Clinical Investigations

Cardiac Resynchronization Therapy in Patients with Heart Failure and Conduction Abnormalities Other than Left Bundle-Branch Block: Analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)

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Summary

Background: Cardiac resynchronization therapy (CRT) has been proposed as a treatment for patients with congestive heart failure (CHF) and prolonged QRS durations. Previous studies have predominantly included patients with left bundle-branch block (LBBB). The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) investigators assessed the efficacy of CRT in patients with CHF with QRS durations ≥ 130 ms and found that CRT lead to improvement in several measures of functional capacity and exercise tolerance.

Hypothesis: We designed this retrospective study to determine whether patients with CHF who have conduction abnormalities other than LBBB also respond favorably to CRT.

Methods: We divided patients enrolled in the MIRACLE trial into three subgroups according to conduction abnormality – LBBB, right bundle-branch block (RBBB), and nonspecific interventricular conduction delay (IVCD) – and compared the response among and within these groups to CRT or no CRT at baseline and 6-months' follow-up.

Results: We found 313 patients with LBBB, 43 with RBBB, and 35 with IVCD. When they received CRT, significant improvement was achieved in functional class ($p = 0.001$) by patients with RBBB, and in quality of life ($p = 0.038$) by patients with IVCD. Patients in the RBBB and IVCD groups

showed improvement in exercise time and peak oxygen consumption after CRT. Most patients with RBBB (82%) also had either left anterior fascicular block or left posterior fascicular block.

Conclusions: Patients with CHF with RBBB and IVCD do benefit from CRT. Improvement with CRT in patients with RBBB may be due to concomitant left-sided conduction abnormalities. Further subgroup analyses of other CRT trials are necessary to validate these results.

Key words: cardiac resynchronization therapy, congestive heart failure, conduction abnormalities

Introduction

Congestive heart failure (CHF) affects an estimated 4.9 million Americans, with 550,000 new cases diagnosed annually. In recent years, clinical trials have demonstrated favorable long-term effects of angiotensin-converting enzyme inhibitors, beta blockers, and aldosterone antagonists on morbidity and mortality in patients with CHF.^{1–6} Despite these considerable advancements in pharmacologic therapy, hospitalization of patients with advanced CHF remains frequent and quality of life remains poor.

There is increasing evidence suggesting that cardiac resynchronization therapy (CRT) improves cardiac performance in patients with CHF with prolonged QRS duration and refractory symptoms despite maximal medical therapy.^{7–9} Patients with prolonged QRS duration have conduction abnormalities which occur in three categories: left bundle-branch block (LBBB), right bundle-branch block (RBBB), and nonspecific interventricular conduction delay (IVCD). Research supporting the role of CRT in CHF has been performed almost entirely in patients with LBBB. The clinical effects of CRT in patients with CHF conduction abnormalities other than LBBB have not been clearly demonstrated. The purpose of this analysis was to assess whether patients with CHF with

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RBBB or IVCD obtain the same benefits from CRT as those with LBBB.

Methods

Patient Selection

We used data from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) to assess the efficacy of CRT in patients with CHF and prolonged QRS durations, and compared those results among subgroups defined by conduction abnormality. The MIRACLE study design, patient population, methods, and results have been published previously.⁸ In brief, 453 patients with New York Heart Association (NYHA) functional class III or IV CHF were implanted with CRT pacemakers and randomly assigned to either CRT or a control group (no pacing) for 6 months. Primary endpoints included changes in NYHA functional class, quality of life (measured by scores on the Minnesota Living with Heart Failure Questionnaire), and 6-min hall walk distance. Secondary endpoints included changes in exercise time and peak oxygen consumption (MVO_2).

For the present analysis, baseline 12-lead electrocardiograms (ECGs) from patients in the MIRACLE trial were analyzed by one reviewer and classified as either LBBB (monophasic complex QS in V_1 , and monophasic R wave in V_6), RBBB (triphasic complex rsR¹ in V_1 and deep terminal S wave in V_6), or IVCD (prolonged QRS duration that did not meet the criteria for either LBBB or RBBB). The reviewer was blinded to all endpoint data.

Statistical Analyses

Baseline demographics were compared among groups (LBBB, RBBB, and IVCD) using chi-square tests for discrete variables and analysis of variance methods for continuous variables. For demographic variables that were significantly different among groups, paired comparisons were made to identify which groups were different. The Tukey studentized range test was used to adjust for multiple comparisons of continuous variables. For discrete variables, pairwise comparisons were made using a Fisher's exact test with a Bonferroni corrected p value.

