Cardiac electrical and mechanical synchrony of super-responders to cardiac resynchronization therapy

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Abstract

Background: Super-responders (SRs) to cardiac resynchronization therapy (CRT) regain near-normal or normal cardiac function. The extent of cardiac synchrony of SRs and whether continuous biventricular (BIV) pacing is needed remain unknown. The aim of this study was to evaluate the cardiac electrical and mechanical synchrony of SRs.

Methods: We retrospectively analyzed CRT recipients between 2008 and 2016 in 2 centers to identify SRs, whose left ventricular (LV) ejection fraction was increased to ≥50% at follow-up. Cardiac synchrony was evaluated in intrinsic and BIV-paced rhythms. Electrical synchrony was estimated by QRS duration and LV mechanical synchrony by single-photon emission computed tomography myocardial perfusion imaging.

Results: Seventeen SRs were included with LV ejection fraction increased from 33.0 ± 4.6% to 59.3 ± 6.3%. The intrinsic QRS duration after super-response was 148.8 ± 30.0 ms, significantly shorter than baseline (174.8 ± 11.9 ms, $P = 0.004$, $t = -3.379$) but longer than BIV-paced level (135.5 ± 16.7 ms, $P = 0.042$, $t = 2.211$). Intrinsic LV mechanical synchrony significantly improved after super-response (phase standard deviation [PSD], 51.1 ± 16.5° *vs.* 19.8 ± 8.1°, $P < 0.001$, $t = 5.726$; phase histogram bandwidth (PHB), 171.7 ± 64.2° *vs.* 60.5 ± 22.9°, $P < 0.001$, $t = 5.376$) but was inferior to BIV-paced synchrony (PSD, 19.8 ± 8.1° *vs.* 15.2 ± 6.4°, $P = 0.005$, $t = 3.414$; PHB, 60.5 ± 22.9° *vs.* 46.0 ± 16.3°, $P = 0.009$, $t = 3.136$).

Conclusions: SRs had significant improvements in cardiac electrical and LV mechanical synchrony. Since intrinsic synchrony of SRs was still inferior to BIV-paced rhythm, continued BIV pacing is needed to maintain longstanding and synchronized contraction.

Keywords: Cardiac resynchronization; Super-responders; Electrical synchrony; Mechanical synchrony

Introduction

Cardiac resynchronization therapy (CRT) is a cornerstone in contemporary heart failure (HF) management due to the reduction in morbidity and mortality after implantation.[1-3] It corrects cardiac electrical and mechanical dyssynchrony by simultaneous pacing of the left and right ventricles, thus improving pump efficiency.[4] Following CRT, approximately 10% to 25% of recipients, commonly termed super-responders (SRs), improve enough to recover near-normal or normal cardiac function and diameters.[5-7] There is a lot of scientific evidence in support of SRs often appearing a better prognosis than non-responders and other responders.[5-7] Manne *et al* revealed that SRs (left ventricular ejection fraction (LVEF) ≥ 50%) could achieved similar survival to the normal population.[8]

However, after normalization of cardiac function and prognosis, the extent to which cardiac synchrony SRs is regained has not been previously studied. Whether these exceptional patients still need continuous biventricular (BIV) pacing to correct cardiac electrical and mechanical dyssynchrony remains unclear. The aim of this study was to evaluate the cardiac electrical and mechanical synchrony of SRs, especially with regard to their intrinsic rhythm after super-response. The major hypothesis of the study is whether SRs could maintain normal cardiac mechanical synchrony and still need continuous BIV pacing after recovery of cardiac function.

Methods

Ethical approval

The study protocol was approved by the Local Medical Ethics Committee, and written informed consent was obtained from every participant.

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Patient selection and study design

This was a two-center observational study. We analyzed data from all patients who received CRT or CRT defibrillator (CRTD) between November 2008 and December 2016 at the Affiliated Zhangjiagang Hospital of Soochow University (Suzhou, China) and the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) to identify SRs consecutively. The indication for CRT/CRTD implantation was determined according to the guidelines at the time of implantation. Echocardiography was performed, and related parameters, including LVEF, were measured by experienced technicians. Super-response was defined as an absolute LVEF $\geq$ 50% after implantation. All patients who met the super-response criteria were included. Patients who had persistent atrial fibrillation (AF) or atrial ventricular block (AVB) or who died during follow-up were excluded.

