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Cardiac Resynchronization Therapy

Clinical Efficacy of Cardiac Resynchronization Therapy Using Left Ventricular Pacing in Heart Failure Patients Stratified by Severity of Ventricular Conduction Delay

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OBJECTIVES We assessed the clinical efficacy of single-site left ventricular (LV) pacing and determined the impact of baseline conduction delay severity on the magnitude of benefit.

BACKGROUND Multisite biventricular pacing can improve heart failure (HF) symptoms in patients with an intraventricular conduction delay by resynchronizing abnormal ventricular contractions and improving LV systolic function.

METHODS Eighty-six patients with at least New York Heart Association functional class II HF, chronic LV systolic dysfunction, normal sinus rhythm, and a QRS interval over 120 ms were implanted for atrial-synchronized LV pacing. The single-blinded, randomized, controlled, crossover study stratified patients 1:1 by the baseline QRS interval into long (QRS >150 ms) and short (QRS 120 to 150 ms) groups, which were compared during a three-month period of active (univentricular) pacing and a three-month period of inactive (ventricular inhibited) pacing. The primary end point was peak oxygen consumption (Vo_2) followed by anaerobic threshold, distance walked in 6 min, and quality-of-life questionnaire score.

RESULTS Twelve patients were withdrawn before randomization and 17 could not complete both study periods. The short QRS group did not improve in any end point with active pacing. For the long QRS group, peak Vo_2 increased 2.46 ml/min/kg ($p < 0.001$), the anaerobic threshold increased 1.55 ml/min/kg ($p < 0.001$), the distance walked in 6 min increased 47 m ($p = 0.024$), and the quality-of-life score improved 8.1 points ($p = 0.004$).

CONCLUSIONS Left ventricular pacing significantly improves exercise tolerance and quality of life in patients with chronic HF, LV systolic dysfunction, and a QRS interval over 150 ms. (J Am Coll Cardiol 2003;42:2109–16) © 2003 by the American College of Cardiology Foundation

Despite pharmacologic treatments with angiotensin-converting enzyme inhibitors (1,2), beta-blockers (3–5), and spironolactone (6), chronic heart failure (HF) remains a leading cause of hospitalization and an economic burden (7,8). Multisite biventricular pacing has recently been

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shown to improve exercise capacity and quality of life, reduce hospitalization, and slow disease progression in severe HF patients with an intraventricular conduction delay associated with abnormal ventricular contraction sequences (9–11). Biventricular pacing is believed to resynchronize the abnormal contraction sequences to increase pumping effectiveness without increasing the heart rate or myocardial oxygen consumption (12,13).

Using only left ventricular (LV) pacing may simplify cardiac resynchronization therapy (CRT) (14). Hemodynamic studies have shown that atrial-synchronized biventricular and LV pacing are nearly equivalent in their ability to increase LV pump function in HF patients in normal sinus rhythm (15,16). A small, short-term, randomized, crossover study found that either kind of pacing similarly increased exercise capacity and improved quality of life (17).

A prolonged QRS duration is widely regarded as a prerequisite for using CRT, but a threshold for clinical effectiveness has not been established, although hemodynamic improvement is more frequently observed in patients with a QRS interval >155 ms (18). A prolonged QRS

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Abbreviations and Acronyms

AV	= atrioventricular
CI	= confidence interval
CRT	= cardiac resynchronization therapy
HF	= heart failure
ICD	= implantable cardioverter-defibrillator
LV	= left ventricle/ventricular
LVAD	= left ventricular assist device
NYHA	= New York Heart Association
PATH-CHF	= PAcing THerapies for Congestive Heart Failure
RV	= right ventricle/ventricular
V_{O_2}	= oxygen consumption

duration may also predict a therapy benefit for patients with indications for an implantable cardioverter-defibrillator (ICD) (19), but it has not been shown to predict a benefit for patients in New York Heart Association (NYHA) functional class II.

