

Repetitive optimizing left ventricular pacing configurations with quadripolar leads improves response to cardiac resynchronization therapy

A single-center randomized clinical trial

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Abstract

Background: This study aimed to investigate whether repetitive optimizing left ventricular pacing configurations (LVPCs) with quadripolar leads (QUAD) can improve response to cardiac resynchronization therapy (CRT).

Methods: Fifty-two eligible patients were enrolled and 1:1 randomized to either the quadripolar LV leads (QUAD) group or the conventional bipolar leads (CONV) group. In the QUAD group, optimization of LVPC was performed for all patients before discharge and for nonresponders at 3 months follow-up. Clinical evaluations and transthoracic echocardiograms were performed before, 3, and 6 months after CRT implantation.

Results: At 3 months follow-up, 16 of 25 (64%) patients in the CONV group (1 patient was lost to follow-up) and 18 of 26 (69%) patients in the QUAD group were classified as responders. After optimizing the LVPCs in 3-month nonresponders in the QUAD group, 21 of 26 (80.8%) patients in the QUAD group were classified as responders at 6 months as compared with 17 of 25 (68%) patients in the CONV group. Left ventricular end-systolic volume (LVESV) reduction, left ventricular ejection fraction (LVEF) increase, and New York Heart Association (NYHA) functional class reduction at 6 months were significantly greater in the QUAD group than in the CONV group (LVESV: -26.9 ± 13.8 vs $-17.2 \pm 13.3\%$; $P = .013$; LVEF: $+12.7 \pm 8.0$ vs $+7.8 \pm 6.3$ percentage points; $P = .017$; NYHA: -1.27 ± 0.67 vs -0.72 ± 0.54 functional classes; $P = .002$).

Conclusions: Compared with conventional bipolar leads, CRT using quadripolar leads with repetitive optimized LVPCs resulted in an additional increase in LVEF and reduction in LVESV and NYHA functional class at 6-month follow-up.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin-receptor antagonist, AV = atrial-ventricular, CONV = conventional leads, CRT (D) = cardiac resynchronization therapy (defibrillator), CS = coronary sinus, ECG = electrocardiogram, HF = heart failure, ICD = implantable cardioverter defibrillator, LAO = left anterior oblique, LV = left ventricular, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, LVPC = left ventricular pacing configuration, LVPS = left ventricular pacing site, MD = medical doctor, NYHA = New York Heart Association, PNS = phrenic nerve stimulation, QRSd = QRS duration, QUAD = quadripolar leads, RA = right atrial, RAO = right anterior oblique, RV = right ventricular.

Keywords: biventricular pacing, cardiac resynchronization therapy, left ventricular pacing configuration, left ventricular pacing site, quadripolar left ventricular lead

1. Introduction

Cardiac resynchronization therapy (CRT) can reverse myocardial remodeling and reduce hospitalization rate and mortality in

patients with systolic heart failure (HF) and dyssynchrony.^[1] Unfortunately, a significant proportion of patients do not respond to CRT, adversely affecting the utility and cost-effectiveness of the treatments.^[2] The left ventricular pacing site (LVPS) has been increasingly recognized as an important determinant of CRT response in individual patients.^[3,4]

Unlike conventional left ventricular (LV) leads, the quadripolar LV pacing leads, with 4 pacing poles, can stimulate different sites of left ventricle by device programming after implant without replacing or repositioning the LV lead. Initial experience has shown that CRT using quadripolar leads with an optimized left ventricular pacing configuration (LVPC) improved acute hemodynamics, synchrony, and also hospitalization rate.^[5,6] Moreover, the method of improving the CRT response by multipoint left-ventricular pacing (MultiPoint Pacing [MPP]; St Jude Medical, Sylmar, CA), which recruits more left ventricular volume of myocardium at the same time based on LV quadripolar leads, has been confirmed by clinical practice.^[7] Forleo et al have demonstrated that MPP improves clinical status and leads to an extra increase in LV ejection fraction (LVEF) compared with conventional CRT.^[8] However, there is paucity on data about the

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The authors declare that they have no conflict of interest.

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potential benefit of the quadripolar leads in terms of clinical and echocardiographic response to CRT.¹⁹ Moreover, whether repetitive optimizing LVPCs during follow-up for the non-responders will further improve response to CRT is unclear.

