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ECHOCARDIOGRAPHIC, ELECTROCARDIOGRAPHIC CHANGES AND CLINICAL OUTCOMES OF PATIENTS WHO RESPOND TO CARDIAC RESYNCHRONIZATION THERAPY AFTER ONE YEAR

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BACKGROUND: Response to cardiac resynchronization therapy (CRT) is commonly assessed after 6 or 12 months. We evaluated subsequent echocardiographic changes, serial QRS duration, and clinical outcomes in patients showing delayed responses to CRT after 12 months.

METHODS: Among all patients who received CRT in Seoul St. Mary's Hospital, 36 one-year survivors were enrolled. Indicators of a positive CRT response were ≥ 15% reduction in left ventricular end-systolic volume (LVESV) or ≥ 10% increase in left ventricular ejection fraction (LVEF) on any follow up echocardiogram. We defined the early responders as patients responding before one year, the late responders as patients responding after one year, and the non-responders as patients who did not respond on any follow-up echocardiogram.

RESULTS: We identified 17 early responders, 10 late responders, and 9 non-responders. The late responders showed modest improvement in LVESV and LVEF at two years after CRT. QRS duration was shortened the day after CRT in all three groups. Narrowed QRS was maintained for two years in early and late responders, whereas it was continuously prolonged over time in non-responders. Incidence of all-cause death or heart failure hospitalization was comparable between early and late responders, while non-responders showed worst prognosis.

CONCLUSION: Patients responding to CRT after one year show modest echocardiographic improvement but clinical outcome is similar to early responders. Shorter baseline QRS duration and long-term maintenance of QRS duration shortening are important features of the late responders to CRT.

KEY WORDS: Cardiac resynchronization therapy · QRS duration · Echocardiography · Prognosis.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is currently recommended in drug-refractory heart failure with reduced left ventricular (LV) ejection fraction (LVEF) and prolonged QRS duration. CRT improves heart failure symptoms as well as LV function and size and is associated with a reduction in morbidity and mortality.[1)] Especially in patients who show LV reverse remodeling after 6 months of CRT implantation, improved survival and quality of life have been reported.[2)] Patients who achieve the abovementioned benefits from CRT are termed "responders", and many studies have been performed to define the characteristics of such individuals. In the previous literature, the response criteria occasionally included improved clinical status or echocardiographic findings of reduction in left ventricular end-systolic volume (LVESV) or increase in LVEF. The majority of these studies classified responders at 6 months

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or 12 months after CRT.[3-5)] However, LV reverse remodeling as a result of CRT appears not to be limited to 12 months. In a multi-center large trial, serial echocardiogram revealed a constant decrease in mean LVESV and an increase in mean LVEF up to 29 months after CRT implantation.[6)] Accordingly, some initial non-responders showed delayed echocardiographic responses one year after CRT implantation.[7)] Currently, there are limited data regarding the characteristics of the late responders to CRT and no factor has been found to predict later response in non-responders at one year. Since baseline QRS duration and QRS shortening after CRT are thought to be important features of CRT responders,[8)] we hypothesized that long-term changes in QRS duration after CRT may affect later LV reverse remodeling.

Thus, the present study aimed to investigate the echocardiographic changes, serial QRS duration, and long-term clinical outcomes in patients showing late responses to CRT after one year. To identify distinct characteristics of the late responders, we compared the data of the late responders to the early (< one year) responders and persistent non-responders.

METHODS

STUDY POPULATION

We performed a retrospective, single center study in patients who were followed up after CRT at Seoul St. Mary's Hospital between February 2006 and March 2015. Patient data were analyzed using medical records, echocardiograms, and electrocardiographic (ECG) data. The indications for CRT were drug-refractory symptomatic [New York Heart Association (NYHA) class ≥ 3] heart failure with LVEF ≤ 35% and QRS duration ≥ 120 ms. Among 44 subjects, patients who expired within 12 months (n = 1) or lost to follow up within 12 months (n = 5) after CRT were excluded because we could not differentiate them between late responders and non-responders. Additionally, two patients who were missing echocardiographic data after 12 months of CRT were excluded. The remaining 36 patients formed the final study group. The Institutional Review Board of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea approved this study (No. KC16RISI0779) and waived the need for informed consent.

