

ORIGINAL ARTICLE

Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes

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ABSTRACT

BACKGROUND

Indications for cardiac-resynchronization therapy (CRT) in patients with heart failure include a prolonged QRS interval (≥ 120 msec), in addition to other functional criteria. Some patients with narrow QRS complexes have echocardiographic evidence of left ventricular mechanical dyssynchrony and may also benefit from CRT.

METHODS

We enrolled 172 patients who had a standard indication for an implantable cardioverter-defibrillator. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for 6 months. The primary end point was the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months.

RESULTS

At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary end point (46% and 41%, respectively). In a prespecified subgroup with a QRS interval of 120 msec or more, the peak oxygen consumption increased in the CRT group ($P=0.02$), but it was unchanged in a subgroup with a QRS interval of less than 120 msec ($P=0.45$). There were 24 heart-failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%), but the difference was not significant.

CONCLUSIONS

CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT. (ClinicalTrials.gov number, NCT00132977.)

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CARDIAC-RESYNCHRONIZATION THERAPY (CRT) has been shown to improve the rate of survival, quality of life, exercise capacity, and functional status in patients with a prolonged QRS interval and moderate-to-severe heart failure that is resistant to optimal medical therapy. CRT is thought to improve the left ventricular ejection fraction and functional status by minimizing regional left ventricular delay caused by prolonged ventricular conduction, reducing mitral regurgitation and left ventricular reverse remodeling, and normalizing neurohormonal factors.¹⁻⁴ Current guidelines support the use of CRT in patients with an ejection fraction of 35% or less, moderate or severe heart failure (New York Heart Association [NYHA] class III or IV), and a prolonged QRS interval (≥ 120 msec).

Although a prolongation in the QRS interval identifies patients who are likely to benefit from CRT, there still exists a substantial population of patients who have left ventricular mechanical dyssynchrony and a narrow QRS interval.⁵⁻⁷ Tissue Doppler imaging and other such techniques have shown that some patients with narrow or slightly prolonged QRS intervals (< 130 msec) also have mechanical dyssynchrony. Thus, these imaging techniques may be a more specific marker of regional intraventricular-conduction delay than the surrogate marker of electrical dyssynchrony on electrocardiography, as shown by a prolonged QRS interval.⁸⁻¹⁴ Small, single-center studies have suggested that patients with mechanical dyssynchrony and a narrow QRS interval may also benefit from CRT,⁹⁻¹¹ but to date no prospective, randomized, controlled clinical trial has evaluated this hypothesis.

METHODS

PATIENTS

The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) study was a double-blind clinical trial evaluating the efficacy of CRT in patients with a standard indication for an implantable cardioverter-defibrillator (ischemic or nonischemic cardiomyopathy and an ejection fraction of 35% or less), NYHA class III heart failure, a QRS interval of less than 130 msec, and evidence of mechanical dyssynchrony as measured on echocardiography.

Eligibility criteria included an ejection frac-

tion of less than 35%, moderate chronic heart failure (NYHA class III) caused by either ischemic or nonischemic cardiomyopathy, and a QRS interval of less than 130 msec. Although a narrow QRS complex is typically defined as an interval of less than 120 msec, patients with a QRS interval of 120 to 130 msec were included to provide additional data on this group, which had not been studied extensively. Patients were required to receive optimal pharmacologic therapy as described previously.¹⁵ Patients were excluded from the study if they had a standard indication for cardiac pacing or had undergone previous CRT. Additional reasons for exclusion have been described previously.¹⁵

STUDY DESIGN

Patients meeting eligibility requirements underwent a 6-minute walking test and echocardiography to evaluate mechanical dyssynchrony and the ejection fraction. All patients underwent implantation of a CRT device (Epic HF or Atlas+ HF, St. Jude Medical) with a standard right atrial, right ventricular defibrillator and left ventricular leads.

After successful implantation of the device, patients completed a baseline evaluation at 14 days, including cardiopulmonary exercise testing (maximal exercise tolerance on treadmill or bicycle ergometry with the measurement of heart rate, minute ventilation, oxygen uptake, and carbon dioxide output),¹⁶ NYHA functional class assessment, a 6-minute walking test,¹⁷ a quality-of-life evaluation (with the use of the Minnesota Living with Heart Failure Questionnaire, with scores ranging from 0 to 105 and with higher scores indicating a poorer quality of life),¹⁸ an assessment of medication stability, echocardiography for optimization of atrioventricular and inter-ventricular delay, and 12-lead electrocardiography. The echocardiography core laboratory reviewed all echocardiography data.

Patients were then randomly assigned to the CRT group or to the control group (no CRT) in a 1:1 ratio. The device for each group was programmed as described previously.¹⁵ Randomization assignments were created in S-plus software, version 6.2 (Insightful) and were provided to site personnel (who were aware of study-group assignments) with the use of an interactive voice-response system at the baseline visit. Randomization was performed according to center and stratified according to the cardiomyopathy clas-

sification and the QRS interval (<120 msec and \geq 120 msec) within each center.