We hypothesized that implantation of a quadripolar LV lead, which allows adjustment of LVPC both at predischarge and during follow-up, would further improve the clinical and echocardiographic response to CRT.

2. Methods

2.1. Study population

This was a single-centre, double-blinded, randomized trial to compare the mid-term outcomes of biventricular pacing using quadripolar versus conventional bipolar LV leads in HF patients. Fifty-two consecutive patients with New York Heart Association (NYHA) class II, III, or IV HF despite optimal medical therapy, echocardiographic LVEF $\leq 35\%$, and QRS duration ≥ 120 ms, who were scheduled for implantation of a cardiac resynchronization therapy-defibrillator (CRT-D) devices, were recruited between September 2013 and November 2015. Before implant, patients were assigned 1:1 to either the quadripolar LV leads (QUAD) group or the conventional bipolar LV leads (CONV) group according to a computer-generated table of random numbers.

The study protocol was approved by local institutional ethics committee, and all patients gave written informed consent. Patients were excluded if they were aged < 18 , had a pre-existing pacemaker or implantable cardioverter defibrillator (ICD) device, required intravenous inotropic drug therapy, were not able or willing to give informed consent, or had an estimated life expectancy of < 12 months due to a cause other than HF.

2.2. LV lead characteristics

The quadripolar and conventional bipolar leads used in this study were the Quartet LV lead (St. Jude Medical Ltd., Sylmar) and the 1258T LV lead (St. Jude Medical Ltd., Sylmar), respectively. When connected to their corresponding CRT-D generators (Unify [model CD 3231–40] for bipolar leads and Unify Quadra [model CD3249–40Q] for quadripolar leads), the availabilities of the LVPS and LVPC for each can be found in Table 1. Patients were blinded to the type of LV lead that they received.

2.3. Implantation procedure

The leads and implantation procedure were described in detail previously.^{10,11} Briefly, we use a long guiding sheath to

cannulate the coronary sinus (CS). The LV lead was placed in the venous system in the lateral or posterolateral vein preferably. The right atrial (RA) and right ventricular (RV) leads were positioned at the RA appendage, and the RV apex. LV leads were connected to the corresponding CRT-D device. All procedures were performed under local anesthesia. Fluoroscopy was used to determine the final position of the LV lead.

Biventricular pacing was simultaneous: the V-V interval was programmed to 0 ms and no change was allowed during follow-up. In both study groups, the AV interval was optimized at predischarge using an algorithm (QuickOpt) provided by the CRT-D device.

2.4. Viable LVPCs

The threshold test began to decrease step by step at 7.5 V until the loss of capture, and the phrenic nerve stimulation (PNS) was lost with the 0.5-ms pulse width. LVPC was defined as the capture threshold ≤ 2.5 V/0.5 ms at both the sitting position and the left-lateral position, and the ratio of the PNS threshold to the LV pacing threshold was ≥ 2 .

2.5. Paced QRS duration

In the LVPC line of each viable biventricular pacing, 12-lead electrocardiogram (ECG) was recorded at a rate of 50 mm/s. Pacing QRS duration is from the beginning of ventricular pacing to the end of the QRS complex, taking the maximum pacing QRS duration in any of the 12 ECG leads. Biventricular ventricular pacing was performed in the VDD mode (atrioventricular delay interval was 130 ms). The VV interval was always set to 0 ms.

2.6. Selection of LVPC

In the CONV group, a conventional pacing configuration (tip to ring) was programmed; other configurations were used when the conventional pacing configuration was not available due to PNS or unsatisfactory capture thresholds. In the QUAD group, CRT devices were programmed based on a “tailored approach,” described in Fig. 1, which was determined by the best

Table 1
List of included LVPS and LVPC for quartet and bipolar leads.

Quartet leads		Bipolar leads	
LVPS	LVPC	LVPS	LVPC
D1	D1-M2 D1-P4 D1-RV coil	Tip	Tip-Ring — Tip-RV coil
M2	M2-P4 M2-RV coil	Ring	— Ring-RV coil
M3	M3-M2 M3-P4 M3-RV coil		— — —
P4	P4-M2 P4-RV coil		— —

LVPC=left ventricular pacing configuration, LVPS=left ventricular pacing site.