DEVICE IMPLANTATION

All procedures were done under deep sedation. After subcutaneous dissection above the left pectoralis muscle, a pacing lead was inserted transvenously via a subclavian or axillary route. The right atrial lead was positioned in the right atrial appendage or side wall and the right ventricular lead was positioned in the right ventricular apex or septum with the best pacing and sensing threshold. The LV lead was positioned in the lateral wall of the LV through the coronary sinus and lateral vein. Of the 36 subjects, 34 received CRT combined with implantable cardioverter defibrillator (CRT-D). The CRT device was newly implanted in 28 patients and upgraded from a prior pacemaker in 8 patients.

ELECTROCARDIOGRAPHIC AND ECHOCARDIOGRAPHIC DATA

All patients routinely visited the clinic at a maximal interval of 6 months for assessment of 12-lead surface ECG. ECG data obtained pre-implantation and after one day, 6, 12, and 24 months of CRT implantation were analyzed. The QRS duration was measured as global QRS duration, defined as the maximal duration of the QRS waveform in any lead. QRS duration and morphology were determined by two experienced physicians and averaged.

Transthoracic echocardiographic data obtained before and after 6, 12, and 24 months of CRT implantation were analyzed in a Core Echo Laboratory by experienced physicians in Seoul St. Mary's Hospital. LVESV and LVEF were calculated using biplane Simpson's method and the severity of mitral regurgitation was assessed as the area of the color Doppler regurgitation jet divided by the area of the left atrium in systole. Serial change in QRS duration and echocardiographic parameters were compared among the three groups.

DEFINITIONS AND OUTCOMES

A positive response to CRT was defined as ≥ 15% reduction in LVESV or ≥ 10% increase in LVEF on any follow-up echocardiogram after CRT implantation. The patients who did not meet those criteria were classified as non-responders. We defined early responders as patients who responded before one year and late responders as patients who responded after one year. The protocol for the optimization of the CRT device was not standardized, so the timing or the manner of optimization was left to each physician's discretion. Generally, there were two electrophysiology specialists working in Seoul St. Mary's Hospital and they preferably optimized the CRT device based on the ECG features.

Adverse clinical outcomes were defined as all-cause death or heart failure events requiring hospitalization during whole follow-up period. A heart failure event was confirmed when a patient had signs and symptoms of congestion requiring intravenous diuretics or emergent hemofiltration in cases of renal failure. The composite of adverse clinical outcomes and the number of annual heart failure events requiring hospitalization were compared in the three groups.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± SD for normally distributed data or median (25th, 75th percentiles) for non-normally distributed data. Categorical variables are presented as count (percentage). The baseline characteristics of the three groups were compared using χ^2 tests for categorical values and Kruskall-Wallis tests for non-normally distributed continuous variables. Changes in LVESV, LVEF, and QRS duration in each group were verified using the Wilcoxon signed-rank test. Kaplan-Meier analysis and Cox regression were used to analyze survival in the three groups, and the results were analyzed by the log rank test. Number of heart failure events requiring hospitalization per year was compared using the Kruskall Wallis test with post-hoc analysis using a Mann-Whitney U-test. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