The objective of this single-blinded, randomized, controlled, crossover study was to assess the clinical efficacy of atrial-synchronized LV pacing in patients with stable NYHA functional class ≥II HF, including patients with standard indications for an ICD but without standard pacemaker indications (20), who were stratified by QRS duration as an index of the severity of intraventricular conduction delay.

METHODS

Patient selection. Patients 18 to 75 years old who met the selection criteria were enrolled after giving written, informed consent. Patients had dilated cardiomyopathy of any etiology with a LV ejection fraction ≤30% and peak oxygen consumption (V_{O_2}) ≤18 ml/min/kg on the maximum exercise test. All patients were in normal sinus rhythm. Patients were in NYHA functional class ≥II on optimal individual drug therapy and had not been hospitalized for HF in the month before enrollment. One-half of the patients enrolled had a QRS duration between 120 and 150 ms and the other one-half had QRS >150 ms.

Patients were excluded if they had a history of chronic or recurrent atrial fibrillation or flutter within the last six months, aortic or mitral valve stenosis or previous valve replacement or reconstruction, previous (within three months) or scheduled coronary revascularization or other cardiac surgery, unstable angina, myocardial infarction (within previous three months), acute cardiac failure crisis or dependency on intravenous inotropes, renal insufficiency requiring hemodialysis, severe obstructive pulmonary disease, hypertrophic obstructive cardiomyopathy, amyloidosis, poorly controlled diabetes mellitus, or a life expectancy <6 months due to other medical conditions.

Study design. The study was performed at nine investigational centers, following local ethics committee approval. Enrollment began September 1998 and ended January 2001. The study was designed as a six-month, randomized crossover comparing three months of atrial-synchronized univentricular (active) pacing with three months of ventricular-inhibited (inactive) pacing at a lower rate of 40 beats/min, with the two pacing periods occurring in random order for each patient (Fig. 1). After a baseline evaluation, patients were stratified prospectively into two groups according to their QRS duration, as assessed by 12-lead surface electrocardiography and measured by the electrocardiographic core center. Patients with QRS >150 ms were assigned to the long QRS group, and those with QRS between 120 and 150 ms to the short QRS group. Then patients underwent an invasive procedure to evaluate their acute hemodynamic response to pacing and to select the best site for permanent ventricular pacing. The device was implanted in a second procedure, and proper device operation subsequently was verified within five days. Then patients were randomly assigned to a treatment sequence (active pacing first or inactive pacing first) following randomization in blocks of size 8, which was separate for each QRS group. Randomization was followed by the two crossover periods during which patients were switched between active and inactive pacing while blinded as to treatment. After the crossover periods, devices were programmed to active pacing in all patients, who were followed until one year after implantation. Only the six-month crossover study results are reported here.

Hemodynamic evaluation. Patients were evaluated in the electrophysiology laboratory to select the pacing site and atrioventricular (AV) delay that provided the best hemodynamic response. This was determined by the largest increase in aortic pulse pressure and LV maximum pressure rate increase measured by a dual-pressure transducer catheter

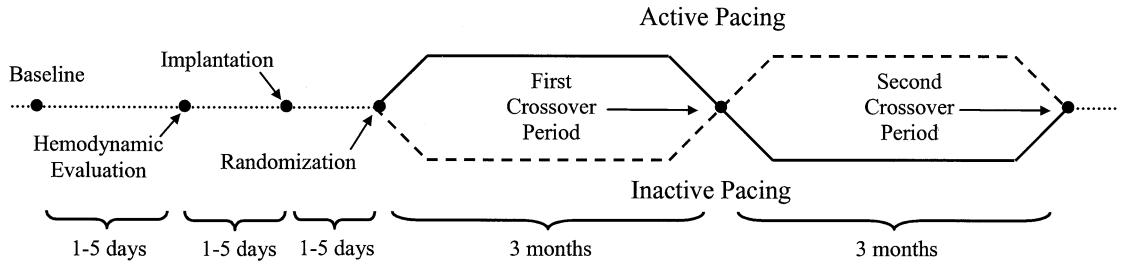

Figure 1. Study design. Patients were randomly assigned to three months each of active pacing (atrial-synchronous ventricular) and inactive pacing (ventricular-inhibited with a minimum pacing rate of 40 beats/min).

