Impact of Cardiac Resynchronization Therapy Using Hemodynamically Optimized Pacing on Left Ventricular Remodeling in Patients With Congestive Heart Failure and Ventricular Conduction Disturbances

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OBJECTIVES   We sought to investigate the impact of six months of cardiac resynchronization therapy (CRT) on echocardiographic variables of left ventricular (LV) function.

BACKGROUND   Cardiac resynchronization therapy has recently been introduced as a new therapeutic modality in patients with advanced heart failure (HF) and conduction abnormalities. However, most studies have only investigated the early hemodynamic effects of CRT.

METHODS   Twenty-five patients (12 women and 13 men; 59.8 ± 5.1 years old) with advanced HF caused by ischemic (n = 7) or idiopathic dilated cardiomyopathy (n = 18) and a prolonged QRS complex were analyzed. All patients underwent early hemodynamic testing with a randomized testing protocol; echocardiographic measurements were compared before implantation and after six months of CRT.

RESULTS   Left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD, respectively) were significantly reduced after six months (LVEDD from 71 ± 10 to 68 ± 11 mm, p = 0.027; LVESD from 63 ± 11 to 58 ± 11 mm, p = 0.007), as were LV end-diastolic and end-systolic volumes (LVEDV from 253 ± 83 to 227 ± 112 ml, p = 0.017; LVESV from 202 ± 79 to 174 ± 101 ml, p = 0.009). Ejection fraction was significantly increased (from $22 \pm 7\%$ to $26 \pm 9\%$, p = 0.03). "Nonresponders," with regard to LV volume reduction, had significantly higher baseline LVEDV, compared with "responders" (351 ± 52 vs. 234 ± 74 ml, p = 0.018). Overall, there was only mild mitral regurgitation at baseline, with a minor reduction by semiquantitative analysis. The results of early hemodynamic testing did not predict the volume response.

CONCLUSIONS   Cardiac resynchronization therapy may lead to a reduction in LV volumes in patients with advanced HF and conduction disturbances. Volume nonresponders have significantly higher baseline LVEDV.   (J Am Coll Cardiol 2001;38:1957–65) © 2001 by the American College of Cardiology

Cardiac resynchronization therapy (CRT) acts by recoordinating ventricular activation using atrial synchronous left or biventricular (BV) pacing. Early hemodynamic improvement using this approach has been demonstrated in patients with systolic heart failure (HF) (1–3). However, not all patients improve hemodynamically with pacing (2), and

variables predictive of early hemodynamic and long-term functional improvement with pacing have not been fully

elucidated. Moreover, there are only few reports on the long-term response of patients treated with this new approach (4). It is not yet clear whether early changes observed during invasive testing predict a favorable long-term outcome. Left ventricular (LV) volumes and ejection fraction (EF), as assessed by two-dimensional echocardiography, have been shown to be of prognostic importance in patients with LV dysfunction (5). Thus, the aim of the present study was to investigate whether CRT leads to long-term improvement in LV diameters and function in patients with HF and a wide QRS complex and whether baseline echocardiographic variables are predictive of long-term improvement.

METHODS

Patient group and study design. The PAcing THerapies in Congestive Heart Failure (PATH-CHF) study included 42 patients. All patients gave written, informed consent to take part in the study, which was performed in compliance

Abbreviations and Acronyms

BV   = biventricular
CRT   = cardiac resynchronization therapy
HF   = heart failure
LVEDD = left ventricular end-diastolic diameter
LVEDV = left ventricular end-diastolic volume
LVESD = left ventricular end-systolic diameter
LVESV = left ventricular end-systolic volume
EF   = ejection fraction
LV   = left ventricular
MR   = mitral regurgitation
RV   = right ventricular

with the Human Studies Committee of each institution. The design and inclusion and exclusion criteria of the study have been described previously (6). In brief, patients with HF of both ischemic and nonischemic origin were included if they were in New York Heart Association (NYHA) functional class III or IV HF and had sinus rhythm, a PR interval ≥150 ms and a QRS width >120 ms in at least two surface electrocardiographic (ECG) leads. QRS durations were automatically measured as the maximum of leads II, V_1 and V_6 and validated manually by two independent observers. All patients underwent implantation of two separate DDD pacemakers—one connected to a right atrial and right ventricular (RV) screw-in pacing lead (Sweet-Tip, Guidant Corp.) and the other connected to another right atrial and epicardial LV pacing lead (model 4316, Guidant Corp., or model 4965, Medtronic)—by a limited thoracotomy. This configuration allowed for a change of the pacing site from RV to LV and BV pacing both during implantation and at long-term follow-up. Biventricular pacing was achieved by programming one device in the VDD mode and the second device in the ventricular triggered mode (VVT).