Among 36 study subjects, 17 (47.2%) were early responders, 10 (27.8%) were late responders and 9 (25.0%) were non-responders. Of the 2 patients who received CRT-pacemaker, one was in the early responder group and the other was in the late responder group. The majority of patients who were upgraded from a prior pacemaker were early responders (5/8, 62.5%). The baseline clinical characteristics of the subjects are shown in Table 1. There was no significant difference in age, gender, heart failure etiology or underlying comorbidities among the three groups. On the baseline ECG, the late responders showed a trend toward a lower prevalence of typical left bundle branch block (LBBB) (91.7% vs. 66.7% vs. 71.4%, in early, late and non-responders, respectively, $p = 0.264$) compared to early responders. Pre-implant QRS duration of the late responders was shorter than the early responders and not significantly different to non-responders [174 ms (156–192 ms) vs. 158 ms (140–170 ms) vs. 148 ms (132–164 ms), $p = 0.029$ ($p = 0.021$ for early vs. late responders and $p = 0.497$ for late vs. non-responders)]. On the baseline echocardiogram, the late responders showed the lowest LVESV [158 mL (110–194 mL) vs. 144 mL (101–183 mL) vs. 185 mL (137–192 mL), $p = 0.133$] and highest LVEF [24.0% (18.0–29.0%) vs. 26.8% (20.5–30.4%) vs. 21.0% (18.5–25.3%), $p = 0.335$] among the three groups. Medications prescribed prior to CRT implantation did not significantly differ between groups. During 2 years after CRT, device optimization was performed in 5/17 (29.4%) in early responders, 6/10 (60.0%) in late responders, and 7/9 (77.8%) in non-responders.

Table 1. Baseline characteristics of the study subjects

Characteristic	Total (n = 36)			p-value
	Early responders (n = 17)	Late responders (n = 10)	Non-responders (n = 9)	
Age, yr	70 (65.5–76.0)	64 (53.0–64.0)	69 (55.5–75.5)	0.236
Male, n (%)	7 (41.2)	5 (50.0)	3 (33.3)	0.762
ICMP, n (%)	3 (17.6)	2 (20.0)	1 (11.1)	0.557
SBP, mm Hg	112 (100.0–121.0)	108 (101.5–121.0)	100 (95.5–114.0)	0.319
DBP, mm Hg	66 (60.0–70.0)	60 (56.0–71.0)	69.5 (58.0–70.0)	0.920
Hypertension, n (%)	5 (29.4)	6 (60.0)	4 (44.4)	0.292
Diabetes, n (%)	4 (23.5)	6 (60.0)	4 (44.4)	0.159
Coronary artery disease, n (%)	6 (35.3)	3 (30.0)	2 (22.2)	0.788
Chronic kidney disease, n (%)	2 (11.8)	2 (20.0)	4 (44.4)	0.159
Stroke, n (%)	1 (5.9)	0 (0)	2 (22.2)	0.191
Atrial fibrillation, n (%)	1 (5.9)	0 (0)	0 (0)	0.563
Baseline ECG findings				
Typical LBBB, n (%)*	11/12 (91.7)	6/9 (66.7)	5/7 (71.4)	0.264
QRS duration, ms	174 (156–192)	158 (140–170)	148 (132–164)	0.029†
Medication, n (%)				
ACEi/ARB	15 (88.2)	9 (90.0)	8 (88.9)	0.990
Beta-blocker	12 (70.6)	8 (80.0)	5 (55.6)	0.441
Furosemide	17 (100)	9 (90.0)	8 (88.9)	0.386
Spironolactone	14 (82.4)	6 (60.0)	7 (77.8)	0.416
Creatinine, mg/dL	1.07 (0.75–1.24)	1.02 (0.76–1.48)	1.15 (0.93–1.93)	0.202
Pro-BNP, pg/mL	2203 (1411–8362)	2807 (977–6455)	4552 (2765–9020)	0.208
LVESV, mL	158 (110–194)	144 (101–183)	185 (137–192)	0.133
LVEF, %	24.0 (18.0–29.0)	26.8 (20.5–30.4)	21.0 (18.5–25.3)	0.335
Mitral regurgitation (≥ moderate), n (%)	8 (53.3)	4 (40.0)	2 (22.2)	0.374

Continuous values are presented as median (25–75th percentiles). $p < 0.05$ indicates a significant difference between the three groups. *Patients having paced rhythm at pre-implantation were excluded, †$p = 0.021$ for early vs. late responders, and $p = 0.497$ for late vs. non-responders. ICMP: ischemic cardiomyopathy, SBP: systolic blood pressure, DBP: diastolic blood pressure, ECG: electrocardiographic, LBBB: left bundle branch block, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BNP: brain natriuretic peptide, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction

Echocardiographic and electrocardiographic changes

Changes in LVESV in the three groups are shown in Fig. 1A. In early responders, reduction in LVESV was observed at 6 months with continuous decrease over the course of 24 months. In the late responders, a reduction in LVESV was not prominent at 6 months, but gradual decline in LVESV persisted to show a significant reduction at 24 months, which was smaller than early responders [percentage reduction in LVESV at 24 months: 66.3% (35.6–75.4%) vs. 34.4% (31.5–41.2%) for early and late responders, $p = 0.035$] (Fig. 2A). Non-responders showed a continuous increase in LVESV throughout 2-years of follow-up. A similar trend was observed in LVEF (Fig. 1B). While early responders showed rapid improvement in LVEF from 6 months, late responders did not show significant change in LVEF at 6 and 12 months. At 24 months, a modest increase in LVEF was shown in late responders [absolute increase in LVEF: 25.0% (12.7–27.2%) vs. 8.6% (1.4–12.0%) for early and late responders, $p = 0.015$] (Fig. 2B). In non-responders, LVEF was more decreased than baseline value at 24 months. In consequence, LVESV and LVEF in late responders were in between those of early responders and non-responders at 24 months.

The changes in QRS duration in the three groups are shown in Fig. 3. The early responders had the longest QRS duration at baseline, and exhibited a pronounced reduction after CRT implantation; the shortening of QRS duration was maintained over the course of 24 months [174 ms (156–192 ms) and 148 ms (130–168 ms) at baseline and 24 months, $p = 0.006$]. In non-responders, QRS duration was immediately shortened after CRT implantation but QRS duration became longer and reached a value similar to that at baseline at 24 months [148 ms (132–164 ms) and 152 ms (134–182 ms) at baseline and 24 months, $p = 0.483$]. On the other hand, in late responders, shortened QRS after CRT was further narrowed at 6 months and maintained for 24 months [158 ms (140–170 ms) and 125 ms (118–146 ms) at baseline and 24 months, $p = 0.008$].

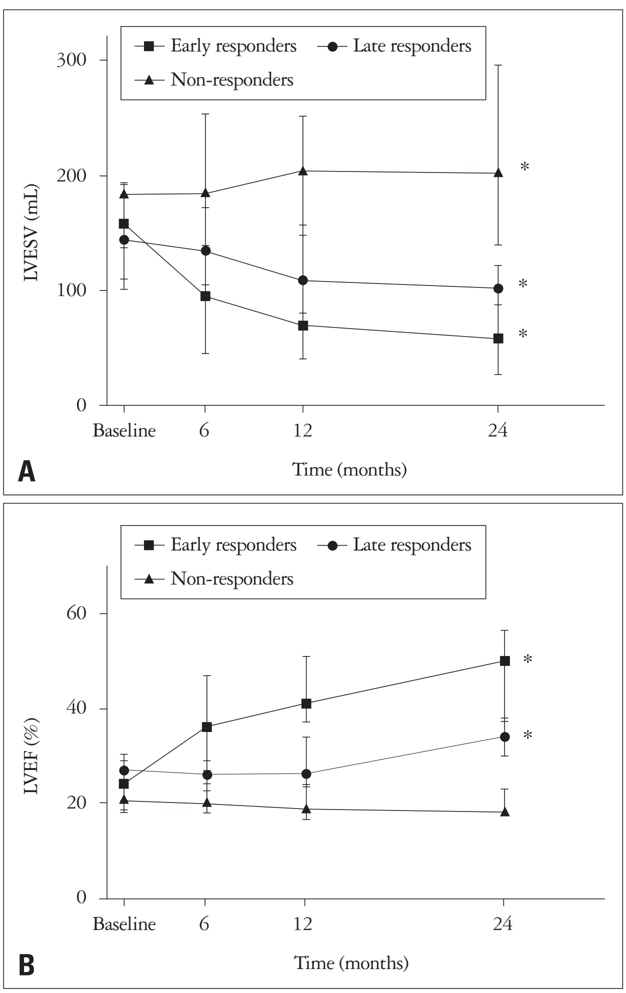

Fig. 1. Serial changes in LVESV and LVEF in the three groups. Values represent medians (25–75th percentiles).*$p < 0.05$ compared to baseline. LVESV was significantly increased in non-responder group and reduced in early and late responder groups at 24 months (A). LVEF was significantly improved in early and late responder groups and not changed in non-responder group at 24 months (B). LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction.