In this study, we evaluated cardiac synchrony (both electrical synchrony and mechanical synchrony) of SRs with regard to three different rhythms: (1) the pre-CRT rhythm, which was the intrinsic rhythm before CRT implantation, (2) the off-pace rhythm, which was the intrinsic rhythm after super-response, and (3) the BIV-paced rhythm, which was the BIV pacing after super-response.

Assessments of cardiac electrical synchrony

Cardiac electrical synchrony was assessed by standard 12-lead surface electrocardiograms (ECGs), which were recorded at a speed of 25 mm/s and a gain setting of 10 mm/mV. QRS morphology and intervals were manually measured by two independent electrophysiologists. Intrinsic QRS duration was defined as the widest interval in any of the 12 leads. Paced QRS duration was measured from the pulse signal to the end of the QRS complex on the lead with the widest QRS. Left bundle branch block (LBBB) diagnosis was defined according to the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations published in 2009.[9]

Assessments of cardiac mechanical synchrony

Cardiac mechanical synchrony was evaluated by phase analysis on gated single photon-emission computed tomography (SPECT) myocardial perfusion imaging, which has been widely accepted as a method of assessing LV mechanical synchrony.[10] Two quantitative LV mechanical synchrony indices, phase standard deviation (PSD) and phase histogram bandwidth (PHB), were measured. Earlier studies have shown that PSD in normal subjects was 12.2° ± 4.9° and PHB in normal subjects was 36.5° ± 12.0°.[11] Moreover, patients with more mechanical dyssynchrony have larger PSDs and PHBs.[12]

The process of recording the 3 different rhythms

The intrinsic rhythm before CRT implantation (pre-CRT rhythm) was recorded 1 to 3 days before CRT implantation. The off-pacing rhythm and BIV-paced rhythm were recorded after super-response was identified. When recording off-pacing rhythm, the device was temporarily programmed to VVI 40 beats/min to obtain the intrinsic rhythm after super-response. The status of intrinsic rhythm should be held on for at least 5 min before recording ECG and held on for at least 30 min before performing gated SPECT myocardial perfusion imaging. When recording BIV-paced rhythm, the device was programmed to simultaneous right and left ventricular pacing and AV delay was programmed to 100 ms to make sure effective BIV pacing. The status of BIV-paced rhythm should be held on for at least 5 min before recording ECG and held on for at least 30 min before performing gated SPECT myocardial perfusion imaging.

Statistical analysis

Statistical analysis was performed using IBM SRS Statistics, version 21 (IBM Corp., Released 2012, IBM SRS Statistics for Windows, Armonk, NY, USA). Data are summarized as the mean ± standard deviation for continuous variables and as counts and percentages for categorical variables. Clinical and echocardiographic characteristics between baseline and super-response were compared using paired *t*-test or the Chi-squared test as appropriate. The comparisons of QRS duration, PSD, and PHB between any two rhythms in SRs were assessed by paired *t*-tests. The comparisons of PSD change (ΔPSD) and PHB change (ΔPHB) in intrinsic rhythm from baseline to super-response between SRs with shortened intrinsic QRS duration and SRs with unchanged QRS duration were analyzed by independent sample *t*-test. A P-value $<$ 0.05 was considered statistically significant for all analyses.

Results

Patient selection and clinical characteristics

Figure 1 shows a flow chart of the patient selection. In total, 191 patients received CRT/CRTD implantation. Thirty-four (17.8%) patients were identified as SRs. Of these, one patient died of hematencephalon during follow-up. Seven patients with AVB and two with AF were excluded. Another seven patients were lost to follow-up. Finally, 17 SRs were included in our study. The mean follow-up time was 3.3 ± 2.1 years. The mean age of the SRs was 62.6 ± 11.0 years. Six (6/17, 35.3%) were females, all (17/17, 100%) were non-ischemic, 16 (16/17, 94.1%) had a LBBB QRS morphology and one (1/17, 5.9%) had nonspecific intraventricular conduction delay (NICD).