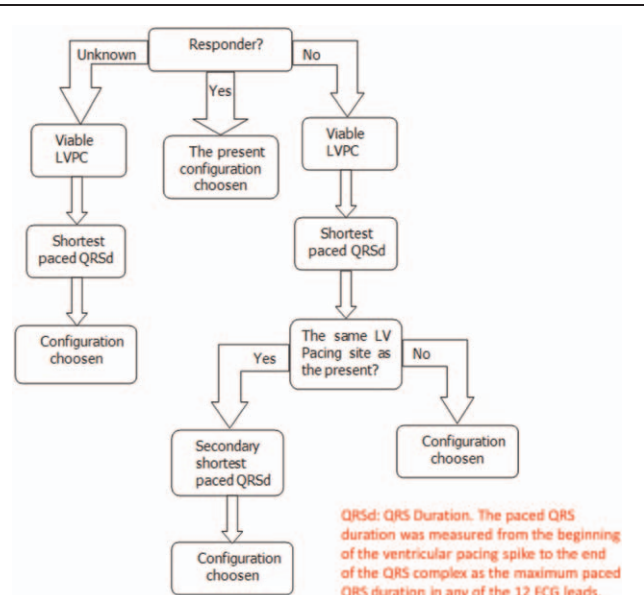


Figure 1. Decisional algorithm adopted for LVPC programming. LVPC=left ventricular pacing configuration.

compromise between the response status to CRT, the viable LVPC, and the shortest paced QRS duration, consecutively considered. In the QUAD group, optimization of LVPCs was performed for all patients at predischarge and for nonresponders at 3 months follow-up. No optimization of LVPC was performed in the CONV group at predischarge or during follow-up. In case of device programming adjustments required during the observation period due to changes in capture threshold or the occurrence of PNS, LVPC would be reselected according to the aforementioned algorithm (Fig. 1).

2.7. Echocardiographic and clinical evaluation

Echocardiographic and clinical evaluation was performed at baseline, and also at 3 and 6-month follow-up visits. The echocardiographic parameters, including LV end-systolic (LVESV) and LV end-diastolic volume (LVEDV), were measured by a transthoracic echocardiography system (iE33, Philips, Amsterdam, The Netherlands), equipped with a 3.5-MHz transducer and offline cine loop analysis software. LVEF was calculated using the modified biplane Simpson rule from apical imaging planes. The above mentioned operation was performed by an observer who was blinded to the patients' LV pacing configuration.

2.8. Study endpoints

Patients were considered to be responders to CRT if they were alive and experienced an improvement of NYHA functional class ≥ 1 and a reduction in LVESV $\geq 15\%$ relative to baseline.^[12] The primary endpoint of the study was the response rate to CRT in the QUAD group versus the CONV group, at 3 and 6 months follow-up. The second endpoint of the study was the change in LVESV, LVEF, and NYHA class from baseline to 3 and 6 months follow-up in the QUAD group versus the CONV group. Post hoc subgroup analyses of the change in LVESV, LVEF, and NYHA class from baseline to 6 months follow-up were conducted in 3-month nonresponders.

2.9. Statistical analysis

Statistical analysis was performed according to the intention-to-treat principle. Continuous variables were reported as mean \pm standard deviation (SD) and were compared using an unpaired *t* test. Categorical variables were reported as number and percentage of the total, and were compared using the Fisher exact test or chi-square test. A *P* value of $<.05$ was considered significant. Data were analyzed by the SPSS 20.0 statistical software (SPSS Italia, Inc, Florence, Italy).

2.10. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. Results

3.1. Baseline patient characteristics

Fifty-two patients were enrolled and 1:1 randomized to the CONV group or the QUAD group. CRT was successfully implanted in all patients. One patient in the CONV group was

lost to follow-up at 3 months and excluded from the following analysis. Baseline patient characteristics were comparable between the 2 groups, as shown in Table 2. The distribution of LV lead tip position in left anterior oblique and right anterior oblique fluoroscopy is shown in Table 2. Lead placement was similar between the 2 groups.

