing a benefit of NYHA functional class and physical endurance (17). In that study, patient inclusion was based on a QRS duration above 150 ms, and previous studies have emphasized the predictive value of the QRS duration in relation to an improvement in LV function during CRT (18). Our data, however, do not support the use of the QRS duration as the primary selection criterion. Indeed, it appears that the detection of mechanical asynchrony, as reflected by DLC, is a superior predictor of CRT efficacy. This is further supported by the observations in patients who died during follow-up. These patients had QRS widths comparable to those of survivors, but they had less extensive mechanical asynchrony (i.e., areas with DLC that could potentially be resynchronized into systole). Therefore, it seems that pre-implantation TDI screening could improve on the selection of candidates prone to benefit from CRT, a hypothesis that is currently being tested in a substudy in the Cardiac Resynchronization in Heart Failure study (CARE-HF) (19).

Echocardiography in the evaluation of CRT. In the present study, we applied two new TDI modalities. One advantage of TT is the "at-a-glance" visualization of the extent of myocardium with DLC (Fig. 2B), although more conventional TDI may also be useful (5). Tissue tracking also facilitates the demonstration of improvement in regional and global longitudinal contraction (Fig. 4), and it was shown that the improvement in overall longitudinal contraction reflected the improvement in LVEF. In patients with bundle branch block, the LV commonly exhibits awkward rocking throughout the heart cycle, and it is often impossible to decide whether motion reflects fiber shortening or merely passive stretching. In this setting, SR analysis (Fig. 3) is a valuable tool to document when DLC represents contraction and thus a potential contractile "reserve" that could be resynchronized into systole.

The LVEF measurements by three-dimensional echocardiography show excellent reproducibility, and according to our most recent studies, the patient group required in a two-dimensional echocardiographic study should be four times larger, equivalent to 80 patients, to achieve identical statistical power (6).

Conclusions. Cardiac resynchronization therapy immediately improves LV function. However, according to three-dimensional echocardiography, the gain is even greater on a long-term (one-year) basis, when the improvement includes reversion of LV remodeling. Tissue Doppler imaging seems to add important pathophysiologic information on the degree, location and reduction of mechanical LV asynchrony during continuous biventricular pacing and on regional and global LV function. Finally, TDI may result in the better selection of potential responders to CRT.

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