The clinical and echocardiographic characteristics are listed in Table 1. As expected, following CRTD/CRTP implantation, SRs had a significant improvement in LVEF (from 33.0 ± 4.6% to 59.3 ± 6.3%, $P < 0.001$, $t = -17.416$), left ventricular end-diastolic diameter (LVEDD) (from 68.9 ± 7.8 mm to 51.6 ± 3.4 mm, $P < 0.001$, $t = 9.935$), left ventricular end-systolic diameter (LVESD) (from 57.9 ± 7.6 mm to 35.3 ± 4.2 mm, $P < 0.001$, $t = 12.961$), and New York Heart Association (NYHA) class (from 3.3 ± 0.5 to 1.3 ± 0.5, $P < 0.001$, $t = 13.466$). The use of diuretics was markedly decreased

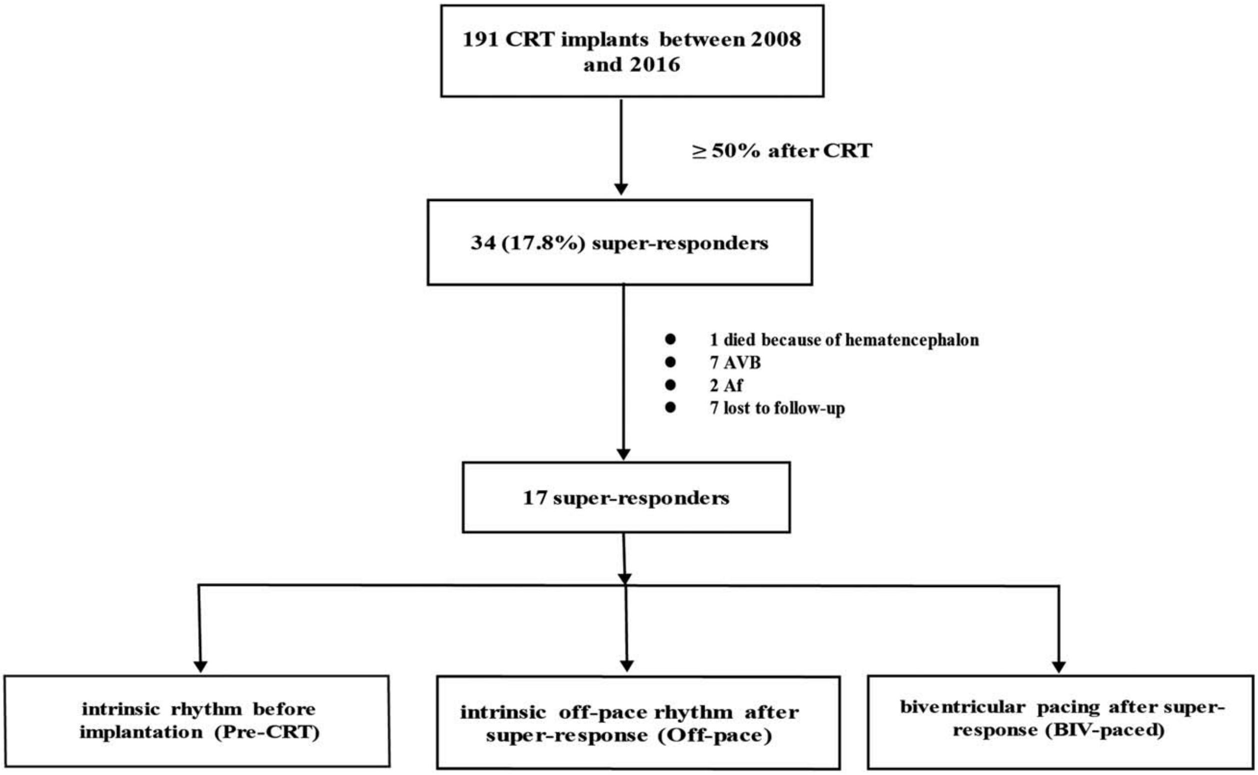

Figure 1: Flow chart of patient selection.

Table 1: The clinical and echocardiographic characteristics of super-responders.

Parameter	Pre-CRT	Super-response	t	χ^2	P
LVEF (%)	33.0 ± 4.6	59.3 ± 6.3	−17.416	–	<0.001
LVEDD (mm)	68.9 ± 7.8	51.6 ± 3.4	9.935	–	<0.001
LVESD (mm)	57.9 ± 7.6	35.3 ± 4.2	12.961	–	<0.001
NYHA functional class	3.3 ± 0.5	1.3 ± 0.5	13.466		<0.001
Medical therapy					
ACEI or ARB	16 (94.1)	17 (100.0)	–	1.030	0.500
B-blockers	17 (100.0)	17 (100.0)	–	–	–
Diuretics	16 (94.1)	3 (17.6)	–	20.161	<0.001
Aldosterone	16 (94.1)	5 (29.4)	–	15.070	<0.001
Amiodarone	3 (17.6)	1 (5.9)	–	1.133	0.301
Digoxin	5 (29.4)	0	–	5.862	0.022