Early hemodynamic testing. All patients underwent early hemodynamic testing during pacemaker implantation, under general anesthesia. Two 8F dual-transducer pressure catheters (model SPC-780c, Millar Instruments) were placed to measure the right atrial, RV, LV and aortic pressures. Pressure catheters and pacing leads were connected to a customized external pacing computer (FlexStim, Guidant Corp.) to acquire hemodynamic signals and execute an early pacing protocol (FlexStim protocol) (6). The FlexStim protocol is designed to measure the immediate effects of pacing, account for local baseline shifts and allow statistical comparison of multiple pacing combinations within individuals. Briefly, the RV, LV or both ventricles were stimulated in the VDD mode at one of five atrioventricular delays preset to a percentage of the patient's intrinsic PR interval, as measured with the pacing leads. Each combination of pacing chamber and atrioventricular delay was randomly repeated five times by pacing for five beats separated by 15 nonpaced beats. The hemodynamic variables used to determine the optimized pacing mode were

the changes in aortic pulse pressure and maximal upward slope of the LV systolic pressure curve (+dP/dt) (2).

Pacing protocol. For intra-individual comparisons of the primary end point of the trial—improvement of functional capacity (6)—patients were randomized to one month of optimized univentricular or BV pacing followed by one month of no pacing. During the third month, patients were crossed over to the other pacing mode. After three months, all patients were paced in the mode with the optimal early response during intra-operative testing. The functional status of the patient was assessed by a physician who had no knowledge of the pacing mode before implantation and after six months. Twenty-five patients (13 men and 12 women; 60 ± 5 years old) were analyzed; 17 patients had to be excluded for the following reasons: 4 patients died (1 due to sudden cardiac death, 1 due to nonsudden cardiac death, 1 due to liver cancer, 1 postoperatively [this patient was later classified as having an inclusion criteria violation, according to the Data Safety Monitoring Committee, because of an underestimated aortic stenosis]); 1 patient was in atrial fibrillation at the six-month follow-up; 1 patient underwent cardiac transplantation; 3 patients were not effectively paced because of an increased LV pacing threshold; and 1 patient withdrew consent. In the remaining seven patients, either one of the echocardiograms was judged as insufficient for reliable analysis by one or both independent observers.

Echocardiographic measurements. Transthoracic echocardiography was performed shortly before pacemaker implantation during intrinsic conduction and after six months when patients were paced with the optimal mode and settings. Left atrial and LV diameters were determined using M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, according to the guidelines of the American Society of Echocardiography (7). Left ventricular mass was calculated according to the Penn convention (8). The end of diastole was defined by the onset of the QRS complex in the simultaneously recorded ECG; the end of systole was defined by the smallest cavity area before mitral valve closure. For measurement of LV end-systolic and end-diastolic dimensions (LVEDD and LVESD, respectively), images were obtained in the apical two- and four-chamber views. Percent fractional shortening was calculated as: (LVEDD−LVESD)/LVESD × 100. Longitudinal and transverse LV diameters were measured in the apical four-chamber view at end diastole, and the sphericity index was calculated as the LV transverse diameter/longitudinal diameter ratio (9). Biplane LV end-systolic and end-diastolic volumes (LVESV and LVEDV, respectively) were calculated from the two-chamber and four-chamber views, according to the modified Simpson's rule (10); measurements were averaged from three cardiac cycles. Left ventricular EF was calculated as: (LVEDV − LVESV)/LVEDV × 100. Patients were classified as volume "responders" if LVESV decreased by >15%, as "stable" if LVESV changes were ≤15% and as "nonresponders" if LVESV increased by >15%, based on data

Table 1. Individual Patient Data (n = 25)