inserted into the LV via the femoral artery. For this test, standard electrophysiologic catheters were advanced from the femoral vein to pace inside the right ventricle (RV). An over-the-wire EASYTRAK lead (model 4512, Guidant Corp., St. Paul, Minnesota) was advanced from the jugular vein into the coronary sinus to pace LV sites through the coronary veins. Left ventricular pacing was compared at two to four different sites in all patients. Right ventricular pacing was tested only in patients having right bundle branch block. The best pacing site was documented radiographically to guide permanent lead placement during device implantation. Details of the hemodynamic evaluation protocols and instrumentation have been previously described (21,22).

Device implantation. All patients received dual-chamber pulse generators for atrial-synchronized univentricular pacing. In accordance with current ICD guidelines (20), patients at high risk of sudden death received an ICD (model 1831, 1851, 1821, or 1823, Guidant Corp.) and an endocardial shocking lead implanted in the RV (Endotak models 0125, 0135, 0145, 0144, 0148, and 0155, Guidant Corp.). All other patients received a pacemaker (model 1273, 1274, 1270, 1280, or 1241, Guidant Corp.). A conventional atrial lead was placed high in the right atrium. One ventricular lead for pacing was placed at the site selected by the hemodynamic evaluation. For the RV, a conventional RV pacing lead was implanted. For the LV, an epicardial lead (Medtronic, models 4968 and 10366 [Minneapolis, Minnesota]; Guidant Corp., model 4316) was implanted via a limited thoracotomy in all patients with an ICD and initially in some patients with a pacemaker. Later, pacemaker patients were implanted with a transvenous LV pacing lead (EASYTRAK model 4512 or ITM 428-07, Guidant Corp.). Positioning of the LV lead was guided by a venogram and fluoroscopy during implantation to be as close as possible to the site selected by the hemodynamic evaluation and confirmed later by chest X-ray.

At randomization, devices were programmed to a minimum pacing rate of 40 beats/min and a maximum pacing rate determined by the patient's heart rate during maximum exercise at the baseline evaluation. Inactive pacing was selected by programming a ventricular demand mode causing inhibition of ventricular pacing. Active pacing was selected by programming the atrial-synchronous mode with the AV delay determined by the hemodynamic evaluation.

Clinical assessment. Four clinical measures were assessed at the baseline evaluation and at the end of each crossover period. A maximum exercise test on a bicycle was performed to measure peak V_{O_2} and V_{O_2} at the anaerobic threshold, using the V-slope method (23). Submaximal exercise was measured by the distance walked in 6 min, according to the method of Bittner (24). Quality of life was assessed by the Minnesota Living With Heart Failure Questionnaire score, which ranges from 0 (best) to 105 (worst) (25). Patient functional status was assessed by the NYHA functional classification.

End points. The primary end point was an improvement in exercise capacity, as assessed first by peak V_{O_2}, second by V_{O_2} at the anaerobic threshold during maximum exercise testing, and third by the distance walked in 6 min. The secondary end points were quality-of-life score and NYHA functional classification.

Statistical analysis. Enrollment and sample size were estimated from the results of the PAcing THerapies for Congestive Heart Failure (PATH-CHF) study (17,22), based on an expected improvement of 12.5% in the weakest primary end point (V_{O_2} at the anaerobic threshold). For a 5% significance level and 80% power, a total sample size of 64 full crossover data sets was required. Due to the expected mortality and dropout rates, we planned to enroll 100 patients.