Atrioventricular and interventricular timing was optimized with the use of Doppler echocardiography. The use of the maximum velocity–time integral measured in the aortic valve as an estimate of stroke volume was recommended for the optimization of atrioventricular timing. However, mitral valve inflow on pulsed Doppler (iterative or Ritter method) was also accepted. Interventricular timing was optimized with the use of the maximum velocity–time integral of the aortic outflow tract on Doppler imaging.

At 6 months, we repeated the cardiopulmonary-exercise testing, evaluation of NYHA functional class, 6-minute walking test, quality-of-life evaluation, and echocardiography. Site personnel who were unaware of study-group assignments administered all evaluations at 6 months.

The study was an investigator-initiated clinical trial with the protocol designed and written by a steering committee consisting of physicians who also served as investigators. A publications committee that included investigators from the top-enrolling centers analyzed the data, and all members contributed to the writing of the manuscript and vouch for the accuracy and completeness of the data reported. Investigators had full access to all data and performed analyses without restrictions or limitations from the sponsor.

ECHOCARDIOGRAPHIC ANALYSIS

We determined the level of intraventricular mechanical dyssynchrony in all patients with the use of both tissue Doppler imaging (which measured mechanical delay in the septal-to-lateral and anteroseptal-to-posterior walls¹⁹) and M-mode echocardiography (which measured the mechanical delay in the septal-to-posterior wall, obtained by M-mode in the parasternal long-axis view²⁰). The interval from QRS onset to the first distinct and maximal septal-to-posterior displacement was defined as the septal delay, and the interval from QRS onset to the peak of the greatest anterior displacement of the basal posterior wall was determined to be the posterior-wall delay. The difference was defined as the mechanical dyssynchrony in the septal-to-posterior wall, with an interval of at least 130 msec defining the presence of significant dyssynchrony.²⁰

Color Doppler imaging was performed by first acquiring standard apical views of two chambers,

three chambers, and four chambers at high frame rates. Atrioventricular opening and closure were determined by sampling the flow through the left ventricular outflow tract with the use of pulsed Doppler echocardiography. A region of interest (5×10 mm) was placed off-line in the basal one third of the myocardium at least 1 cm below the mitral annulus, and velocity curves were generated. The interval from the QRS onset to peak systolic velocity (occurring within the aortic ejection period) was defined as the mechanical delay for the four basal segments (anteroseptal, septal, posterior, and lateral). The higher peak in velocity was selected when double peaks were encountered within the aortic ejection period. The difference between the anteroseptal-to-posterior delay and the septal-to-lateral delay was defined as the opposing-wall mechanical delay. An opposing-wall delay between the anteroseptal-to-posterior wall or the septal-to-lateral wall of 65 msec or more was defined as a significant intraventricular mechanical delay.¹⁹ Left ventricular volumes were determined with the use of the biplane Simpson's method of disks, and the ejection fraction was calculated with a formula calling for the subtraction of the end-systolic volume from the end-diastolic volume and the difference divided by the end-diastolic volume. Mitral regurgitation was assessed according to the guidelines of the American Society of Echocardiography.²¹

STATISTICAL ANALYSIS

The primary efficacy end point was the proportion of patients who had an increase of at least 1.0 ml per kilogram of body weight per minute in peak oxygen consumption during cardiopulmonary exercise testing at 6 months after baseline. The secondary efficacy end points included improvement in the quality-of-life score and the NYHA class at 6 months after baseline.

The study was powered to detect a difference of 23% in the proportion of patients who achieved the primary end point in the CRT group, as compared with the control group. The proportion that improved in the control group was assumed to be 25%. The sample size required to detect this difference with a statistical power of 80% at the 0.05 significance level was 76 patients in each group, with the use of Fisher's exact test. On the basis of an attrition rate of 40%, the study required a total enrollment of 250 patients.¹⁵ The secondary end points of the quality-of-life score

and the NYHA class were each evaluated at a significance level of 0.025 and were considered significant only if the primary efficacy end point was met with the use of the gatekeeper method.²² All end points were analyzed according to the intention-to-treat principle; patients who crossed over were analyzed according to their original treatment assignment. All P values were calculated with the use of a two-sided test.