Patient No.	Age (years)	Gender	Etiology	NYHA Functional Class	Interval PR (ms)	Duration QRS (ms)	BBB Type	Early Response Maximal PP Increase (%)	Early Response +dP/dt Increase (%)	Long-Term Pacing Site and AV Delay (ms)	EDV (ml) Baseline	EDV (ml) 6 Months	ESV (ml) Baseline	ESV (ml) 6 Months	EF (%) Baseline	EF (%) 6 Months
1	61	F	Nonischemic	3	200	220	LBBB	13.8	16.1	LV:110	364	362	312	258	14	29
2	58	M	Nonischemic	4	210	160	LBBB	19.8	45.0	BV:100	334	296	305	242	9	18
3	59	M	Nonischemic	4	210	160	LBBB	13.0	24.0	LV:90	315	262	244	227	23	13
4	65	F	Ischemic	3	180	140	LBBB	2.2	17.2	BV:140	93	94	70	55	25	42
5	60	F	Nonischemic	3	165	140	LBBB	24.8	34.1	BV:100	167	90	123	73	27	19
6	63	M	Nonischemic	3	220	200	LBBB	5.8	6.9	RV:110	205	172	147	134	28	22
7	66	M	Ischemic	3	240	120	IVCD	0.8	0.6	RV:160	175	119	110	76	37	36
8	47	M	Nonischemic	3	180	160	LBBB	16.6	45.3	BV:70	254	219	224	168	12	23
9	63	M	Nonischemic	3	250	190	LBBB	25.4	31.9	BV:100	423	528	396	461	6	13
10	62	M	Nonischemic	3	270	130	IVCD	0.9	1.6	BV:190	239	224	164	179	32	20
11	54	M	Nonischemic	3	160	200	LBBB	31.9	54.9	BV:70	362	421	285	361	21	14
12	61	F	Nonischemic	3	160	180	LBBB	15.7	20.6	LV:70	174	147	130	108	25	27
13	61	F	Ischemic	3	200	120	IVCD	2.5	2.7	LV:140	168	128	139	96	18	25
14	59	M	Ischemic	3	180	160	LBBB	2.0	13.1	BV:120	292	286	225	233	23	19
15	64	M	Ischemic	3	220	180	LBBB	41.3	39.5	LV:70	279	320	198	236	29	26
16	62	F	Nonischemic	3	220	160	LBBB	18.9	33.0	LV:120	179	122	146	78	18	36
17	64	F	Nonischemic	3	220	200	LBBB	10.7	20.7	LV:100	318	218	265	149	17	32
18	59	F	Ischemic	3	140	160	RBBB	0.3	5.0	BV:110	243	164	186	126	24	23
19	58	M	Nonischemic	3	200	140	LBBB	4.4	1.8	RV:150	342	385	270	328	21	15
20	49	M	Ischemic	3	220	150	LBBB	6.1	25.7	LV:80	156	155	131	101	16	35
21	59	F	Nonischemic	3	220	170	LBBB	6.8	14.9	BV:90	241	121	179	89	26	27
22	65	F	Nonischemic	3	250	150	LBBB	1.6	4.5	BV:150	291	238	221	151	24	37
23	67	F	Nonischemic	3	160	175	LBBB	12.3	17.7	LV:100	332	277	285	206	14	26
24	50	F	Nonischemic	3	205	130	LBBB	2.6	9.3	LV:130	163	166	121	105	26	37
25	59	M	Nonischemic	3	230	180	LBBB	15.7	25.4	BV:100	220	160	168	101	24	37
Mean ± SD	60 ± 5			3.1 ± 0.3	204 ± 33	163 ± 27		11.8 ± 10.8	20.5 ± 15.3		253 ± 83	227 ± 112	202 ± 79	174 ± 101	22 ± 7	26 ± 9

AV = atrioventricular; BBB = bundle branch block; BV = biventricular; +dp/dt = maximal rise of left ventricular pressure; EDV and ESV = end-diastolic and end-systolic volume, respectively; EF = ejection fraction; IVCD = intraventricular conduction disturbance; LBBB and RBBB = left and right bundle branch block, respectively; LV = left ventricle; NYHA = New York Heart Association; PP = pulse pressure; RV = right ventricle.

showing a variability of ≤15% for repeated volume calculations derived from two-dimensional echocardiographic measurements (11). For statistical analysis, responders and stable patients were analyzed as one group, because both reduced and stable volumes were regarded as a positive clinical response to CRT. Mitral regurgitation (MR) was semiquantitatively graded on a 4-point scale (grades 0 to 3) using color-coded Doppler signals, as previously described (12), and the maximal jet area was measured in the parasternal and apical views (13). All examinations were recorded, stored on videotape and analyzed at the responsible core center (RWTH University of Technology, Aachen, Germany). Final analysis was performed off-line (from videotape) by two independent observers, after manual recalibration on an Agilent Sonos 2500 ultrasound scanner.