Clinical outcomes

The mean follow up duration was 45.7 ± 28.3 months. The

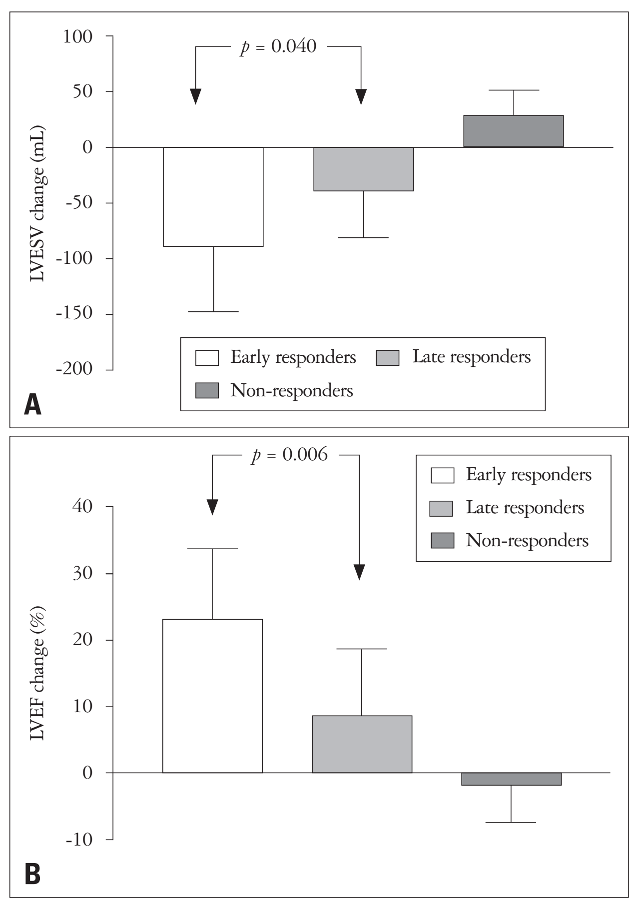

Fig. 2. Absolute changes in LVESV (A) and LVEF (B) at two years compared to the baseline values in the three groups. Values represent mean with standard deviation. LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction.

incidence of adverse clinical outcome (a composite of all-cause death or heart failure hospitalization) was 4/17 (23.5%) in the early responder group, 3/10 (30.0%) in the late responder group, and 7/9 (77.8%) in the non-responder group (p = 0.021) (Table 2). The clinical outcome was similar between early and late responders, while non-responders showed significantly worse prognosis (p = 0.711 for early vs. late responders, and p = 0.037 for late vs. non-responders). There was no significant difference in overall death rate in three groups but significantly higher number of patients in non-responder group experienced heart failure event requiring hospitalization than the other two groups (23.5% vs. 30.0% vs. 77.8% in early, late and non-responders, p = 0.021). The number of heart failure hospitalizations per year among late responders was similar to that in early responders and significantly lower than that in non-responders (0.05 ± 0.11 vs. 0.11 ± 0.23 vs. 0.95 ± 1.47 in early, late and non-responders, respectively, p = 0.006).

Discussion

In the present study, we identified patients showing late responses to CRT after one year. Those subjects had relatively shorter QRS duration, smaller ventricular volume, and higher LV contractility at baseline compared to early responders. Among such patients, echocardiographic improvement was blunted and later accelerated after 6 months of CRT. Furthermore, we found that shortening of QRS duration was maintained throughout the follow-up period in the late responders, while it was not observed for the non-responders. Long-term clinical outcome, as estimated by all-cause death or heart failure events requiring hospitalization was comparable between the early responders and the late responders, and the non-responders had the worst outcomes.