Survival curves were constructed according to the Kaplan–Meier method, and the differences between curves were examined by the log-rank statistic. Data for all patients were censored at 196 days, the last day of the 6-month window for clinical visits. Confidence intervals for survival were computed on a log–log scale.²³

All analyses were performed with the use of SAS software, version 9.1. For continuous variables, data are presented as median changes between baseline and 6 months. Confidence intervals for the median were computed with the use of a distribution-free approach.²⁴ Comparisons of changes from baseline to 6 months between the control group and the CRT group were evaluated for significance by the Wilcoxon rank-sum test. Mean (\pm SD) values are presented. For categorical variables, differences in the distribution of re-

sponses to treatment at 6 months in the two groups were compared by Fisher's exact test. Confidence intervals for proportions were computed by exact methods.²⁴ The protocol specified that end-point analyses be performed for patients with data available at 6 months and for those who died, withdrew, or were unable to perform the evaluation at 6 months owing to worsening heart failure. The latter patients were included in the analysis with their worst values imputed as follows: 0 ml per kilogram per minute for peak oxygen consumption, a score of 105 on the quality-of-life scale, NYHA class IV, and 0 m for the 6-minute walking test. Independent committees whose members were unaware of study-group assignments and investigational center adjudicated all deaths and adverse events.

RESULTS

PATIENTS

From August 2005 to January 2007, 250 patients were enrolled at 34 centers (Fig. 1). Of these patients, four did not undergo successful implantation of a CRT device; furthermore, before the baseline visit, two patients died, and three withdrew from the study. An additional 69 patients did not meet enrollment criteria and did not undergo randomization. The remaining 172 patients were randomly assigned to study groups: 87 to the CRT group and 85 to the control group. The majority (97%) of left ventricular leads were implanted in a lateral position. The baseline clinical characteristics were similar between the two groups (Table 1).

At 6 months, analysis could be performed on data for 76 patients in the CRT group and 80 patients in the control group. Patients were not included in this analysis because they did not complete a cardiopulmonary exercise test for reasons other than worsening heart failure (two patients in the CRT group and one in the control group), did not complete a 6-month visit (three patients in the CRT group and four in the control group), died from causes not associated with heart failure (three patients in the CRT group), or withdrew from the study for reasons not associated with heart failure (three patients in the CRT group).

CROSSOVERS AND THERAPY COMPLIANCE

Three patients in the control group who crossed over to the CRT group because of worsening

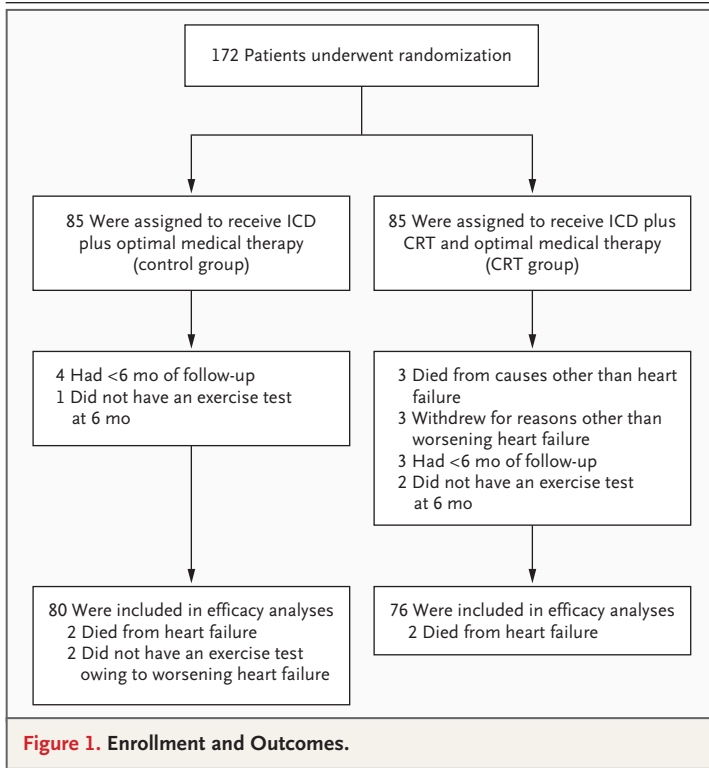


Figure 1. Enrollment and Outcomes.

Table 1. Characteristics of the Patients at Baseline.*

Variable	Control Group		CRT Group	
	No. of Patients	Value	No. of Patients	Value
Age — yr	85	58±14	87	60±12
Male sex — no. (%)	85	49 (58)	87	62 (71)
NYHA class III — no. (%)	85	84 (99)	87	87 (100)
QRS interval	85		87	
Mean — msec		106±13		107±12
<120 msec — no. (%)		60 (71)		66 (76)
≥120 msec — no. (%)		25 (29)		21 (24)
Underlying heart disease — no. (%)	85		87	
Ischemic		43 (51)		47 (54)
Nonischemic		42 (49)		40 (46)
Indication for ICD — no. (%)	85		87	
Primary prevention		73 (86)		74 (85)
Secondary prevention		12 (14)		13 (15)
Pre-ejection period — msec	85	112±22	86	112±21
Interventricular mechanical delay — msec	82	8±31	85	9±28
Intraventricular mechanical dyssynchrony — msec†				
Septal-to-posterior wall	33	112±51	24	106±45
Septal-to-lateral wall	85	86±38	85	81±39
Anteroseptal-to-posterior wall	81	81±45	83	78±34
Left ventricular size and function				
Ejection fraction — %	85	26±6	87	25±5
End-diastolic diameter — mm	84	65±9	85	66±9
End-systolic diameter — mm	84	53±9	85	56±9
End-diastolic volume — ml	85	210±75	87	216±78
End-systolic volume — ml	85	156±64	87	163±65
Mitral regurgitation — no. (%)	83		87	
None or mild		55 (66)		59 (68)
Moderate		23 (28)		25 (29)
Severe		5 (6)		3 (3)
Medication at baseline — no. (%)	85		87	
ACE inhibitor or substitute‡		77 (91)		77 (89)
Beta-blocker		79 (93)		84 (97)
Diuretic		74 (87)		73 (84)
Antiarrhythmic		10 (12)		7 (8)
Peak oxygen consumption — ml/kg/min	85	12.4±4.5	87	12.1±3.3
Exercise duration — min	85	9.0±3.8	87	8.9±3.0
Quality-of-life score§	85	57±26	87	54±24
Results on 6-min walking test — m	85	297±100	87	301±94