Concomitant drug treatment. Patients had to be in stable NYHA functional class III HF without a change in medication or in class IV without the need for intravenous inotropic drugs during the last month to be eligible for study inclusion. Of the 25 patients, 24 (96%) were taking angiotensin-converting enzyme inhibitors, 22 (88%) were receiving digitalis, and 11 (44%) were receiving nitrates. Of 14 patients (56%) initially taking beta-blockers, the dosage was constant in nine, reduced in two and increased in three after six months. In only one patient was a beta-blocker started during the study period. Of 24 patients (96%) taking diuretics before implantation, the dosage was kept constant in 12, reduced in 10 and increased in two. One patient began to receive diuretics during the six-month period, whereas diuretics were withdrawn in one patient.

Statistical analysis. The statistical methods used for analysis of the invasively measured hemodynamic variables have been described elsewhere (2). In brief, relative changes of +dP/dt and pulse pressure (%) in the second to fifth paced beats of each run of five paced beats were compared with the average value during the immediately preceding six nonpaced beats. A paired t test was used to evaluate the effects of pacing compared with no pacing. Cardiac dimensions and volumes were compared intra-individually by using a paired t test. Baseline volumes were compared with early changes in +dP/dt and pulse pressure by using linear regression analysis. All numeric data are expressed as the mean value ± SD. A p value <0.05 was considered significant. Interobserver and intra-observer variabilities were defined as the difference of measurements between two observers, expressed as the percent difference (± SD) of the first observer.

RESULTS

Baseline evaluation. Table 1 shows the clinical data of the 25 analyzed patients. The ECG pattern of intraventricular conduction delay was classified as left bundle branch block (LBBB) type in 21 patients (84%), right bundle branch block type in one patient (4%) and intraventricular conduction delay in three patients (12%), according to previously

Table 2. M-Mode Echocardiographic Variables

	Before Implantation	6 Months	p Value
LVEDD (mm)	71 ± 10 (57–98)	68 ± 11 (52–94)	0.027
LVESD (mm)	63 ± 11 (44–87)	58 ± 11 (45–83)	0.007
FS (%)	12 ± 6 (4–24)	15 ± 7 (4–33)	NS
LAD (mm)	40 ± 6 (33–52)	41 ± 8 (31–67)	NS
IVST (mm)	9 ± 2 (5–14)	10 ± 2 (7–13)	NS
LV mass (g)	372 ± 120	387 ± 134	NS

Data are presented as the mean value ± SD.
FS = fractional shortening; IVST = interventricular septal thickness; LAD = left atrial diameter; LVEDD = left ventricular enddiastolic diameter; LVESD = left ventricular endsystolic diameter.

published criteria (14). The optimal pacing site was BV in 12 (48%), LV in 10 (40%) and RV in 3 patients (12%). The mean NYHA functional class improved from 3.0 ± 0.1 at baseline to 1.9 ± 0.7 after six months of CRT, with no difference between volume responders and stable patients (n = 21; from 3.0 ± 0.2 to 1.9 ± 0.7) and volume nonresponders (n = 4; from 3.0 ± 0 to 2.1 ± 0.9; p = NS).

Changes in LV dimensions, EF and mass. Table 2 shows the M-mode echocardiographic variables. After six months of therapy, LVESD and LVEDD were both reduced, without a significant increase in fractional shortening. Left atrial diameter and septal thickness remained unaffected. Two-dimensional echocardiography revealed a significant decrease of the transverse (6.8 ± 1.1 vs. 6.2 ± 1.4 cm, p = 0.02), but not the longitudinal (9.3 ± 1.3 vs. 8.9 ± 1.2 cm, p = NS), LV diameter. Changes in the sphericity index failed to reach the level of statistical significance (0.75 ± 0.1 vs. 0.70 ± 0.11, p = 0.07). Figure 1 shows an example of the volume changes observed; Figures 2 and 3 illustrate the changes in LVEDV and LVESV, as well as LVEF. There was a significant decrease in both LVEDV and LVESV after six months of CRT, whereas EF showed a modest increase. Intra-observer variability was 8.4 ± 6.4% for LVEDV and 9.4 ± 7.1% for LVESV, compared with 33 ± 30% for EF. For inter-observer variability, the corresponding values were 7.4 ± 5.7%, 9.3 ± 5.6% and 34.6 ± 37.2%, respectively. There was no change in LV mass (372 ± 120 vs. 387 ± 144 g, p = NS) or mean heart rate (78.5 ± 17.2 vs. 74.4 ± 20.2 beats/min, p = NS).