3.2. Follow-up

During the follow-up period, 1 patient in the QUAD group experienced rise in capture threshold and another patient experienced PNS, both of which were resolved by reprogramming to a different LVPC. In the CONV group, PNS occurred in 1 patient and was resolved by reprogramming to another LVPC. All patients remained in stable sinus rhythm during the study and a percentage of biventricular pacing $>95\%$ was achieved in all subjects of both groups.

3.3. Echocardiographic and clinical outcomes at 3 months follow-up

The mean follow-up period in the CONV group and the QUAD group was 93 ± 7 days and 94 ± 5 days, respectively ($P = .56$). Overall, 16 of 25 (64%) patients in the CONV group and 18 of 26 (69%) patients in the QUAD group were classified as responders at 3 months follow-up ($P = .69$; Fig. 2A). No significant difference was found in LVESV reduction and LVEF increase relative to baseline between the 2 groups. (LVESV: -21.3 ± 14.5 vs $-16.1 \pm 15.2\%$; $P = .22$, Fig. 3A; LVEF: $+10.7 \pm 8.4$ vs $+7.3 \pm 7.5$ percentage points; $P = .14$, Fig. 3B). NYHA functional class reduction relative to baseline favored the QUAD group, and was also not statistically significant. (NYHA: -1.04 ± 0.72 vs -0.68 ± 0.56 functional classes; $P = .053$, Fig. 3C)

3.4. Response status at 6 months follow-up

The mean follow-up time in the CONV group and the QUAD group was 183 ± 4 days and 182 ± 6 days, respectively ($P = .49$). Overall, 17 of 25 (68%) patients in the CONV group and 21 of 26 (80.8%) patients in the QUAD group were defined as responders at 6 months follow-up ($P = .30$; Fig. 2B).

From 3 to 6 months, 3 of 25 patients (12%) in the CONV group experienced response conversion, with 1 of 16 responders (6.3%) becoming nonresponders and 2 of 9 nonresponders (22.2%) becoming responders. In the QUAD group, 5 of 26 patients (19.2%; $P = .70$) experienced response conversion, with 1 of 18 responders (5.6%; $P = 1.0$) becoming nonresponders and 4 of 8 nonresponders (50%; $P = .33$) becoming responders (Fig. 2C).

3.5. Echocardiographic and clinical changes from BASELINE to 6 months follow-up

A significantly greater LVESV reduction and LVEF increase relative to BASELINE were found in the QUAD group than in the CONV group (LVESV: -26.9 ± 13.8 vs $-17.2 \pm 13.3\%$; $P = .013$, Fig. 4A; LVEF: $+12.7 \pm 8.0$ vs $+7.8 \pm 6.3$ percentage points; $P = .017$, Fig. 4B). Moreover, QUAD group had a greater reduction relative to BASELINE in NYHA functional class than in the CONV group (NYHA: -1.27 ± 0.67 vs -0.72 ± 0.54 functional classes; $P = .002$, Fig. 4C).

Of the nonresponders at 3 months follow-up, LVESV reduction and LVEF increase from BASELINE to 6 months

Table 2
Baseline characteristics and LV lead positions of the 2 study groups.