An independent statistician performed all data analyses. End points could be assessed only in patients with no missing data after completion of both crossover periods. Baseline characteristics were compared by the unpaired *t* test for continuous variables, the Wilcoxon test for walk distance and quality-of-life score, and the Fisher exact test for discrete data. The clinical effects of pacing were tested by calculating for each clinical measure the difference of the second minus the first crossover period value for each patient and then comparing all the patient differences between the two pacing sequences (active first or inactive first) by the unpaired *t* test for V_{O_2} measures and by the Wilcoxon rank-sum test for walk distance, quality-of-life score, and NYHA functional classification (26,27). Parametric estimation of treatment effects and confidence intervals was used for all variables and calculated from the differences between the active and inactive pacing mean values for the two pacing sequences. The treatment-period interaction (residual or carryover effect) was tested by a *t* test applied to the individual sums of the first and second period data. When a pacing effect was significant for all patients, the effect was tested by the same statistical methods for the long and short QRS patient groups. A statistical result of $p < 0.05$ was considered necessary for significance.

RESULTS

Study population. A total of 101 patients were enrolled in the study. After three patients were withdrawn for valve replacement and limited life-expectancy, a hemodynamic evaluation was attempted in 98 patients and successful in 92 patients. The coronary sinus could not be cannulated in two patients; a lateral or posterior LV coronary vein was inaccessible in two patients; and there was dissection of the coronary venous intima in two patients. Three other patients were withdrawn after hemodynamic evaluation due to consent withdrawal, recurrent atrial tachycardia, and infection. The remaining 89 patients were randomized. The results of all randomized patients have been reported at a conference (28). Three of these patients received RV pacing for right bundle branch block. They have been excluded

Table 1. Baseline Clinical Characteristics of Patients Randomized in the Study

Characteristic	All Patients (n = 86)	Randomization Group: Active First (n = 43)	Inactive First (n = 43)	p Value*	Long QRS Active First (n = 20)	Long QRS Inactive First (n = 21)	p Value†	Short QRS Active First (n = 23)	Short QRS Inactive First (n = 22)	p Value‡
Gender (M/F)	57/29	30/13	27/16	0.649	15/5	11/10	0.197	15/8	16/6	0.749
Age (yrs)	60 ± 9	61 ± 9	58 ± 8	0.102	60 ± 11	62 ± 6	0.457	63 ± 8	55 ± 9	0.002
NYHA class (II/III or IV)	28/58	16/27	12/31	0.490	8/12	4/17	0.181	8/15	8/14	1.000
CAD	38%	44%	33%	0.375	45%	24%	0.197	43%	41%	1.000
LBBB	88%	91%	86%	0.738	95%	95%	1.000	87%	77%	0.459
QRS interval (ms)	155 ± 20	154 ± 18	157 ± 23	0.463	169 ± 13	176 ± 16	0.143	140 ± 9	139 ± 7	0.513
PR interval (ms)	195 ± 32	190 ± 36	200 ± 27	0.132	181 ± 39	206 ± 30	0.027	197 ± 32	194 ± 24	0.754
SBP (mm Hg)	113 ± 16	112 ± 17	114 ± 15	0.422	111 ± 14	113 ± 20	0.711	112 ± 19	116 ± 9	0.438
Beta-blocker	73%	72%	74%	1.000	80%	71%	0.719	65%	77%	0.514
Antiarrhythmic	16%	26%	7%	0.038	30%	10%	0.130	22%	5%	0.187
LV ejection fraction (%)	23 ± 7	23 ± 7	23 ± 8	0.619	25 ± 8	20 ± 8	0.100	23 ± 6	25 ± 7	0.233
Peak oxygen uptake (ml/min/kg)	13.3 ± 2.7	13.2 ± 2.8	13.4 ± 2.5	0.650	12.3 ± 2.6	12.9 ± 2.1	0.425	14.0 ± 2.8	13.9 ± 2.8	0.957
Distance walked in 6 min (m)	407 ± 81	400 ± 69	413 ± 91	0.557	415 ± 54	381 ± 87	0.197	387 ± 79	444 ± 86	0.043
Quality-of-life score	42 ± 18	41 ± 21	43 ± 15	0.622	44 ± 21	45 ± 12	0.990	38 ± 21	41 ± 17	0.679

*Comparison of active first and inactive first groups. †Comparison of long QRS active first and inactive first groups. ‡Comparison of short QRS active first and inactive first groups. Data are presented as the number of patients, mean value ± SD, or percentage of patients.