Comparison of responders and stable patients versus nonresponders. Sixteen patients showed a reduction of >15% in LVESV; five were stable; and only four were classified as nonresponders. These four patients had a significantly higher mean baseline LVEDV value (Table 3). The baseline volumes of responders (LVEDV: 232 ± 78 ml; LVESV: 187 ± 74 ml) and stable patients (LVEDV: 243 ± 62 ml; LVESV: 180 ± 52 ml) did not differ significantly. There were no significant differences in baseline EF between the groups. After six months of CRT, EF showed an increase only in volume responders (22 ± 7% to 28 ± 8%, p < 0.001), whereas the nonresponders showed a nonsignificant decrease in EF (20 ± 10% to 17 ± 6%, p = NS). Eleven of 16 volume responders were receiving beta-
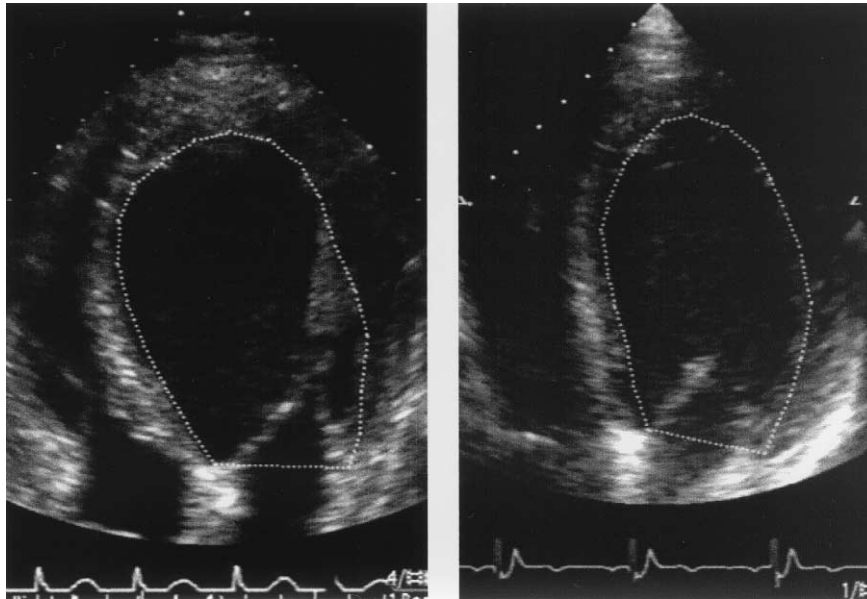
Figure 1. These end-diastolic echocardiographic images were obtained in the apical four-chamber view before device implantation **(left)** and after six months of cardiac resynchronization therapy **(right)**, where a volume reduction is demonstrated. The endocardial borders were manually delineated, and the left ventricular (LV) cavity area surrounded by these borders was used for LV volume calculation, as explained in the text. Note the reduction in end-diastolic volume and the reduced sphericity of the LV shape in the right image.

blocker therapy, as were two of five stable patients and one of four nonresponders.

Effect on MR. Most patients showed either no MR (grade 0, n = 6) or only mild MR (grade 1, n = 13) before implantation. Five patients were classified as grade 2 and one patient as grade 3. In the 19 patients who had at least some degree of MR at baseline, there was improvement in nine and increase in two. In the remaining eight patients, the severity of MR was unaltered. No patient developed new MR with pacing. The MR jet area was not significantly altered (3.8 ± 3.6 vs. 3.3 ± 2.1 cm², p = NS). There were no differences in the degree of MR before implantation or after six months of CRT between volume responders, stable patients and nonresponders.
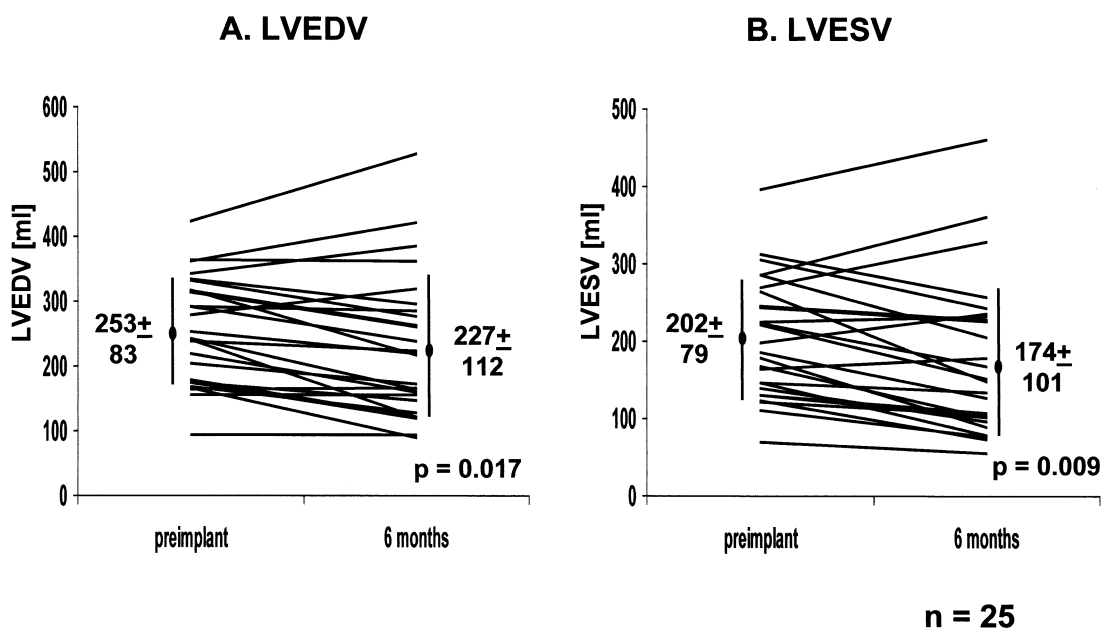