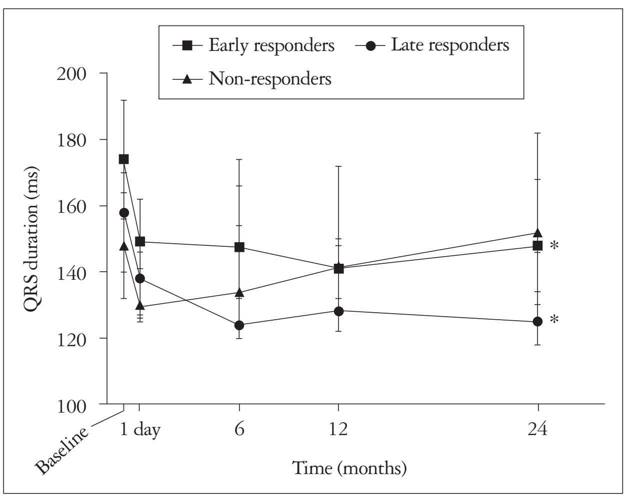

Fig. 3. Serial changes in QRS duration in the three groups. Values represent medians (25–75th percentiles). Baseline values are pre-implantation QRS duration, and one day indicates the day after CRT implantation. *p < 0.05 compared to baseline. QRS duration remained shortened at 24 months in early and late responders. In non-responders, QRS duration at 24 months was not significantly different to the pre-implant value. CRT: cardiac resynchronization therapy.

CRT significantly ameliorates symptoms and reduces death and the rate of hospitalization for heart failure. Besides, it also improves LV volume and contractility.[9] However, approximately 30% of patients did not respond to CRT when assessed at 6 or 12 months in previous studies.[10][11] These non-responders did not show an improvement in LV volume or function, and the risk of adverse clinical outcomes increased in that group.[4] In general, two types of response criteria for CRT have been used: one is the clinical endpoint, which includes death, hospitalization for heart failure, heart transplantation, subjective symptom (NYHA class), and capacity for exercise, while the second uses remodeling criteria via a reduction in LVESV or increase in LVEF. Those criteria have been used alone or in conjunction with one another in previous studies. According to a meta-analysis, the percentage of non-responders was lower when clinical endpoint was used (20–27%) than when remodeling endpoint was used (40–47%).[10] This result implies that clinical responders could be included in the group of patients who do not show acceptable LV reverse remodeling at 6 or 12 months after CRT implantation. Ghio et al.[6] reported a long-term study of echocardiographic reverse remodeling in patients enrolled in the CARE-HF trial. Of the 365 patients who received CRT, serial follow-up echocardiogram revealed a further reduction in mean LVESV and an increase in LVEF at 29 months. This long-term LV reverse remodeling effect was observed not only in the initial responders who meet the response criteria at 6 or 12 months, but also in some of the initial non-responders. Recently, van't Sant et al.[7] studied time-dependent responses to CRT after 6 months. Using the criteria of a 15% reduction in LVESV, 6/30 non-responders at 6 months became responders at 14 months. Likewise, 43% of non-responders at one year showed delayed echocardiographic responses at three years in an observation study.[12] In the current study, patients showing positive respons-

Table 2. Adverse clinical outcomes in the three groups

Outcome	Early responders (n = 17)	Late responders (n = 10)	Non-responders (n = 9)	p-value
Death or heart failure hospitalization, n (%)	4 (23.5)	3 (30.0)	7 (77.8)	0.021*
Death from any cause	1 (5.9)	1 (10.0)	3 (33.3)	0.144
Any heart failure hospitalization	4 (23.5)	3 (30.0)	7 (77.8)	0.021
Number of heart failure hospitalizations per year	0.05 ± 0.11	0.11 ± 0.23	0.95 ± 1.47	0.006†

Continuous values are presented as medians (25–75th percentiles). p < 0.05 indicates significant differences between the three groups. *p = 0.711 for early vs. late responders, and p = 0.037 for late vs. non-responders, †p = 0.625 for early vs. late responders, and p = 0.012 for late vs. non-responders es to CRT after one year had more favorable clinical outcomes than did sustained non-responders. Therefore, although most of the response to CRT occurs within the initial 12 months, we believe it is important to identify those who respond after 12 months amongst initial non-responders.