Parameter	QUAD group (n=26)	CONV group (n=26)	P
Age, y	55.8±11.1	58.7±9.3	.32
Sex, male	19 (79.2%)	17 (65.4%)	.55
Etiology			
Ischemic	4 (15.4%)	4 (15.4%)	1
Nonischemic	22 (84.6%)	22 (84.6%)	1
NYHA functional class	2.65±0.56	2.69±0.55	.8
Class II/III/IV	10/15/1	9 /16/1	.96
Comorbidities			
Diabetes mellitus	7 (26.9%)	5 (19.2%)	.51
History of AF	1 (3.8%)	3 (11.5%)	.61
Hypertension	9 (34.6%)	10 (38.5%)	.77
Serum creatinine, mg/dL	0.96±0.25	1.03±0.24	.31
Left bundle branch block	19 (73.1%)	20 (76.9%)	.75
QRS duration, ms	161.8±16.3	159.7±13.0	.6
Echocardiogram/Doppler			
LVEF	28.2±6.6	28.7±6.7	.82
EDV, mL	262.0±81.1	272.0±82.3	.66
ESV, mL	173.3±68.8	185.6±73.1	.54
Moderate/severe mitral regurgitation	7 (26.9%)	9 (34.6%)	.55
Medications at baseline			
Aldosterone antagonist	26 (100%)	26 (100%)	1
Amiodarone	2 (7.7%)	5 (19.2%)	.42
ACEI or ARB	23 (88.5%)	21 (80.8%)	.7
Antiplatelet	7 (26.9%)	7 (26.9%)	1
Beta-blockers	26 (100%)	25 (96.2%)	1
Digitalis	17 (65.4%)	20 (76.9%)	.36
Diuretics	25 (96.2%)	26 (100%)	1
Lipid-lowering statin drugs	12 (46.2%)	11 (42.3%)	.78
Nitrate	10 (38.5%)	8 (30.8%)	.56
LV lead position			
LAO projection			
Anterolateral	2 (7.7%)	3 (11.5%)	1
Lateral	7 (26.9%)	7 (26.9%)	1
Posterolateral	16 (61.5%)	14 (53.8%)	.58
Posterior	1 (3.8%)	2 (7.7%)	1
RAO projection			
Apical	12 (46.2%)	8 (30.8%)	.25
Midventricular	11 (42.3%)	12 (46.2%)	1
Basal	3 (11.5%)	6 (23.1%)	.47

Cell values are n (%) or mean ±SD.

ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin-receptor blocker, EDV = end-diastolic volume; ESV = end-systolic volume, LAO = left anterior oblique, LV = left ventricle, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, RAO = right anterior oblique.

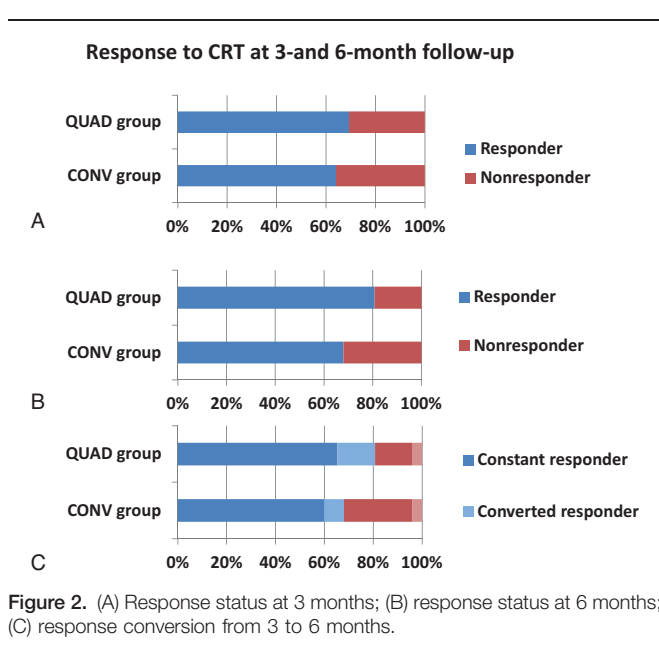


Figure 2. (A) Response status at 3 months; (B) response status at 6 months; (C) response conversion from 3 to 6 months.

follow-up favored the QUAD group, although the difference was not statistically significant. (LVESV: -18.5 ± 17.6 vs $-3.6 \pm 12.6\%$; $P=0.06$, Fig. 5; LVEF: $+9.9 \pm 10.2$ vs $+3.0 \pm 6.1$ percentage points; $P=0.11$, Fig. 6). The percentage of patients with a reduction in at least 1 NYHA class level at 6 months follow-up was 62.5% (5/8 patients) in the QUAD group and 33.3% (3/9) in the CONV group.

4. Discussion

In this prospective randomized study, we compared the response to CRT in patients implanted with the quadripolar LV leads or conventional bipolar leads. Our results showed that: choosing the LVPCs associated with the shortest biventricular paced QRS duration is feasible in CRT device programming; biventricular pacing using quadripolar leads with optimized LVPCs is superior to conventional bipolar leads based on 6-month echocardiographic and clinical outcomes; reselection a LVPS for non-responders during follow-up is promising to further improve response to CRT.