Figure 2. A comparison of left ventricular end-diastolic volume (LVEDV) **(A)** and left ventricular end-systolic volume (LVESV) **(B)** before pacemaker implantation and after six months of hemodynamically optimized pacing. There was a significant decrease in both volumes after six months.
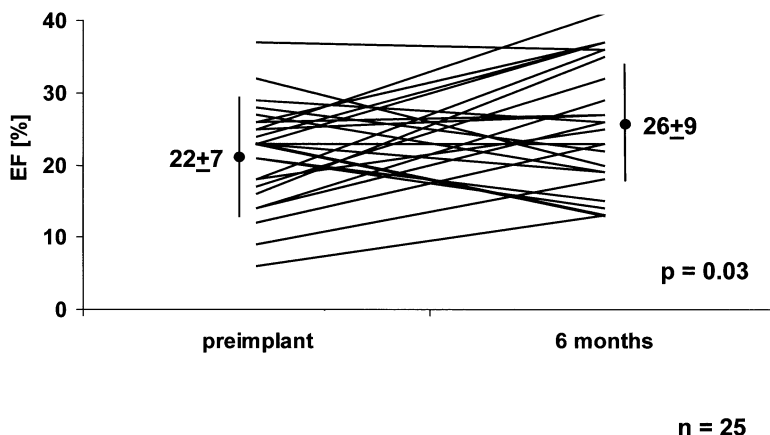
Figure 3. A comparison of echocardiographically determined ejection fraction (EF) before pacemaker implantation and after six months of hemodynamically optimized pacing. There was a small but significant increase in EF after six months.

Comparison of pre-implantation volumes, early hemodynamic responses and long-term volume responses. No correlation between baseline volumes and the early increase in either aortic pulse pressure or $+dP/dt$ induced by CRT was observed (Fig. 4A and 4B). Volume nonresponders were found among those with very large and only minimal early hemodynamic response.

DISCUSSION

Main findings. This study demonstrates that CRT achieved by hemodynamically optimized pacing leads to a long-term reduction in LV volumes in the majority of patients with systolic HF and ventricular conduction disturbances. Recent data in larger populations have indicated reduced LVEDD after CRT (15). However, measurements of LV volumes are more reliable in assessing LV remodeling (16). The fact that the effect on LV diameters was more pronounced for the transverse than for the longitudinal diameter underscores a "reverse remodeling" effect caused by CRT, although changes in the derived sphericity index failed to reach statistical significance because of a minor, nonsignificant decrease in the longitudinal LV diameter. The spherical shape in dilated hearts is associated with increased wall stress (17), and changes in LV sphericity have been correlated to an increase in exercise capacity (18).

Table 3. Baseline Volumes of Chronic "Volume Non-responders" Compared to Stable Patients and "Volume Responders"

	Volume Non-Responders (n = 4)	Volume Responders and Stable Patients (n = 21)	p
Baseline EDV [ml]	351 ± 60	234 ± 74	0.018
EDV change [%]	17.1 ± 4.7	−18.6 ± 15.1	<0.001
Baseline ESV [ml]	287 ± 82	178 ± 67	0.083
ESV change [%]	21.1 ± 3.8	−24.6 ± 15.8	*
Baseline EF [%]	19.5 ± 9.5	21.9 ± 6.9	n.s.
EF change [%]	−2.6 ± 6.2	5.8 ± 9.7	0.066

*Used as criterion to define responders and non-responders; for abbreviations see text.