CAD = coronary artery disease; LBBB = left bundle branch block; LV = left ventricular; NYHA = New York Heart Association; SBP = systolic blood pressure.

from the present analysis in order to report the results on the 86 randomized patients receiving LV pacing. Table 1 lists their baseline clinical characteristics. The intraventricular conduction delay was diagnosed as left bundle branch block in 76 patients (88%) and right bundle branch block in 1 patient (1%); it was nonspecific in 9 patients (11%). All patients were symptomatic despite optimal pharmacologic treatment at baseline, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in 99% of patients and beta-blockers in 73% of patients. Study investigators were prospectively instructed to not modify the patients' medications during the crossover study, except for diuretics, unless such a change would be required for patient safety. There were no significant changes in medication from baseline to the conclusion of the crossover study in any patient group.

Hemodynamic evaluation. Based on the hemodynamic evaluation, the best univentricular pacing was LV pacing for all 85 patients presenting with left bundle branch block or nonspecific block and for one patient presenting with right bundle branch block. The best LV pacing site was in a lateral or posterior vein rather than the anterior vein (29). When pacing at the selected pacing sites with the best AV delay (mean 119 ± 32 ms), the aortic pulse pressure increased an average of 9.9 ± 11%, and the LV maximum positive pressure rate change increased 19.9 ± 20%.

Implantation. Thirty-four patients were implanted with an ICD and 52 patients were implanted with a pacemaker. All 86 patients were implanted with a LV pacing lead; 61 patients received an epicardial lead and 25 received a transvenous lead. Transvenous lead implantation was successful in 93% of patients (25 successes of 27 attempts).

Randomization. The 86 implanted patients were randomized to the two treatment sequences with a nearly equal distribution of long and short QRS group patients in each sequence (Table 1). There were no significant differences in

Table 2. End Points After Three Months of Inactive or Active Pacing

Study Group	n	Active Pacing	Inactive Pacing	p Value
Peak oxygen uptake (ml/min/kg)				
Active first sequence	31	15.1 ± 3.2	13.5 ± 3.0	<0.001
Inactive first sequence	32	15.3 ± 3.2	14.1 ± 3.2	
Oxygen uptake at anaerobic threshold (ml/min/kg)				
Active first sequence	31	10.4 ± 2.2	9.4 ± 2.0	<0.001
Inactive first sequence	32	10.3 ± 2.0	9.6 ± 2.0	
Distance walked in 6 min (m)				
Active first sequence	34	437 ± 83	409 ± 91	0.021
Inactive first sequence	35	468 ± 85	444 ± 74	
Quality-of-life score				
Active first sequence	31	23 ± 18	28 ± 25	0.015
Inactive first sequence	34	20 ± 18	25 ± 14	

Data are presented as the mean value ± SD.