Response to biventricular pacing may vary according to the site of LV pacing. Some studies demonstrated that the mid-ventricular and basal portions of the lateral LV wall were

ECHO and clinical findings at 3 months

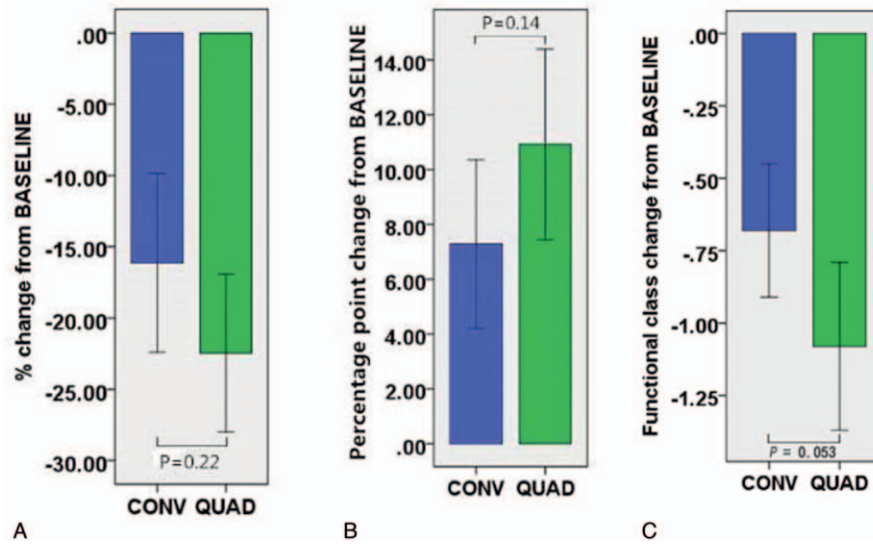


Figure 3. Echocardiographic and clinical findings at 3 months. (A) ESV; (B) LVEF; (C) NYHA class. ESV=end-systolic volume, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association.

associated with the best response.^[13] Other studies showed that pacing at sites of late LV electrical or mechanical delay is associated with better reverse remodeling response, quality of life, and clinical outcomes, regardless of lead position.^[14,15] However, for patients implanted with a conventional unipolar LV lead, the LV pacing site cannot be changed after implant. However, the quadripolar LV lead Quartet offers 10 different pacing configurations, with a wider possibility of CRT device reprogramming. Although it is well-recognized that changes in LVPCs can be associated with a lower pacing threshold or with avoidance of PNS.^[16] However, there is paucity on data about

the potential benefit of the Quartet leads in terms of clinical and echocardiographic response to CRT.^[9]

Bencardino et al^[17] recently found that selecting a better LVPC with quadripolar leads on the basis of QRS shortening was associated with an improvement of LVEF greater than that observed in patients receiving a bipolar LV lead. In our study, we found that at 3 months follow-up, LVESV reduction, LVEF increase, and NYHA functional class reduction relative to BASELINE favored the QUAD group, although it was not statistically significant. Our results, together with findings of previous studies, emphasized that choosing a LVPC with

ECHO and clinical findings at 6 months

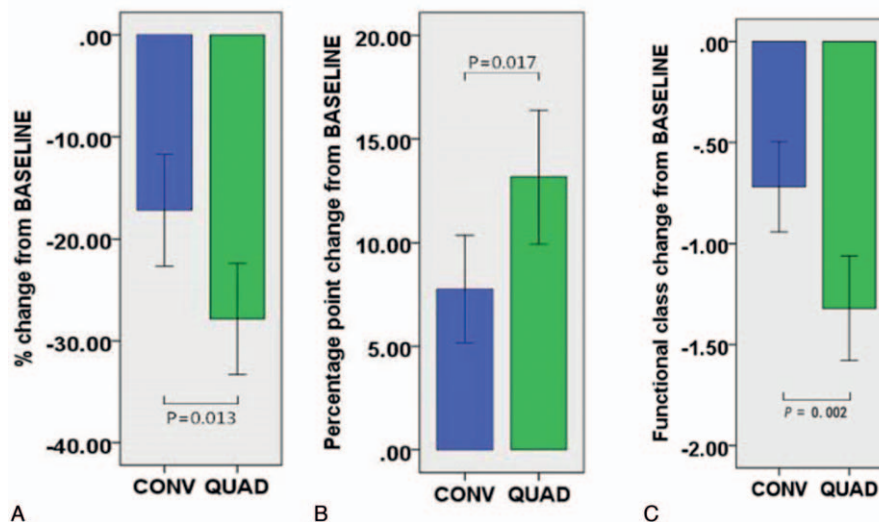


Figure 4. Echocardiographic and clinical findings at 6 months. (A) ESV; (B) LVEF; (C) NYHA class. ESV=end-systolic volume, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association.