Effect on MR. Some investigators have speculated that LV-based pacing leads to a reduction in MR (19), which can be explained by 1) a reduction in *presystolic* MR by optimizing atrioventricular delay and 2) a reduction in *systolic* MR by improved coaptation of the valve leaflets, which may be impaired by delayed contraction of the anterolateral papillary muscle. The sphericity associated with LV dilation leads to functional MR (20); thus, reversal of this process may reduce MR. However, the degree of baseline MR in our study was low; thus, despite the fact that some reduction was noted, it seems unlikely that this was the prevailing mechanism for LV volume reduction.

Prediction of volume response. Some patients did not respond to CRT with a reduction in LV volumes, and the extent of the early hemodynamic response was not a good predictor of volume effects. In fact, three of four volume nonresponders were among those with the largest early hemodynamic improvement. Thus, other factors are involved in the reverse remodeling response to CRT, such as baseline geometry and LV size. The fact that volume nonresponders had a higher mean LVEDV is in concordance with data from drug trials indicating that nonresponders to pharmacologic therapy had higher baseline LVEDD values (21). However, our data do not yet allow for the conclusion that CRT is not indicated in very dilated hearts, because the positive early hemodynamic effects of CRT can still lead to symptomatic improvement despite the lack of volume reduction, as shown by a similar improvement in NYHA functional class in volume nonresponders. Moreover, we could not define a cut-off value above which a reduction in LV volumes can no longer be expected.

Interaction with drug treatment. A dose-related "reverse remodeling effect" in HF has been described for beta-blocker treatment (22,23). An additive effect of beta-blockers on volumes in our study cannot be completely ruled out, because there were more volume responders than nonresponders receiving beta-blocker therapy. However, patients were receiving stable drug therapy before study
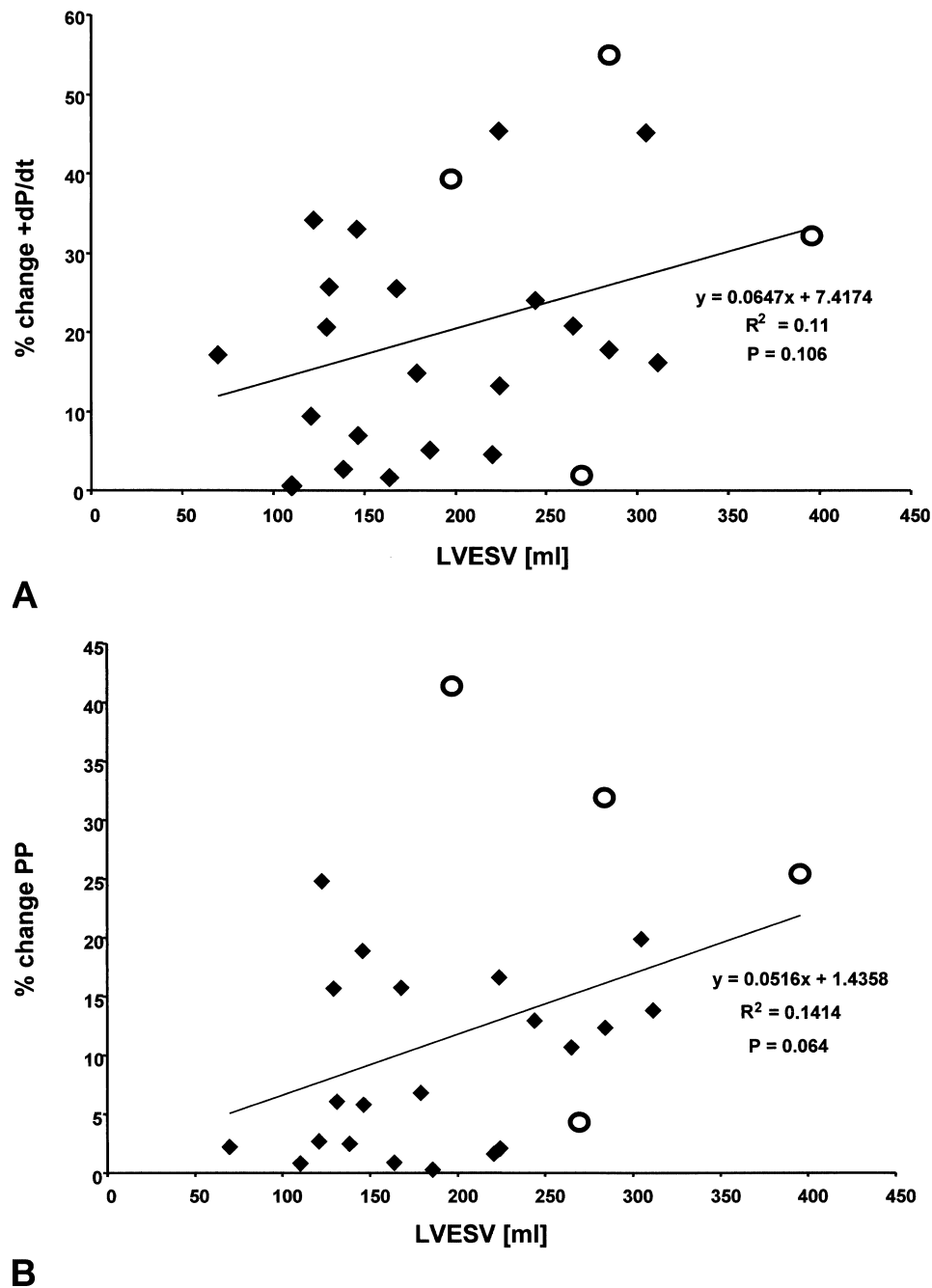
Figure 4. Percent change in +dP/dt **(A)** and pulse pressure (PP) **(B),** plotted against the baseline left ventricular end-systolic volume (LVESV) values, as determined by echocardiography. There was no correlation between early hemodynamic improvement in PP or +dP/dt and baseline left ventricular (LV) volume. Moreover, long-term volume nonresponders **(open circles)** were found among high and low early hemodynamic responders, both for PP and +dP/dt, **(solid diamonds** represent long-term volume responders and stable patients). Three volume nonresponders were among those patients with the highest acute hemodynamic response.