* Plus–minus values are means ±SD. None of the differences between the control group and the CRT group were significant. NYHA denotes New York Heart Association, ICD implantable cardioverter–defibrillator, and ACE angiotensin-converting enzyme.

† The mechanical delays in the septal-to-lateral and anteroseptal-to-posterior walls were measured on tissue Doppler imaging; the mechanical delay in the septal-to-posterior wall was measured on M-mode echocardiography.

‡ ACE substitutes include angiotensin-receptor blockers and hydralazine.

§ The quality of life was evaluated with the use of the Minnesota Living with Heart Failure Questionnaire, with scores ranging from 0 to 105 and with higher scores indicating a poorer quality of life.

heart failure were included in the control group for efficacy analysis. No patients in the CRT group crossed over to the control group. Most patients in the CRT group (97%) received biventricular pacing more than 85% of the time.

EFFICACY END POINTS AND ECHOCARDIOGRAPHIC DATA

At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary end point (46% and 41%, respectively) (Table 2). There was also no significant difference between groups in quality-of-life scores, results on the 6-minute walk test, or echocardiographic measures. The CRT group had a significant improvement in NYHA class (54%), as compared with the control group (29%) ($P=0.006$).

SURVIVAL

Of 172 patients who underwent randomization, 6 died before the scheduled 6-month follow-up visit. Five patients in the CRT group died: two from unknown cardiac causes, two from pump failure, and one from an unknown causes. Two patients in the control group died of pump failure, one before the 6-month visit and one at 7 months, without completing a 6-month follow-up visit. The latter patient was included in the efficacy analysis but not in the survival analysis. At 6 months, cumulative overall survival was 94.2% (95% confidence interval [CI], 86.7 to 97.6) in the CRT group and 98.8% (95% CI, 91.9 to 99.8) in the control group ($P=0.11$ by the log-rank test); cumulative freedom from death caused by worsening heart failure was 97.7% (95% CI, 91.1 to 99.4) in the CRT group and 98.8% (95% CI, 91.9 to 99.8) in the control group ($P=0.58$ by the log-rank test).

QRS INTERVAL AND CARDIOMYOPATHY CLASSIFICATION

Figure 2 shows the results of the prespecified stratified analysis according to the QRS interval (≥ 120 msec or < 120 msec). Peak oxygen consumption and the NYHA class improved in patients in the CRT group with a QRS interval of 120 msec or more. However, no difference was observed in the quality-of-life score and the 6-minute walking test in either stratum. Figure 3 shows the results of the prespecified stratified analysis according to cardiomyopathy classification. In the CRT group, there was a significant improvement in NYHA

class and results on the 6-minute walking test in the nonischemic stratum but no difference in peak oxygen consumption and quality-of-life scores.

ADVERSE EVENTS

Of 172 patients, 3 had a deep venous thrombosis (1.7%), 2 had a pneumothorax (1.2%), 2 had pericarditis (1.2%), and 1 had a coronary sinus perforation (0.6%). Thirteen patients had lead dislodgement (7.6%), with five involving the left ventricular lead (2.9%). Other adverse events included infection in six patients (3.5%), bleeding or hematoma in two patients (1.2%), loss of pacemaker-lead capture in two patients (1.2%), and phrenic-nerve stimulation in three patients (1.7%). There were 24 heart-failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%). The numbers of adverse events did not differ significantly between the two study groups.

DISCUSSION

CRT has been established as effective treatment for patients with heart failure and a QRS interval of more than 120 msec, an ejection fraction of 35% or less, and an NYHA class of III or IV.²⁵⁻³⁰ Our study showed that CRT did not improve peak oxygen consumption, as compared with a control group, in patients with NYHA class III heart failure with an ejection fraction of 35% or less, a QRS interval of less than 130 msec, and mechanical dyssynchrony (which was defined as an opposing-wall delay of 65 msec or more on tissue Doppler imaging or a mechanical dyssynchrony in the septal-to-posterior wall of 130 msec or more on M-mode echocardiography). Although patients in the CRT group had a significant improvement in NYHA class (a secondary end point that was determined by subjective assessment), there was no significant improvement in other end points, including the quality-of-life score, the results on a 6-minute walking test, and left ventricular reverse remodeling. These findings were consistent with the lack of benefit observed in peak oxygen consumption, the primary end point.