The major effect of CRT is ventricular resynchrony. So, longer QRS duration and LBBB morphology on baseline ECG plus QRS shortening after biventricular pacing are thought to predict better response to CRT. Zhang et al.[13] reported a significant positive correlation between a change in QRS duration and LV reverse remodeling in dilated cardiomyopathy patients who received CRT. Additionally, according to Molhoek et al.,[8] QRS duration shortening after CRT was not found in non-responders who were classified by clinical endpoints. The late responders classified in the present study shared similar baseline ECG characteristics to the non-responders, but serial QRS duration was further reduced, in contrast to the non-responder group. There are several possible explanations for this. First, it may be an effect of appropriate CRT optimization. Optimal ventriculo-ventricular delay may vary over time and repeated CRT optimization would contribute to maintaining the narrowest QRS duration. However, the relationship between CRT optimization and long term prognosis is inconsistent in previously published reports.[14-16] In our study, although evaluating the accurate effect of CRT optimization on the late response was difficult because of the retrospective design, we generally performed ECG-based optimization in a routine manner in patients showing suboptimal responses. Especially in some of late responders whose QRS duration was more shortened after one year, one major contributing factor is thought to be later appropriate optimization. However, the frequency of CRT optimization during 2 years in late responders was not higher than in non-responders, and for 4 patients in late responders who did not receive CRT optimization during 2 years, a mechanism other than correct optimization should be responsible. Second, a lesser degree of pre-implant LV dyssynchrony may have resulted in blunted, slower echocardiographic response. Among patients having smaller change in LV hemodynamics after LV resynchrony, certain individuals who maintain this smaller positive effect in long term (reflected by persistently narrowed QRS duration) would be expected to show later responses. To our knowledge, this group of patients has been paid only slight attention in clinical studies, and their characteristics have not been well reported. As our results show, though it is delayed, the LV remodeling response has a favorable effect on long-term prognosis. Baseline shorter QRS duration, lower LVESV, and higher LVEF might be the characteristics of late responders as those characteristics reflect less severe LV dyssynchrony.

The current study has some limitations. The main limitation is the small number of study subjects. Many of the differences between the three groups in baseline variables except QRS duration were not statistically significant. However, clinical outcomes and pattern of serial QRS duration change, which were the major interests of current study, were significantly different between late responders and non-responders despite small sample size in each group. Secondly, a retrospective design entails several confounding factors, such as the absence of a standardized CRT implantation procedure, follow-up protocol, and optimization protocol. Nevertheless, our study clearly shows that the maintenance of shortened QRS duration, whether it is achieved by proper optimization or another mechanism, contributes to later echocardiographic response. Third, it is difficult to predict the accurate prevalence of late responders amongst all subjects who undergo CRT, since patients who expired before one year were excluded from the analysis, and some patients who were classified as non-responders may show very late responses after longer periods of follow up.

There are several important clinical implications in our study. The possibility that patients who do not respond to CRT in one year can change to responders later (a total of 27.8% among one-year survivors in our study), may strengthen patient's and physician's motivation in non-responders. Our finding suggests serial examination of QRS duration would help to predict a delayed response and select candidates for intensive CRT optimization. Previous literature investigating response predictors often assessed CRT response at 6 or 12 months, but if late responders are considered, a broader range of patients could be candidates for CRT.

In conclusion, patients who respond to CRT after one year show favorable long term clinical outcome similar to early responders, although echocardiographic improvement is blunted. Shorter baseline QRS duration and long-term maintenance of QRS duration shortening are important features of late responders to CRT. Thus, patients showing suboptimal responses to CRT in one year should be carefully followed up with particular attention paid to later echocardiographic changes and serial QRS duration. A further large-scale study is required to identify the precise characteristics of the late responders.

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