inclusion, and dose adjustments during the study were minor, as indicated by the lack of a significant change in heart rate. Moreover, recent data suggest that patients with a QRS width >120 ms, as in our study, are less likely to respond to beta-blocker therapy with an improvement in EF, compared with patients with a narrow QRS width (24). It is also noteworthy that 5 of 16 volume responders were not taking beta-blockers. We believe that CRT is complementary to beta-blockers because: 1) it leads to an improve-

ment in exercise capacity (4), which has not been consistently shown for beta-blockers; 2) it minimizes the risk of bradyarrhythmias; and 3) it can be useful in the early treatment phase to overcome the initial negative inotropy and hypotension associated with beta-blockers. Cardiac resynchronization therapy is an attractive alternative to positive inotropic drug therapy for this purpose, because the hemodynamic benefit achieved by CRT is associated with a reduction in myocardial oxygen demand (25). The reason

for this is a more efficient systolic contraction, which leads to a reduction in regional wall stress, because areas of delayed activation, such as the LV free wall in LBBB, are known to have greater regional wall stress (26). A reduction in both wall stress and oxygen demand with CRT can lead to a decrease in sympathetic nervous activation (27), which may contribute to a reduction in LV size.

Study limitations. The number of patients analyzed was small, and the changes observed need to be verified in larger patient cohorts. Because no control group was studied, a positive effect of the close medical follow-up, rather than CRT, cannot be ruled out. The cross-over period during the first three months after implantation may have affected the results because different pacing modes were used and patients were not paced during the second month. However, the differences in the early hemodynamic response between optimal univentricular (LV in most cases) and BV pacing were minor (2), and patients were constantly paced for the last four months before echocardiographic re-evaluation. Thus, we believe that the data are not invalidated by the cross-over period. The study was not designed to assess the impact of CRT on the severity of MR. Thus, no systematic, prospective evaluation of MR severity was performed. The modified Simpson's rule was used for LV volume calculation, which may not be optimal for the spherical shape and asymmetrical contraction in the hearts examined. With the disco-ordinated contraction in LBBB, the smallest cavity area may not truly represent the end of systole, as late activated areas may still be contracting. Finally, echocardiographic data have not been correlated to functional variables.

Conclusions. The data of this study indicate that long-term CRT leads to a reduction in LV volumes in the majority of patients with advanced HF and ventricular conduction disturbances. Patients with higher baseline volumes are less likely to show a decrease in volume. The mechanisms leading to this "reverse remodeling" effect are incompletely understood, but may involve a reduction in regional wall stress, myocardial oxygen demand and functional MR. Further studies in larger patient cohorts are needed to more clearly define the clinical characteristics of patients who show reverse remodeling by CRT.

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APPENDIX

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