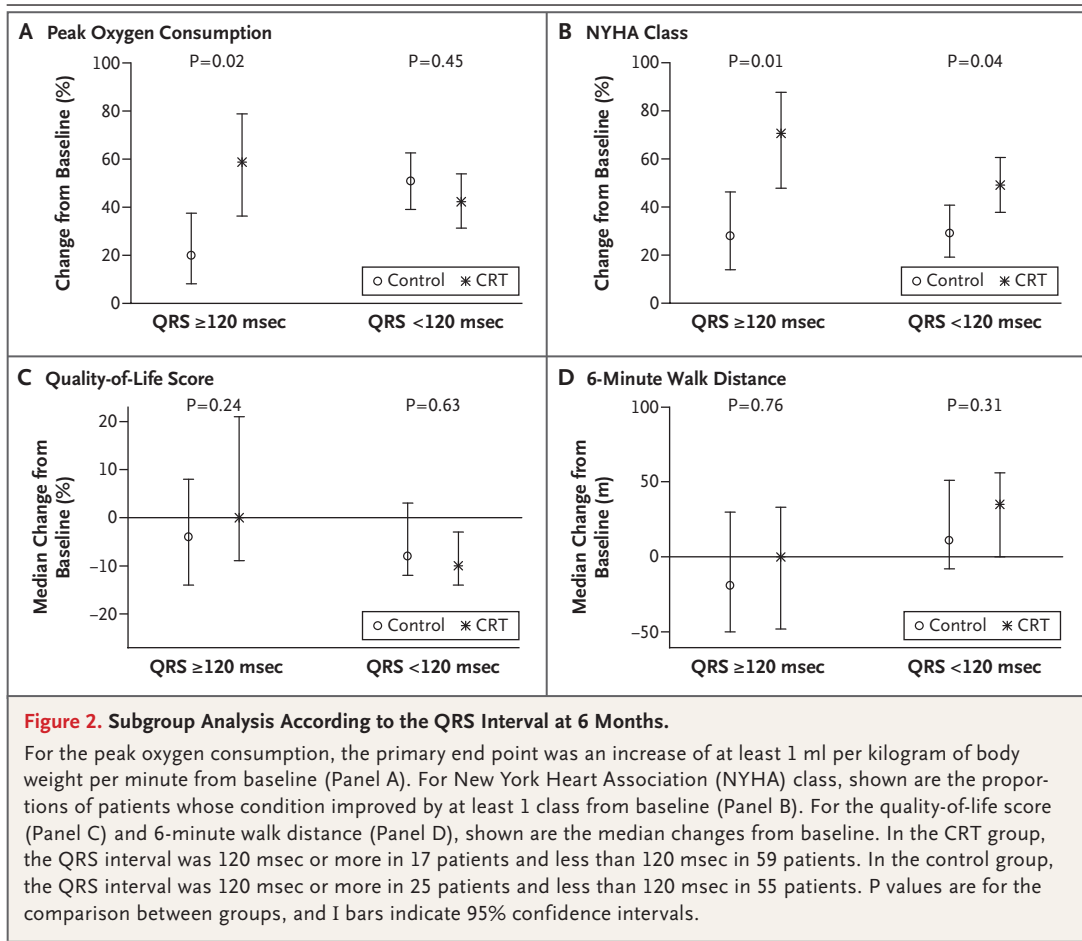
Numerous echocardiographic methods and measurements for the evaluation of mechanical dyssynchrony have been reported to predict a

Table 2. Effect of Cardiac Resynchronization on Primary and Secondary End Points and Other Measures.*