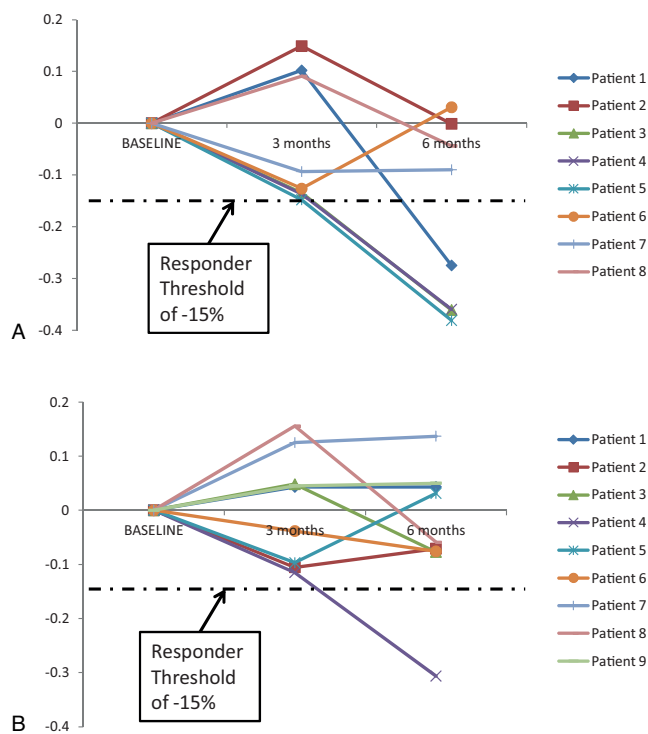


Figure 5. (A) ESV change at 3 and 6 months for 3-month nonresponders in QUAD group. (B) ESV change at 3 and 6 months for 3-month nonresponders in CONV group. CONV=conventional leads, ESV=end-systolic volume, QUAD=quadripolar leads.

quadripolar leads on the basis of QRS shortening was feasible to improve response to CRT.

Previous studies focused on choosing the best LVPC at implant or pre-discharge to improve response to CRT. However, little attention was paid to optimize LVPC during follow-up. To the best of our knowledge, this study was the first to investigate the incremental clinical benefits by optimizing LVPS for nonresponders during follow-up. In our study, we reselected a LVPS for the 3-month nonresponders in the QUAD group and found that more nonresponders were converted into responders in the QUAD group (4/8, 50%) compared with that in the CONV group (2/9, 22%) at 6 months follow-up. Moreover, LVESV reduction and LVEF increase at 6 months relative to BASELINE favored the QUAD group in these 3-month nonresponders.

Several studies have demonstrated that characteristics of the LV pacing region strongly influence response to CRT, and delivering the LV lead to viable myocardium is a prerequisite for response to occur.^[18–20] The position of myocardial scar may influence the response to CRT because scars prevent progression of the activation wavefront and the synchronized engagement of viable tissue.^[18] One previous study found that without image guidance, the delivery of LV lead to a scarred myocardial region occurs in 13% of cases, with 75% of these patients failing to respond to CRT.^[21] Therefore, we hypothesize that reselecting a LVPS for the 3-month nonresponders may offer a chance to pace on the region of viable myocardium rather than the region of scar, thereby acquiring more fast and synchronized LV depolarization. Our following study will test this hypothesis by analyzing the distribution of scar on LV and the relationship with LV-pacing electrodes.