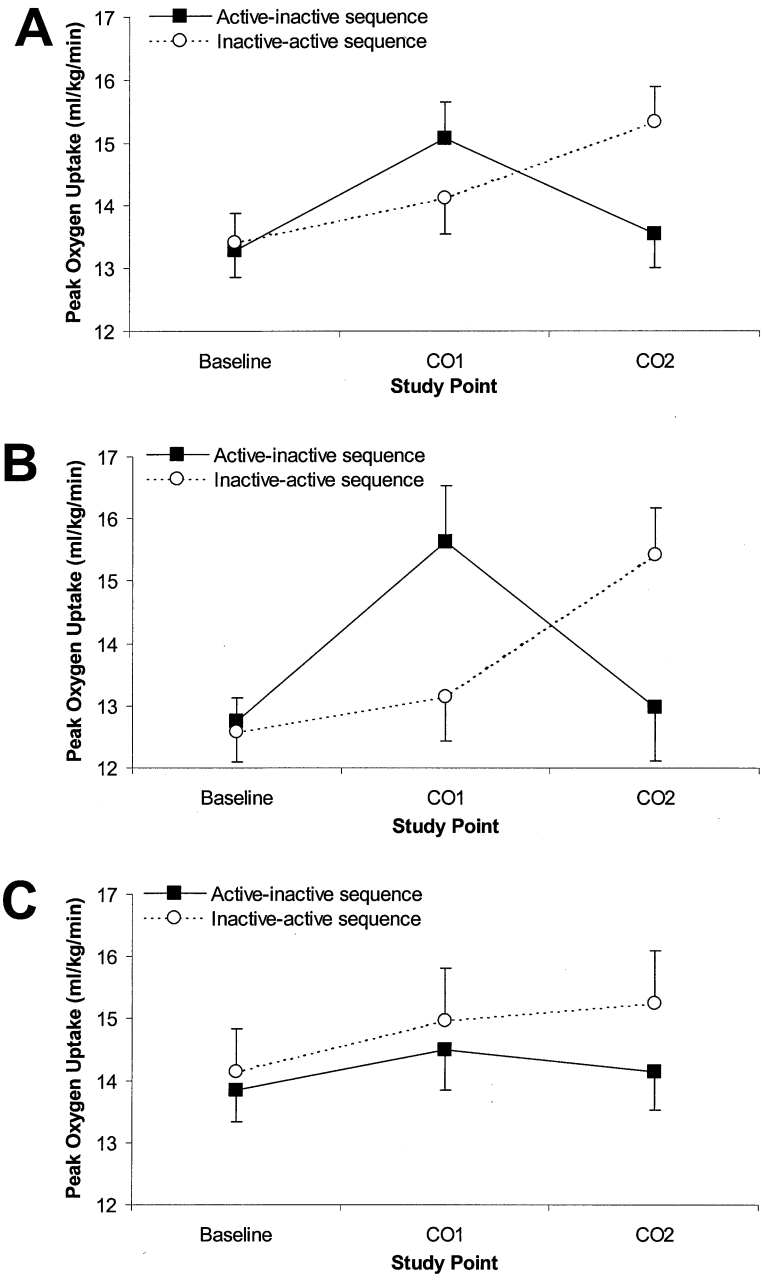

Figure 2. Peak oxygen consumption at each evaluation point during the study. Mean peak oxygen consumption (with standard error of the mean bars) for patients in the active first and inactive first pacing sequences **(A)**, for the subset of patients in the long QRS group (QRS >150 ms) **(B)**, and for the subset of patients in the short QRS group (QRS 120 to 150 ms) **(C)**. CO1 = first crossover period; CO2 = second crossover period.

baseline characteristics between patients assigned to different sequences (Table 1).

Safety. Seventeen patients did not complete the two crossover periods. Three patients were withdrawn immediately after randomization. One had misplaced leads; another received an elective left ventricular assist device (LVAD); and the third was implanted with an ICD device plus a pacemaker.

Five patients dropped out during an active pacing period. Two patients without an ICD had a sudden cardiac death. One patient developed a left-sided pleural effusion related to the epicardial lead implantation. Two patients were unwilling to comply with the study protocol.

Nine patients dropped out during an inactive pacing period. Three patients died (two of them without an ICD by sudden cardiac death). Three patients developed acute HF decompensation (two of them were prematurely switched to active pacing), and the third received a LVAD. One patient developed ventricular tachyarrhythmia and had a replacement biventricular ICD implanted. One patient developed untreatable atrial tachyarrhythmia. One patient developed bronchitis requiring frequent hospitalization.

Table 3. End Points After Three Months of Inactive or Active Pacing for Patients in the Long QRS Group (QRS >150 ms)

Study Group	n	Active Pacing	Inactive Pacing	p Value
Peak oxygen uptake (ml/min/kg)				
Active first sequence	16	15.6 ± 3.6	13.0 ± 3.5	<0.001
Inactive first sequence	15	15.4 ± 2.9	13.1 ± 2.8	
Oxygen uptake at anaerobic threshold (ml/min/kg)				
Active first sequence	16	10.5 ± 2.5	8.9 ± 2.0	<0.001
Inactive first sequence	15	10.7 ± 1.4	9.2 ± 1.3	
Distance walked in 6 min (m)				
Active first sequence	17	462 ± 79	407 ± 117	0.024
Inactive first sequence	17	447 ± 72	407 ± 61	
Quality-of-life score				
Active first sequence	17	24 ± 19	32 ± 27	0.004
Inactive first sequence	17	17 ± 13	25 ± 15	

Data are presented as the mean value ± SD.