Variable	Control Group	CRT Group	P Value
Primary end point			
Change in peak oxygen consumption			0.63
No. of patients	80	76	
Median change (95% CI) — ml/kg/min	0.5 (-0.3 to 1.1)	0.4 (-0.6 to 1.2)	
Increase of ≥ 1.0 ml/kg/min — no. (%)	33 (41)	35 (46)	
Secondary end points			
Change in quality-of-life score [†]			0.91
No. of patients	80	76	
Median change (95% CI)	-7 (-11 to 3)	-8 (-10 to -1)	
Change in NYHA class			0.006
No. of patients	80	76	
Improved by 1 class or more — no. (%)	23 (29)	41 (54)	
No change — no. (%)	51 (64)	31 (41)	
Worsened — no. (%)	6 (8)	4 (5)	
Other end points			
Change in 6-min walking test			0.23
No. of patients	79	75	
Median change (95% CI) — m	6 (-17 to 30)	26 (0 to 46)	
Change in ejection fraction			0.83
No. of patients	74	68	
Median change (95% CI) — %	2.0 (0.3 to 4.2)	1.2 (-0.4 to 4.4)	
Change in end-diastolic volume			0.71
No. of patients	74	68	
Median change (95% CI) — ml	-11 (-30 to -2)	-16 (-29 to -8)	
Change in end-systolic volume			0.81
No. of patients	74	68	
Median change (95% CI) — ml	-18 (-28 to -8)	-19 (-34 to -12)	
Change in end-diastolic diameter			0.49
No. of patients	77	72	
Median change (95% CI) — mm	-1 (-2 to 1)	0 (-2 to 0)	
Change in end-systolic diameter			0.34
No. of patients	77	72	
Median change (95% CI) — mm	0 (-2 to 2)	-1 (-3 to 0)	
Change in degree of mitral regurgitation — no. (%)			>0.99
No. of patients	80	76	
Improved by 1 or more grade	9 (12)	8 (11)	
No change	61 (80)	60 (81)	
Worsened by 1 or more grade	6 (8)	6 (8)	

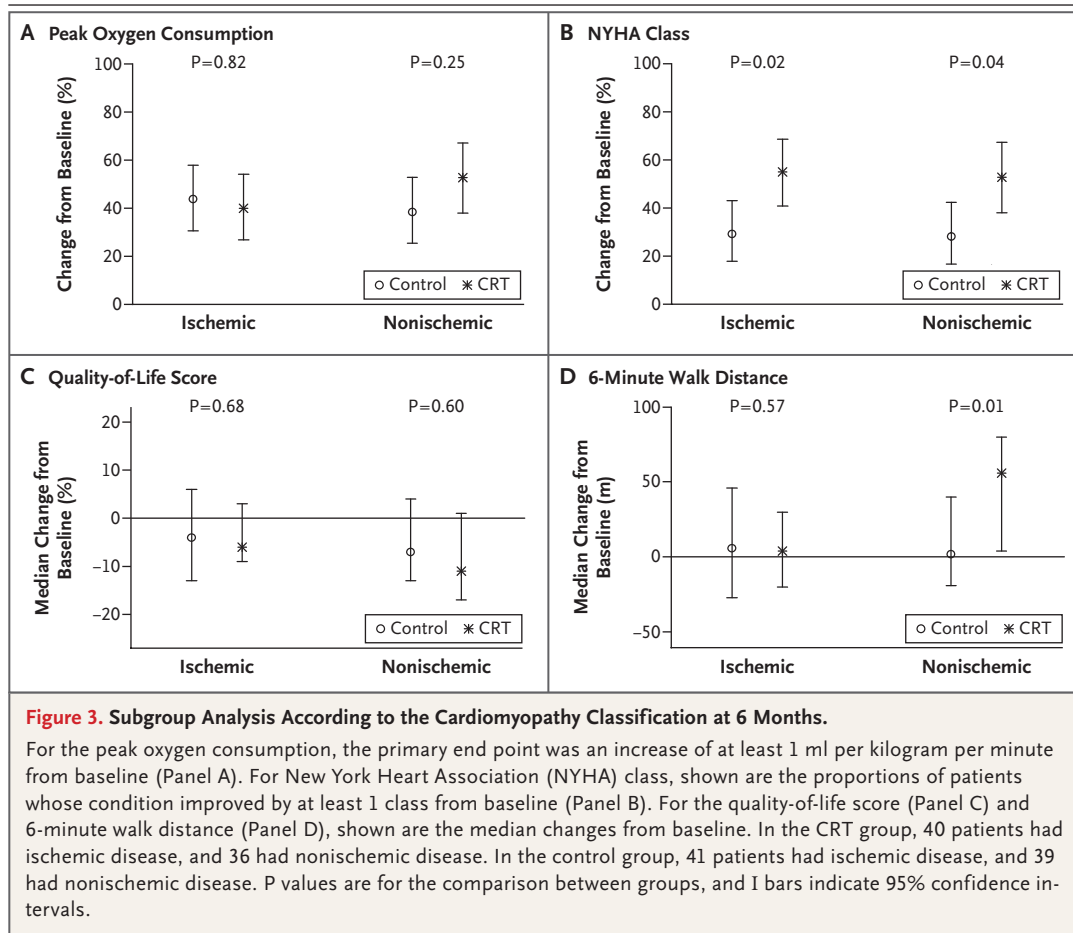
* NYHA denotes New York Heart Association, and CI confidence interval.