Data were shown as mean±standard deviation, or *n*(%). Pre-CRT: Cardiac resynchronization therapy; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; NYHA: New York Heart Association functional class; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; –: Not available.

from 94.1% to 17.6% ($P < 0.001$, $\chi^2 = 20.161$). The use of aldosterone was decreased from 94.1% to 29.4% ($P < 0.001$, $\chi^2 = 15.070$). And the use of digoxin was significantly decreased from 29.4% to 0.0% ($P = 0.022$, $\chi^2 = 5.862$). The included SRs had a mean LVEF of 59.3%, LVEDD of 51.6 mm, and LVESD of 35.3 mm, almost achieving normalization of cardiac function.

Intrinsic electrical synchrony after super-response

The intrinsic QRS duration after super-response was 148.8 ± 30.0 ms, which was significantly shorter than that at the baseline (174.8 ± 11.9 ms, $P = 0.004$, $t = -3.379$) but longer than that in patients with BIV-paced rhythms (135.5 ± 16.7 ms, $P = 0.042$, $t = 2.211$) [Figure 2A].

Figure 3 shows three types of intrinsic QRS changes after the super-response. First, two (2/17, 11.8%) patients had complete electrical reverse remodeling with a QRS morphology that changed from LBBB to normal. Figure 3A shows an ECG example and the mean QRS duration of these two SRs. The intrinsic QRS became completely normal, with a mean duration of 85 ms after super-response. The BIV-paced QRS was 120.0 ms, which was slightly longer than the intrinsic QRS but still much

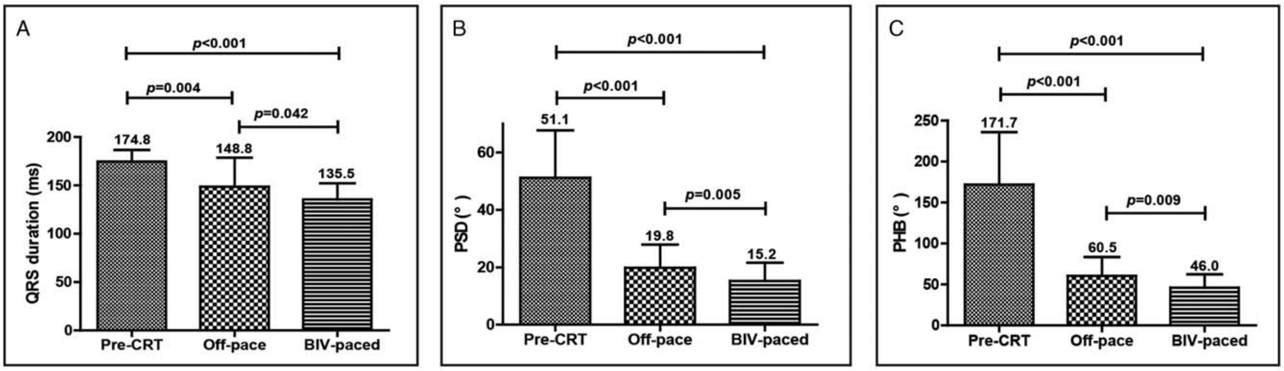

Figure 2: QRS duration (A), PSD (B), and PHB (C) of super-responders in the intrinsic rhythm before implantation (pre-CRT), the intrinsic rhythm after super-response (off-pace) and biventricular pacing after super-response (BIV-paced). PSD: Phase standard deviation; PHB: Phase histogram bandwidth; pre-CRT: Cardiac resynchronization therapy; BIV-paced: Biventricular pacing after super-response.