Analysis of covariance methods was used to compare the effect of CRT among LBBB, RBBB, and IVCD patient groups. Within groups, the effect of CRT on primary and secondary endpoints was assessed by comparing changes from baseline to 6 months between CRT and control patients using the Wilcoxon rank-sum test. Statistical software from SAS, Inc. (Cary, N.C., USA) was used. P values of <0.05 were considered significant.

Results

Baseline demographic data are shown in Table I. In all, 391 patients completed 6 months of follow-up and had verifiable ECGs. Of those patients, 313 had LBBB, 43 had RBBB, and 35 had IVCD. The three groups defined by conduction abnormality were similar with respect to randomization assignment, age, gender, ethnicity, and NYHA functional class.

TABLE I Baseline demographic data of patients enrolled in MIRACLE according to conduction abnormality

Parameter	LBBB (n = 313)	RBBB (n = 43)	IVCD (n = 35)	p Value
Randomization assignment (% CRT)	53.0	48.8	45.7	0.651
Age (years)	63.5 ± 11.0	66.3 ± 11.3	66.8 ± 9.9	0.102
Sex (% male)	63.9	79.1	74.3	0.084
Ethnicity (% Caucasian)	88.8	93.0	91.4	0.645
Heart failure etiology (% ischemic)	49.5	74.4	74.3	<0.001
New York Heart Association (% class III)	92.0	86.0	94.3	0.348
QRS duration (ms)	168.5 ± 20.0 ^a	161.7 ± 19.7	153 ± 20.2 ^a	<0.001
Left ventricular ejection fraction (%)	21.5 ± 6.2 ^a	24.0 ± 6.4 ^a	22.4 ± 5.6	0.042
Left ventricular end diastolic dimension (mm)	69.5 ± 9.9 ^a	65.1 ± 7.8 ^a	69.3 ± 7.8	0.019
Heart rate (beats/min)	73.5 ± 12.1	75.0 ± 14.4 ^a	68.3 ± 12.7 ^a	0.040
Systolic blood pressure (mmHg)	116.1 ± 17.8	113.8 ± 17.2	111.5 ± 16.0	0.278
Diastolic blood pressure (mmHg)	69.1 ± 10.1	67.9 ± 11.1	65.7 ± 10.4	0.172
Six-min hall walk (m)	305 ± 89	304 ± 84	317 ± 88	0.736
Exercise time (s)	476 ± 207	532 ± 262	503 ± 165	0.282
Relative peak VO_2 , ml/kg/min	14.8 ± 4.2	14.8 ± 4.2	15.1 ± 3.9	0.901
ACE-I or ARB use (%)	93.9	93.0	85.7	0.192
Beta blocker use (%)	62.0	51.2	68.6	0.259

Continuous data expressed as mean ± standard deviation.

^a P value statistically significant between groups.

Abbreviations: LBBB = left bundle-branch block, RBBB = right bundle-branch block, IVCD = interventricular conduction delay, CRT = cardiac resynchronization therapy, ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker.

FIG. 1 Change in New York Heart Association (NYHA) class at 6 months compared with baseline in patients with left bundle-branch block (LBBB), right bundle-branch block (RBBB), and interventricular conduction delay (IVCD) according to treatment. CRT = cardiac resynchronization therapy.

Figure 1 demonstrates changes in NYHA class after 6 months in patients with LBBB, RBBB, and IVCD for both the control and CRT groups. Patients receiving CRT had similar trends of improvement in functional class compared with their respective control groups, regardless of conduction abnormality (LBBB, $p < 0.001$; RBBB, $p = 0.001$; IVCD, $p = 0.08$).

Figure 2 shows the change in quality of life after 6 months of CRT according to conduction abnormality. Patients with RBBB receiving CRT demonstrated trends of improvement in quality of life similar to those of patients with LBBB, but these trends were not statistically significant. Patients with IVCD who received CRT had significant improvement in quality of life compared with patients in the control group ($p = 0.038$).

FIG. 2 Change in quality of life at 6 months compared with baseline in patients with LBBB, RBBB, and IVCD according to treatment (decrease in score indicates improvement in quality of life). Abbreviations as in Figure 1.

Figure 3 demonstrates change in 6-min hall walk distance. Patients with IVCD achieved trends of improvement in 6-min hall walk distance similar to those of patients with LBBB. Patients with RBBB receiving CRT did not have any increase in 6-min hall walk distance ($p = 0.463$).