[†] Quality of life was evaluated with the use of the Minnesota Living with Heart Failure Questionnaire, with scores ranging from 0 to 105 and with higher scores indicating a poorer quality of life.



favorable response to CRT in patients with NYHA class III heart failure who have an ejection fraction of 35% or less and a QRS interval of 120 msec or more. Specifically, the commonly applied methods of measuring mechanical dyssynchrony with Doppler imaging and M-mode echocardiography and an SD of at least 33 msec on a 12-segment model have all been shown to predict reverse remodeling in nonrandomized cohort studies.^{19,20,31} However, with the exception of a single clinical trial,²⁹ in which a subgroup of patients with a QRS interval of 120 to 150 msec were enrolled on the basis of echocardiographic criteria for dyssynchrony, no previous randomized trial of CRT included echocardiographic dyssynchrony as a study-entry requirement; in all other studies, the QRS interval was used as the sole determinant for enrollment.^{1-3,28} In our study, tissue Doppler imaging was the primary criterion that was used to define mechanical dyssynchrony for study entry.

Furthermore, since approximately 30% of patients with symptomatic heart failure, an ejection fraction of 35% or less, and a normal QRS interval have been reported to have mechanical dyssynchrony, the use of echocardiography might identify additional patients who could be helped by CRT. Independent investigations in nonrandomized and small-cohort studies have reported a favorable response to CRT in patients with a QRS interval of less than 120 msec when mechanical dyssynchrony was diagnosed on tissue Doppler imaging or in patients with an opposing-wall mechanical delay of at least 65 msec or a 12-segment SD of at least 33 msec.^{10,11} Our study found no benefit to CRT in patients with heart failure with a narrow QRS interval (<130 msec) when study entry was determined by similar echocardiographic Doppler measures. Other echocardiographic measures of mechanical dyssynchrony that have previously shown promise as predictors of CRT success, such as



the aortic pre-ejection period and interventricular delay, did not differ between patients who had a response and those who did not have a response.

The methods that we selected to identify mechanical dyssynchrony may have accounted for the lack of CRT benefit in our study population. Most patients (96%) in our study qualified for enrollment on the basis of the tissue Doppler criterion (i.e., an opposing-wall delay of ≥ 65 msec, rather than the mechanical dyssynchrony in the septal-to-posterior wall of 130 msec or more on M-mode echocardiography). Only 4% of patients were eligible to participate in the study solely on the basis of mechanical dyssynchrony criteria on M-mode echocardiography. The echocardiographic enrollment criteria were selected on the basis of relative technical ease of data acquisition and measurement, the availability of tissue Doppler technology, and the supporting literature at the time of the study design. Although the method

we adopted appears to have lacked specificity, the potential role of a more comprehensive quantification of left ventricular dyssynchrony based on myocardial imaging of radial, longitudinal, and rotational components might be more predictive of responsiveness to CRT.

Consistent with previous studies in patients with a prolonged QRS interval, a prespecified subgroup analysis found a significant improvement in peak oxygen consumption in the CRT group among patients with a QRS interval of 120 msec to 130 msec. Further randomized, prospective studies using more specific myocardial imaging criteria will be necessary to determine the value of these techniques in selecting patients with a QRS interval of 120 msec or less who are likely to have a response to CRT.

We conclude that CRT did not improve peak oxygen consumption in patients with moderate heart failure, a QRS interval of less than 130 msec, and mechanical dyssynchrony. However, a

subgroup of patients with a QRS interval of 120 msec to 130 msec did benefit from CRT.

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APPENDIX

Committee members in the RethinQ trial are as follows: **Clinical Events Committee:** H. Hsia, Stanford University, Palo Alto, CA; B. Knight, University of Chicago, Chicago; A. Sharma, Mercy General Hospital, Sacramento, CA. **Echocardiography Steering Committee:** J.F. Beshai, University of Chicago, Chicago; R.A. Grimm, Cleveland Clinic Foundation, Cleveland; R. Martin, Emory University Hospital, Atlanta; S.F. Nagueh, Methodist Hospital, Houston; M. St. John Sutton, Hospital of the University of Pennsylvania, Philadelphia. **Steering Committee:** J.F. Beshai, University of Chicago, Chicago; R.A. Grimm, Cleveland Clinic Foundation, Cleveland; J.H. Baker II, St. Thomas Hospital, Nashville; H. Hsia, Stanford University, Palo Alto, CA; L.A. Pires, St. John Hospital and Medical Center, Detroit; A. Sharma, Mercy General Hospital, Sacramento, CA; R. Soucier, St. Francis Hospital and Medical Center, Hartford, CT; K.M. Stein, New York–Presbyterian Hospital, New York. **Echocardiography Core Lab:** R. Grimm, Cleveland Clinic Foundation, Cleveland. **Cardiopulmonary Exercise Core Lab:** K. Wasserman and X.-G. Sun, Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Los Angeles.