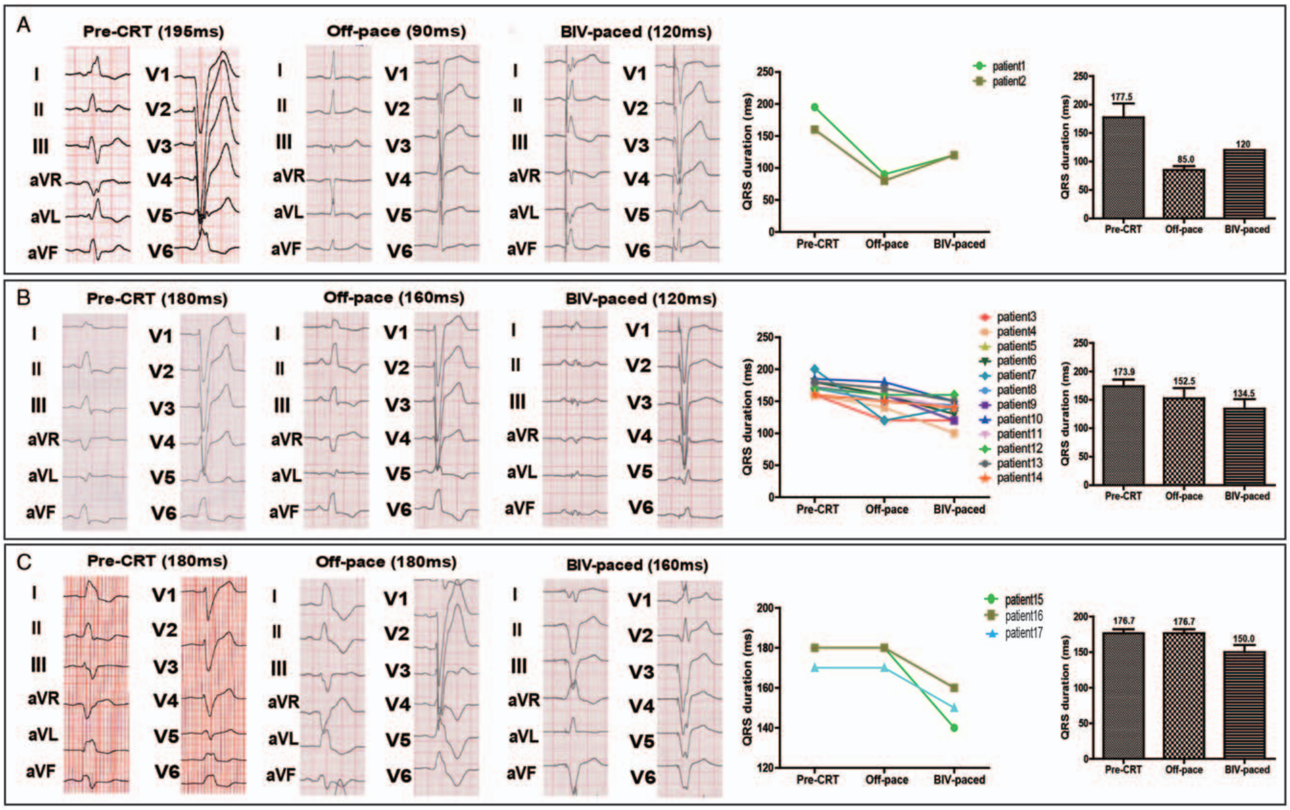

Figure 3: Three types of intrinsic QRS changes in super-responders. (A) Two SRs with complete electrical remodeling showed that intrinsic QRS morphology changed from LBBB to normal. (B) Twelve SRs with partial electrical remodeling showed that intrinsic QRS durations shortened and QRS morphology remained. (C) Three SRs without changes in intrinsic QRS morphology or duration. Pre-CRT: Intrinsic rhythm before implantation; Off-pace: Intrinsic off-pace rhythm after super-response; BIV-paced: Biventricular pacing after super-response; SRs: Super-responders.

shorter than the QRS duration of 177.5 ± 24.7 ms at baseline. Second, 12 (12/17, 70.6%) patients had partial electrical remodeling with shortened intrinsic QRS duration but unchanged QRS morphology. An ECG example and the mean QRS duration are shown in Figure 3B. The QRS duration decreased from 173.9 ± 11.9 ms at the baseline to 152.5 ± 18.2 ms in the intrinsic rhythm ($P = 0.004$, $t = 3.603$), and then from 152.5 ± 18.2 ms to 134.5 ± 16.9 ms in the BIV-paced rhythm ($P = 0.008$, $t = 3.250$), indicating that electrical synchrony improved in the intrinsic rhythm after super-response and then improved even further in the BIV-paced rhythm. Third, as shown in Figure 3C, three (3/17, 17.6%) patients had no change in their intrinsic QRS morphology or duration. The QRS duration remained 176.7 ± 5.8 ms in the intrinsic rhythm after the super-response but declined to 150.0 ± 10.0 ms in the BIV-paced rhythm.