Clinical results. Table 2 shows the results for the 69 patients who completed the crossover period. With active pacing, peak V_{O_2} increased 1.37 ml/min/kg (95% confidence interval [CI] 1.99 to 0.76; $p < 0.001$) (Fig. 2A), and V_{O_2} at the anaerobic threshold increased 0.87 ml/min/kg (95% CI 1.35 to 0.40; $p < 0.001$), compared with inactive pacing. The distance walked in 6 min was 26 m longer with active pacing (95% CI 48 to 5; $p = 0.021$). The quality-of-life score improved 4.7 points with active pacing (95% CI 8.5 to 0.9; $p = 0.015$). The NYHA functional class significantly improved by 0.25 class points with active pacing (95% CI 0.38 to 0.11; $p = 0.001$). No carryover or period effects were observed. There were no significant differences in any end point improvement between patients with a pacemaker and patients with an ICD, or between patients paced with LV coronary vein leads and those with epicardial screw-in leads.

The clinical effects of active pacing were distinctly different between patients in the long QRS group (Table 3) and those in the short QRS group (Table 4). With active pacing, the long QRS group exhibited significant improvements over inactive pacing in peak V_{O_2} (2.46 ml/min/kg) (Fig. 2B), V_{O_2} at the anaerobic threshold (1.55 ml/min/kg), distance walked in 6 min (47 m), and the quality-of-life score (8.1 points), whereas the short QRS group did not have an improvement in peak V_{O_2} (Fig. 2C) nor any other end point measure. Considering individual results, 71% of patients in the long QRS group and 38% of patients in the short QRS group had increased peak V_{O_2} by >1 ml/min/kg with active pacing.

DISCUSSION

This study shows that atrial-synchronized LV pacing significantly improves maximal and submaximal exercise capacity, functional status, and quality of life in patients with moderate to severe HF, normal sinus rhythm, and intraventricular conduction delay, but without a standard pacemaker indication. The short-term benefits were only evident among patients with a QRS duration >150 ms. The clinical improvements with LV pacing of patients with a QRS duration >150 ms are similar in magnitude to those reported for biventricular pacing in a trial with a nearly identical study design (9). These conclusions are unchanged by including the results from the three randomized patients who received RV pacing (28). Also, the results were similar

Table 4. End Points After Three Months of Inactive or Active Pacing for Patients in the Short QRS Group (QRS 120 to 150 ms)

Study Group	n	Active Pacing	Inactive Pacing	p Value
Peak oxygen uptake (ml/min/kg)				
Active first sequence	15	14.5 ± 2.5	14.1 ± 2.4	0.363
Inactive first sequence	17	15.3 ± 3.4	15.0 ± 3.4	
Oxygen uptake at anaerobic threshold (ml/min/kg)				
Active first sequence	15	10.4 ± 2.0	9.9 ± 2.0	0.418
Inactive first sequence	17	10.0 ± 2.5	10.0 ± 2.4	
Distance walked in 6 min (m)				
Active first sequence	17	413 ± 81	411 ± 60	0.382*
Inactive first sequence	18	488 ± 93	479 ± 68	
Quality-of-life score				
Active first sequence	14	22 ± 18	23 ± 23	0.766
Inactive first sequence	17	23 ± 21	24 ± 14	

*Period interaction effect was significant ($p = 0.006$). Data are presented as the mean value ± SD.

for patients paced with different kinds of LV leads, although most patients had epicardial leads, which may have been placed at locations different from those commonly accessible with a transvenous approach.