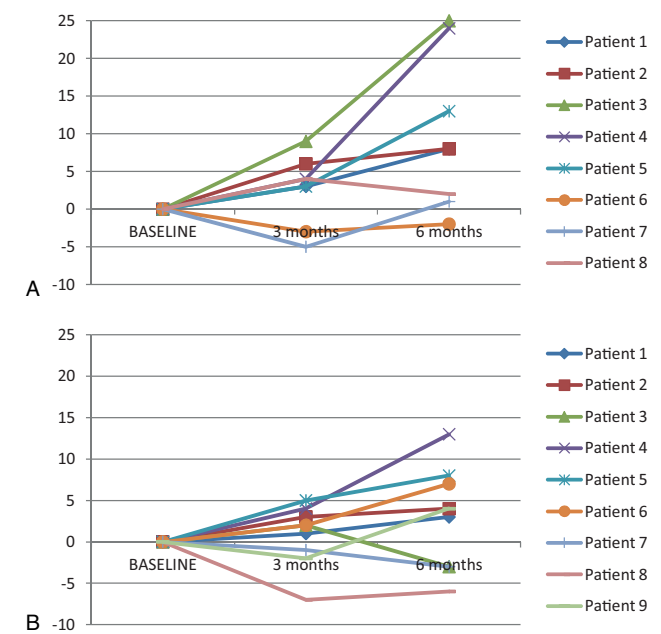


Figure 6. (A) LVEF change at 3 and 6 months for 3-month nonresponders in QUAD group. (B) LVEF change at 3 and 6 months for 3-month nonresponders in CONV group. CONV=conventional leads, LVEF=left ventricular ejection fraction, QUAD=quadripolar leads.

In our study, we used a “tailored approach” in the LVPC optimization in the QUAD group, in which the optimal LVPC for CRT was determined by the response status to CRT, the viable LVPC, and the shortest-paced QRS duration. We found that at 3-month follow-up, LVESV reduction, LVEF increase, and NYHA functional class reduction relative to BASELINE favored the QUAD group, but was not statistically significant. However, after optimization of LVPC for the nonresponders at 3 months, patients randomized to receive quadripolar leads had greater reduction in LVESV, improvement in LVEF, and reduction in NYHA class than patients randomized to receive conventional bipolar leads at 6 months follow-up. Considering the other parameters associated with response to CRT (ie, female sex, presence of LBBB, QRS duration, HF etiology, and position of LV leads) are comparable between the 2 groups, we think that the advantage of quadripolar leads over conventional bipolar leads come from repetitive LVPC optimization. Larger, multicenter studies with longer-term follow-up are needed to further clarify the effect of this “tailored approach” on CRT response.

Although LVPC optimization of bipolar LV lead might be possible and may improve CRT response in theory, there are several reasons we did not perform the LVPC optimization in the CONV group. First, we found that limited LVPCs could be selected for bipolar leads in clinical practice due to PNS or unsatisfied threshold. Second, we found in our practice that these unconventional pacing configurations were associated with a wider QRS in almost all the patients, which is consistent with the findings reported by Bencardino et al.^[17] Finally, priority selection of conventional pacing configuration is an established practice for LVPC programming,^[22] and the purpose of this study was to compare the value of CRT with or without LVPC optimization.

4.1. Limitations

Several limitations in this study must be considered. Firstly, this was a single-center study with relatively small sample size. However, significant differences were found in LVEF improvement and LVESV reduction, and NYHA functional class between the 2 groups. Secondly, 1 patient was lost during follow-up, although it may not affect our analysis. Thirdly, electrocardiographic and echocardiographic measurements can suffer from inter and intraobserver variability. To minimize this limitation, examinations were performed and analyzed by 1 blinded operator. In addition, we did not use other optimization programs (ie, V-V interval optimization) during the study period to avoid more confounders to our results. CRT response might be improved by V-V interval optimization in some nonresponders. Finally, the study included data from a single quadripolar lead design as the Quartet was the only commercially available quadripolar lead in China at the time data were collected. The results of this study may not be applicable to other quadripolar lead designs now in the market.

5. Conclusions

Compared with conventional bipolar leads, CRT using quadripolar leads with repetitive optimized LVPCs resulted in an additional increase in LVEF, and reduction in LVESV and NYHA functional class at 6 months follow-up. Optimizing LVPC for nonresponders during follow-up is promising to further improve response to CRT.

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