Intrinsic LV mechanical synchrony after super-response

LV mechanical synchrony was evaluated in 13 of 17 SRs. Figure 2B and C shows the comparison of two LV mechanical synchrony parameters (PSD and PHB) at the baseline and after super-response. The PSD in the intrinsic rhythm after the super-response was 19.8 ± 8.1°, which was significantly smaller than that at the baseline (51.1 ± 16.5°, $P < 0.001$, $t = -5.726$) but still larger than that of the BIV-paced rhythm (15.2 ± 6.4°, $P = 0.005$, $t = 3.414$). The PHB in the intrinsic rhythm after the super-response was 60.5 ± 22.9°, which was also significantly smaller than that at the baseline (171.7 ± 64.2°, $P < 0.001$, $t = -5.376$) but much larger than that in the BIV-paced rhythm (46.0 ± 16.3°, $P = 0.009$, $t = 3.136$).

Among the 13 SRs, 10 SRs with shortened intrinsic QRS duration had more improvement in intrinsic LV mechanical synchrony than three patients with unchanged QRS duration (ΔPSD: 37.7 ± 16.4° *vs.* 10.0 ± 15.1°, $P = 0.025$, $t = 2.602$; ΔPHB: 135.8 ± 64.3° *vs.* 29.0 ± 39.6°, $P = 0.021$, $t = 2.679$).

Figure 4 shows the LV mechanical synchrony of SRs in patients with complete electrical remodeling ($n = 2$), partial electrical remodeling ($n = 8$), and without electrical remodeling ($n = 3$). First, two SRs with complete electrical remodeling obtained normalization of LV mechanical synchrony in the intrinsic rhythm (PSD: 12.2 ± 1.8°; PHB: 39.5 ± 7.8°). Figure 4A shows that LV mechanical synchrony in the BIV-paced rhythm (PSD: 15.9 ± 1.4°; PHB: 54.0 ± 5.7°) was similar to that in the intrinsic rhythm but still much better than that at the baseline (PSD: 57.4 ± 27.1°; PHB: 173.5 ± 98.3°). An example of a phase histogram is shown in Figure 4A. Second, eight SRs with partial electrical remodeling experienced a significant downward trend in PSD and PHB (PSD from 56.5 ± 12.7° at baseline to 20.7 ± 8.4° in intrinsic rhythm ($P < 0.001$, $t = 6.600$), and then from 20.7 ± 8.4° to 14.7 ± 6.4° in BIV-paced rhythm ($P = 0.004$, $t = 4.158$); PHB from 198.0 ± 51.2° at baseline to 61.8 ± 23.7° in intrinsic rhythm ($P = 0.001$, $t = 5.985$), and then from 61.8 ± 23.7° to 41.8 ± 13.0° in BIV-paced rhythm ($P = 0.003$, $t = 4.410$). Third, in three SRs who had no electrical remodeling showed no improvement of their intrinsic LV mechanical synchrony (PSD from 32.7 ± 6.9° to 22.7 ± 8.2°, $P = 0.372$, $t = 1.140$; PHB from 100.3 ± 17.7° to 71.3 ± 23.0°, $P = 0.332$, $t = 1.268$). However, LV mechanical synchrony at BIV-pacing could reach a better level (PSD: 16.2 ± 9.7° *vs.* 22.7 ± 8.2°, $P = 0.021$, $t = 6.857$; PHB: 52.0 ± 28.4° *vs.* 71.3 ± 23.0°, $P = 0.080$, $t = 3.327$).

Discussion

The main findings of our study can be summarized as follows: (1) SRs demonstrated significant improvements in both cardiac electrical and mechanical synchrony after super-response. (2) The cardiac electrical and mechanical synchrony of SRs with regard to their intrinsic rhythms was still inferior to that in BIV-paced rhythm.