Peak V_{O_2} measured during maximal exercise testing is widely regarded as a reference measure of HF severity (30). Left ventricular pacing increased peak V_{O_2} by a mean of 2.46 ml/min/kg over inactive pacing for patients with a QRS duration >150 ms, which is more than twice the 1-ml/min/kg increase considered clinically significant (31–33). Heart failure patients unable to walk at least 375 m in 6 min are reported to have nearly twice the mortality and hospitalization rates of patients who can walk farther (34). For our patients with a QRS duration >150 ms, the distance walked in 6 min increased by 47 m with LV pacing. For patients with a QRS duration >150 ms, the quality of life, as assessed with the Minnesota Questionnaire (25), improved by a mean 8.1 points with LV pacing, which is more than the 5-point improvement observed in HF patients treated with enalapril (35).

It has been suggested that CRT requires simultaneous stimulation of both ventricles (9). Our results show that LV pacing is similarly effective, at least over a three-month period, for patients with normal sinus rhythm and an intraventricular conduction delay. Differences may emerge with longer treatment periods or in different patient populations. This clinical result mirrors hemodynamic tests that have shown both biventricular and LV pacing to increase LV systolic function equivalently in the presence of normal sinus rhythm (15,16). Nearly all patients in these studies had LV conduction disturbances, often diagnosed as left bundle branch block (which occurred in 88% of our patients). For these patients, pre-exciting only the delayed LV may improve LV contraction synchrony, despite creating a left-to-right electrical asynchrony (36), or may resynchronize the ventricles by combining with the intrinsic depolarization of the interventricular septum and RV.

By prospectively stratifying patients into short and long QRS groups, we were able to show that the degree of benefit from LV pacing depends on the magnitude of the patients' baseline QRS duration. The QRS threshold of 150 ms used to separate patients was suggested by previous hemodynamic studies (16,18). All the statistically significant clinical improvements we observed can be attributed to patients with a QRS duration >150 ms; these patients are also most likely to have improved systolic function (18). However, 38% of individuals with a QRS duration <150 ms had increased peak V_{O_2} by more than 1 ml/min/kg with LV pacing. Therefore, other patient characteristics may be important determinants of pacing effectiveness for patients with a QRS duration between 120 and 150 ms (37–40). The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study, which compared six months of biventricular CRT with no-CRT in a similar HF population, did not find a statistically significant influence of the baseline QRS interval on the magnitude of CRT effect on NYHA functional class, quality-of-life score, and distance walked in 6 min in a retrospective subanalysis ($p > 0.10$) (11). This subanalysis does not necessarily conflict with our prospective results, as the MIRACLE study may have been underpowered to detect the influence of QRS duration, due to, for example, unbalanced representation of short and long QRS patients and/or large variability in their end points.

Earlier studies have focused on NYHA functional class as an indication for patients likely to benefit from resynchronization pacing. Patients in NYHA functional class II have been excluded from previous trials because they were not expected to benefit measurably. We have demonstrated a benefit in a population that included 33% of patients in NYHA functional class II with peak V_{O_2} below 18 ml/min/kg. All of these NYHA functional class II patients exhibited an intraventricular conduction delay, and 43% had a QRS duration >150 ms, putting them in the category of patients most likely to benefit from CRT.

There were no differences in end point outcomes for the 40% of patients who were implanted with an ICD. However, all five deaths during the crossover phase occurred in patients implanted with a pacemaker lacking defibrillation capability, including four who had a sudden cardiac death. Randomized studies with large numbers of patients and long follow-up periods will be necessary to assess the effect of resynchronization with or without ICD on mortality and morbidity (41).

Conclusions. Cardiac resynchronization by LV pacing significantly improved the maximal and submaximal exercise capacity, quality of life, and functional status of HF patients. These benefits were demonstrated for the whole patient cohort, but patients who experienced the most benefit had the longest conduction delays, as indicated by a QRS duration >150 ms. Longer follow-up will determine whether this apparent differential benefit is sustained.

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APPENDIX

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