Changes in exercise time and MVO_2 are shown in Figures 4 and 5. Patients with RBBB and patients with IVCD had improvements with CRT at 6 months compared with control patients, which were similar to those of patients with LBBB, but these improvements did not reach statistical significance.

Univariate analyses for the RBBB and IVCD groups were based on 43 and 35 patients, respectively. As a result of the small sample size, although similar trends were seen in all

FIG. 3 Change in 6-minute hall walk distance at 6 months compared with baseline in patients with LBBB and RBBB according to treatment. Abbreviations as in Figure 1.

FIG. 4 Change in exercise time at 6 months compared with baseline in patients with LBBB, RBBB, and IVCD according to treatment. Abbreviations as in Figure 1.

FIG. 5 Change in MVo₂ at 6 months compared with baseline in patients with LBBB, RBBB, and IVCD according to treatment. Abbreviations as in Figure 1.

three groups, comparisons with the RBBB and IVCD groups did not always achieve statistical significance.

Of the 391 patients whose baseline echocardiograms were analyzed for this report, 36 died during the first 6 months of follow-up. Death rates were similar for the LBBB (5.6%), RBBB (7.8%), and IVCD (7.7%) subgroups. Rates of CHF hospitalizations were also similar (12.1, 7.8, and 12.8%, respectively, for the LBBB, RBBB, and IVCD subgroups). Of note, 56% of patients with RBBB had an associated left anterior fascicular block (electrical axis $-81.5 \pm 33^\circ$) while 26% had left posterior fascicular block (electrical axis $125 \pm 29.3^\circ$).

Discussion

Our analysis of MIRACLE suggests that patients with CHF with RBBB and IVCD demonstrate improvements in quality of life, functional class, and other measurements of functional capacity with CRT similar to those of patients with CHF with LBBB.

Recent studies have documented the potential of CRT for improving cardiac function in patients with CHF and prolonged QRS duration.^{10,11} Most of the patients who have been enrolled in clinical trials of CRT have had LBBB. Left bundle-branch block is frequently present in patients with end-stage left ventricular dysfunction, with a reported incidence of about 25%. Complete RBBB is infrequent in CHF, with an incidence ranging from 2 to 6%.¹²

Previous Experience of Cardiac Resynchronization Therapy in Right Bundle-Branch Block

Published literature regarding RBBB and CRT in CHF is limited. Garrigue *et al.* reported the results of CRT in 12 patients with CHF and RBBB.¹³ Patients with CHF with RBBB, QRS duration > 140 ms, and NYHA class II or III heart failure demonstrated improvement in NYHA functional class ($p <$

0.01), exercise performance (4.7 ± 2.1 METS at baseline vs. 6.1 ± 1.0 METS at 12-month follow-up) ($p = 0.019$), and reduction in left ventricular end-diastolic diameter (72 mm at baseline vs. 68 ± 6 mm) ($p = 0.04$) after 12 months of CRT.

Rationale of Cardiac Resynchronization Therapy in Right Bundle-Branch Block

The pathophysiologic reason for the beneficial effects of CRT in patients with RBBB is unclear. Garrigue *et al.* reported that 66% (8/12) of patients with RBBB had left-axis deviation ($-38 \pm 09^\circ$), while the remainder (4/12) had right-axis deviation ($+135^\circ \pm 17^\circ$). They used Doppler tissue imaging for measuring the electrical mechanical delay of different regions of the ventricle and detected significant inter- and intraventricular dyssynchrony or delay ($p < 0.001$). Thus patients with CHF and RBBB may have concomitant left-sided conduction disorders that cause inter- and intraventricular dyssynchrony, which can be corrected by CRT. Wilensky *et al.*¹⁴ looked at serial ECG changes in idiopathic cardiomyopathy confirmed at necropsy. Right bundle-branch block was rare in dilated cardiomyopathy (9%), but it was associated with left-axis deviation in two thirds of cases, indicating probable left anterior fascicular block. These data are consistent with our observation that pure RBBB is infrequent in patients with CHF.

Study Limitation

The main limitation of this investigation is that this is a subgroup retrospective analysis beyond the primary hypothesis involving a small sample size in the RBBB and IVCD groups.

Conclusions

This subgroup analysis of the MIRACLE study demonstrates that patients with CHF and conduction abnormalities

other than LBBB obtain some of the same benefits from CRT. This improvement may be related to the frequent additional conduction abnormalities that may be associated with RBBB producing interventricular and intraventricular dyssynchrony. Further subgroup analyses of other CRT trials will be necessary to increase sample size and validate these hypothesis-generating results.

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