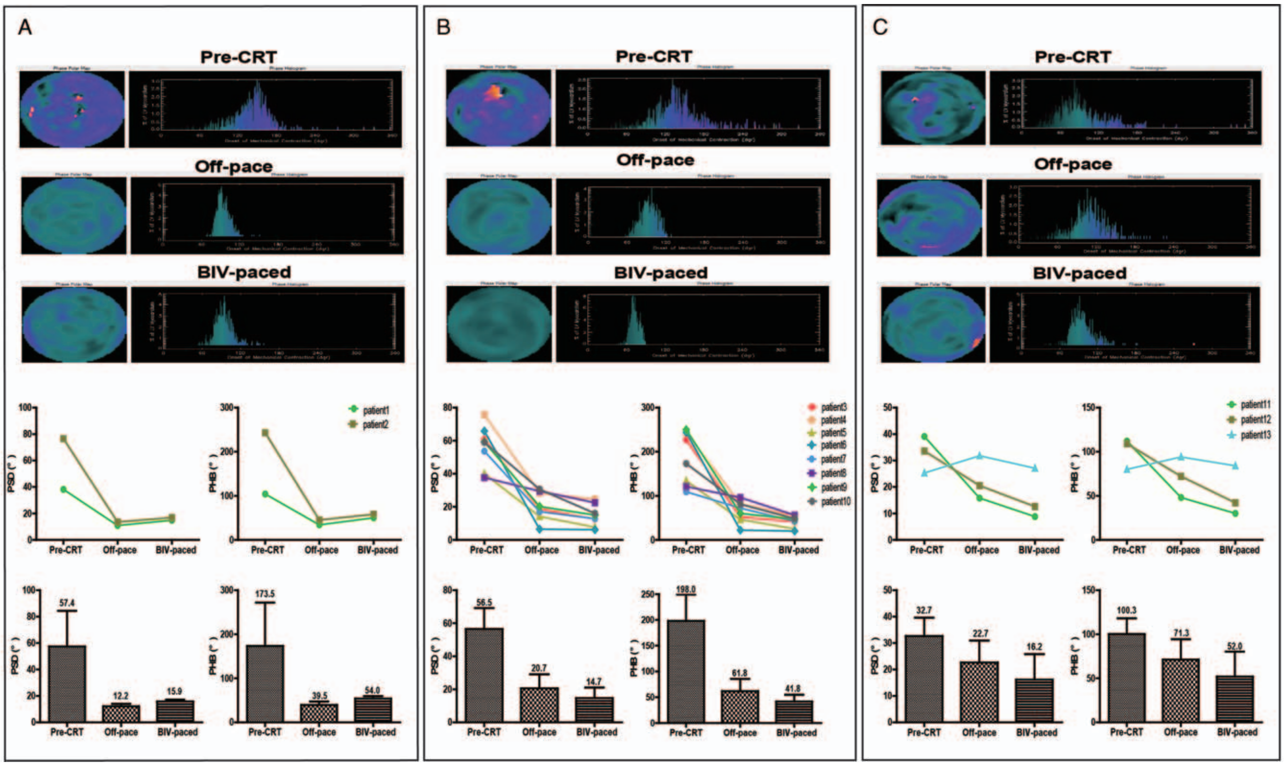

Figure 4: LV mechanical synchrony in SRs with 3 different types of intrinsic QRS changes. (A) Two SRs with complete electrical remodeling: The phase polar map (the left panel) and histogram (the right panel) showed that LV mechanical activation was heterogeneous in pre-CRT and became uniform in off-pace and BIV-paced rhythm. (B) Eight SRs with partial electrical remodeling: LV mechanical synchrony was heterogeneous in pre-CRT but changed to be uniform at off-pace and even better at BIV-paced rhythm. (C) Three SRs without electrical remodeling: There was a declining trend of mechanical synchrony at off-pace compared to that at baseline. However, LV mechanical synchrony significantly improved at BIV-paced rhythm. Pre-CRT: Intrinsic rhythm before implantation; Off-pace: Intrinsic off-pace rhythm after super-response; BIV-paced: Biventricular pacing after super-response.

It is well known that CRT is a powerful tool in HF therapy for improving cardiac function and reducing mortality after CRT implantation.[13] CRT improves ventricular function via BIV pacing to reverse underlying electrical and mechanical dyssynchrony of the failing heart.[4,13,14] CRT SRs may be able to regain normal cardiac function but the extent to which cardiac synchrony is regained remains unclear. In our study, we investigated the extent of cardiac synchrony in SRs and found that SRs still need continuous BIV pacing.

A few studies have shown that SRs have significantly improved electrical and mechanical synchrony. Yang *et al*[15] reported that 27 SRs (LVEF ≥ 50% after CRT) had continuous QRS shortening after CRT, from 175.4 ± 21.4 ms at the baseline to 159.7 ± 20.7 ms at the 6-month follow-up and 149.3 ± 19.2 ms at the time of generator replacement. Dreger *et al*[16] evaluated the longest intraventricular delay using echocardiography as a marker of intraventricular asynchrony and found that CRT significantly reduced the longest intraventricular delay in SRs after 6 months of follow-up. Consistent with previous studies, our study showed that both cardiac electrical and mechanical synchrony were significantly improved after CRT super-response.