Other investigators and institutions that participated in the RethinQ study are as follows: *Arizona Arrhythmia Consultants, Scottsdale* — T. Mattioni; *Arkansas Cardiology, Little Rock* — G.S. Greer; *Arkansas Heart Hospital, Little Rock* — S. Beau; *Baptist Memorial Hospital, Memphis* — F. McGrew; *Baystate Medical Center, Springfield, MA* — J. Cook; *Central Baptist Hospital, Lexington, KY* — G. Tomassoni; *Cleveland Clinic Foundation, Cleveland* — P.J. Tchou; *Deborah Heart and Lung Center, Browns Mills, NJ* — R. Corbisiero; *Elyria Memorial Hospital, Elyria, OH* — S. Moore; *Emory University Hospital, Atlanta* — J.J. Langberg; *Glendale Memorial Hospital, Glendale, CA* — J. McKenzie III; *Hospital of the University of Pennsylvania, Philadelphia* — J. Cooper; *Ingham Regional Medical Center, Lansing, MI* — J. Ip; *Iowa Heart Center, Des Moines* — S. Bailin; *Loyola University Medical Center, Maywood, IL* — N. Varma; *Main Line Health Center, Wynnewood, PA* — S. Rothman; *Massachusetts General Hospital, Boston* — J. Singh; *Medical University of South Carolina, Charleston* — M. Gold; *Mercy General Hospital, Sacramento, CA* — G. O'Neill and A. Sharma; *Mount Sinai Hospital, New York* — D. Mehta; *Nebraska Heart Institute, Lincoln* — M. Fedor; *New York–Presbyterian Hospital, New York* — K.M. Stein; *Ohio State University, Columbus* — G. Haas; *Orlando Regional Medical Center, Orlando, FL* — A. Duran; *Scripps Green Hospital, La Jolla, CA* — T. Heywood; *Shands Jacksonville, Jacksonville, FL* — S. Hsu; *St. Francis Hospital, Roslyn, NY* — S.M. Greenberg; *St. Francis Hospital and Medical Center, Hartford, CT* — R. Soucier; *St. John Hospital and Medical Center, Detroit* — L.A. Pires; *St. Thomas Hospital, Nashville* — J.H. Baker II; *United Hospital, St. Paul, MN* — S. Adler; *University of Alabama at Birmingham, Birmingham* — H. McElderry; *University Hospitals of Cleveland, Cleveland* — R. Goldstein; *University of Chicago, Chicago* — J.F. Beshai.

REFERENCES

- Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA* 2003;289:2685-94.
- Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
- Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-80.
- Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;42:1454-9.
- Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002;39:194-201.
- Shen AY, Wang X, Doris J, Moore N. Proportion of patients in a congestive heart failure management program meeting criteria for cardiac resynchronization therapy. *Am J Cardiol* 2004;94:673-6.
- Gupta SN, Jose VJ, Chandy ST. Heart failure: what proportion of patients satisfy the electrocardiographic criteria for cardiac resynchronization therapy? *Indian Heart J* 2003;55:619-23.
- Ghio S, Constantin C, Klersy C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. *Eur Heart J* 2004;25:571-8.
- Achilli A, Sassara M, Ficili S, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. *J Am Coll Cardiol* 2003;42:2117-24.
- Yu CM, Chan YS, Zhang Q, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. *J Am Coll Cardiol* 2006;48:2251-7.
- Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;48:2243-50.
- Yu CM, Yang H, Lau CP, et al. Regional left ventricle mechanical asynchrony in patients with heart disease and normal QRS duration: implication for biventricular pacing. *Pacing Clin Electrophysiol* 2003;26:562-70.
- Turner MS, Bleasdale RA, Vinereanu D, et al. Electrical and mechanical components of dyssynchrony in heart failure patients with normal QRS duration and left bundle-branch block. *Circulation* 2004;109:2544-9.
- Bax JJ, Marwick TH, Molhoek SG, et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. *Am J Cardiol* 2003;92:1238-40.
- Beshai JF, Grimm R. The resynchronization therapy in narrow QRS study (RethinQ study): methods and protocol design. *J Interv Card Electrophysiol* 2007;19:149-55.
- Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of exercise testing and interpretation. 4th ed. Baltimore: Lippincott, Williams & Wilkins, 2005.
- Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919-23.
- Rector RS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. II. Content, reliability, and validity of a new measure — the Minnesota Living with Heart Failure Questionnaire. *Heart Fail* 1987;3:198-209.
- Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834-40.
- Pitzalis MV, Iacoviello M, Romito R,

- et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;40:1615-22.
21. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802.
22. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Statist Plan Infer* 2001;99:25-40.
23. Nair VN. Confidence bands for survival functions with censored data: a comparative study. *Technometrics* 1984;26:265-75.
24. Hahn GJ, Meeker WQ. *Statistical intervals: a guide for practitioners*. New York: John Wiley, 1991:82-3.
25. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. *Circulation* 2003;108:2596-603.
26. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001;104:3026-9.
27. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;289:730-40.
28. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
29. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
30. McSwain RL, Schwartz RA, DeLurgio DB, Mera FV, Langberg JJ, León AR. The impact of cardiac resynchronization therapy on ventricular tachycardia/fibrillation: an analysis from the combined Contak-CD and InSync-ICD studies. *J Cardiovasc Electrophysiol* 2005;16:1168-71.
31. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-45.

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