The intrinsic QRS duration significantly declined from 174.8 ± 11.9 ms to 148.8 ± 30.0 ms. Most (14/17, 82.4%) of the SRs had shorter QRS durations after CRT super-response. Nearly one-half (8/17, 47.1%) of SRs had a QRS duration that was shorter by more than 20 ms, and two SRs experienced resolution of LBBB. This indicated that the conduction block in HF might be reversible. However, the mechanism for intrinsic QRS shortening and restitution of conduction block after CRT remains unclear. Sebag *et al*[17] presumed that CRT-induced shortening in intrinsic QRS duration would probably be a consequence of multiple factors including reduction in heart size and improvements in conduction system. Wiegerinck *et al*[18] investigated the relationship between QRS duration, conduction velocity, intercellular coupling, and heart size using a rabbit model of HF. They found that although conduction velocity slightly increased in HF, the increased conduction velocity could not compensate for increased strand size of longitudinally coupled cells due to a hypertrophied heart, and consequently, QRS was prolonged. Therefore, we speculated that when the heart size significantly reduced after super-response to CRT, the conduction path was significantly reduced. And consequently, QRS duration would be decreased. In addition, another recent study showed that the shortening of intrinsic QRS duration was observed before the reduction of LV volumes. This result revealed that the QRS shortening after CRT could not be entirely attributed to the reduction of heart size, but may also be due to improvements of conduction system with correction of cardiac gap junction proteins, ion channel remodeling and the reversal of molecular alterations associated with dyssynchronous HF.[19]

The intrinsic LV mechanical dyssynchrony indices (PSD and PHB) in SRs were also significantly decreased after super-response. Furthermore, in the three subgroups in our study, we found that improvement in intrinsic electrical synchrony was highly consistent with that in intrinsic mechanical synchrony. SRs with complete electrical remodeling also achieved normal LV mechanical synchrony. Moreover, SRs with shortened intrinsic QRS durations experienced more improvement in LV mechanical synchrony, while SRs with unchanged intrinsic QRS durations had less LV mechanical synchrony improvement.

It is well known that SRs have a much better prognosis than other CRT recipients.[7,20,21] Manne *et al* compared SRs (LVEF ≥ 50%) with the age- and sex-matched normal population and found that SRs had similar survival to the normal population.[8] In our study, SRs experienced significant improvements in electrical and mechanical synchrony. Therefore, do SRs still need BIV pacing? Two previous studies have tried to answer this question. Cay *et al* stopped pacing in nine SRs and found that both the clinical and echocardiographic parameters deteriorated 12 months after the cessation of pacing.[22] Liang *et al* reported similar results with the LVEF significantly reduced in SRs without pacing at the 6-month follow-up evaluation.[23] As correction of cardiac asynchrony is the major rationale for CRT, our study further characterized SRs with a special focus on the difference in cardiac synchrony between the intrinsic and BIV-paced rhythms, trying to clarify the underlying mechanism. In our study, we found that 88.2% (15/17) of SRs maintained an LBBB/NICD QRS morphology in the intrinsic rhythm and that the intrinsic QRS duration was still much longer than that achieved with BIV pacing after super-response. Moreover, the LV mechanical synchrony of SRs in the intrinsic rhythm was still inferior to that in BIV-paced individuals. This finding suggests that SRs still have an inferior cardiac synchrony in their intrinsic rhythm even when they achieve a normal LVEF (mean LVEF 59.3%). This may explain why the cardiac function of SRs deteriorates after the cessation of BIV pacing, as shown in prior studies.[22,23] This supports continued BIV pacing to maintain better electrical and LV mechanical synchrony in SRs; BIV pacing is still needed in this population.

A major limitation of our study was the small sample size. The small sample size limited our further analysis of the subgroups of three different types of changes in cardiac synchrony. As a result, we only described the change trends in the sub-groups. The main reason for the small sample size was the highly selective super-response criteria for inclusion. We defined the super-response criteria as the normalization of LVEF (≥50%) to ensure that patients enrolled could obtain normal or near-normal LV systolic function. The retrospective design was another limitation. Therefore, we were not able to obtain all cardiac synchrony measurements, which may have affected the findings of this study. Thus, the results need to be confirmed in large-scale prospective trials.

In conclusion, CRT SRs had significant improvements in cardiac electrical and mechanical synchrony. Their intrinsic cardiac synchrony was still inferior to that in BIV pacing rhythm. Therefore, continued BIV pacing is still needed to maintain longstanding cardiac synchrony.

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Conflicts of interest

None.

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