Surface electrogram-guided left ventricular lead placement improves response to cardiac resynchronization therapy

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Abstract

Objective: Failure to select the optimal left ventricular (LV) segment for lead implantation is one of the most important causes of unresponsiveness to the cardiac resynchronization therapy (CRT). In our study, we aimed to investigate the echocardiographic and clinical benefits of LV lead implantation guided by an intraoperative 12-lead surface electrocardiogram (ECG) in patients with multiple target veins.

Methods: We included 80 [42 (62.5%) male] heart failure patients who successfully underwent CRT defibrillator (CRT-D) implantation. Patients were divided into two groups. In group 1, LV lead was positioned at the site with the shortest biventricular-paced (BiV-paced) QRS duration (QRSd), as intraprocedurally measured using surface ECG. In group 2 (control), we included patients who underwent the standard unguided CRT. ECG, echocardiogram, and functional status were evaluated before and 6 months after CRT implantation in all patients.

Results: In group 1, BiV-paced QRSd measurements were successfully performed in 112 of 120 coronary sinus branches during CRT and an LV lead was successfully placed at the optimal site in all patients. Compared with group 2, group 1 had a significantly higher rate (85% vs. 50%, p=0.02) of response (>15% reduction in LV end-systolic volume) to CRT as well as a shorter QRSd (p<0.001) and a greater QRS shortening (ΔQRS) associated with CRT compared with baseline (p<0.001). The mean New York Heart Association functional class was significantly improved in both groups, and no significant differences were found in clinical response to CRT (85% vs. 70%, p=0.181).

Conclusion: Surface ECG can be used to guide LV lead placement in patients with multiple target veins for improving response to CRT. Thus, it is a safe, feasible, and economic approach for CRT-D implantation. *(Anatol J Cardiol 2018; 19: 184-91)*

Keywords: cardiac resynchronization therapy, left ventricular lead placement, electrocardiogram, QRS duration, response to CRT

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for advanced congestive heart failure (CHF) that is refractory to medical treatment. However, a significant proportion of such patients fail to benefit from CRT (1-3). The response to CRT depends on cardiac substrates: presence of correctable left ventricular (LV) mechanical dyssynchrony, presence of myocardial fibrosis (scar), and the position of LV pacing lead. A similar improvement has been demonstrated with CRT in all-cause mortality and in hospitalizations due to heart failure among patients with ischemic and non-ischemic cardiomyopathies (4-6). However, compared with patients with ischemic cardiomyopathy, those with non-ischemic cardiomyopathy show a considerable advantage in terms of LV reverse remodeling and functional improvement (3-5, 7, 8). Clinically, it is a major challenge to identify the reliable predictors of effectiveness of CRT and optimal placement of the LV lead. Individually targeted lead placement, alternative lead implantation strategies, and examination of the intraoperative criteria for mid- to long-term effectiveness of CRT are the methods that have received great interest and have been the subject of trials.

Based on the individual pathophysiological knowledge about electromechanical disorders, a change in QRS duration (QRSd) generated by biventricular (BiV) stimulation should indicate the quality of electrical resynchronization. It also indirectly reflects the degree of correction of electromechanical abnormalities (2). Several studies have demonstrated that the hemodynamic re-

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sponse, extent of LV volumetric changes, and clinical outcomes are affected by baseline or BiV-paced electrocardiogram (ECG) characteristics (2-9). These studies suggest that patients with a longer intrinsic QRSd, left bundle-branch block (LBBB) morphology, and greater QRS shortening (ΔQRS) with BiV pacing have better outcomes.

In our study, we positioned the LV lead at any of the branches of the coronary sinus (CS) with the shortest QRSd measured using an intraoperative 12-lead surface ECG during BiV pacing. We aimed to investigate the clinical and echocardiographic benefits of LV lead placement guided by ECG in patients with multiple target veins.

Methods

Patient population and study protocol

This study was a prospective, double-blind, randomized controlled trial that enrolled 80 consecutive patients who underwent successful implantation of a CRT defibrillator (CRT-D).

All patients were in sinus rhythm with impaired LV systolic function [LV ejection fraction (LVEF) ≤35%], LBBB, and New York Heart Association (NYHA) functional class II-IV symptoms despite being provided the maximum tolerated optimal medical treatment (angiotensin-converting enzyme inhibitor and beta-blocker uptitrated to the maximum tolerated dose; symptoms not alleviated even after addition of mineralocorticoid receptor antagonists). LBBB was defined as QRSd>120 ms; QS or rS in lead V1; broad R waves in leads I, aVL, V5, or V6; and absent Q waves in lateral leads.

We excluded patients with atrial fibrillation and various comorbidities and those with a life expectancy <1 year, inadequate image quality for 2-dimensional (2D) transthoracic echocardiography (TTE), and an acute coronary syndrome diagnosis 3 months prior to CRT-D implantation. The etiology of heart failure was considered to be ischemic in patients with a significant coronary artery disease (>50% stenosis in≥one of the major coronary arteries) and/or in patients with a history of myocardial infarction or previous revascularization. All patients received optimal pharmacological treatment before and after CRT-D implantation. Informed consent was obtained from all patients participating in the study, and the Ethical Committee of the hospital approved this study.

Eighty patients were randomized in a 1:1 ratio to the either group. In group 1, an attempt was made to place the LV lead at the site with the narrowest BiV-paced QRS, as intraprocedurally measured using surface ECG. In group 2 (control), the patients underwent standard CRT implantation without ECG guidance, preferentially in a lateral, posterior, or posterolateral vein.

Baseline assessment and collection of outcome measurements

The following variables were recorded at the baseline and up to 6 months after CRT system implantation: (i) NYHA functional class, (ii) QRSd (ms), (iii) echocardiographic measurements of LV volume and LVEF.

Standard 2D TTE was performed using a commercial machine (Vivid 7, General Electric Medical Systems, Horten, Norway) equipped with a 3.5-MHz phased-array transducer. LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) were measured using the parasternal long-axis view, and LVEF was calculated using Simpson's biplane method according to the guidelines of the American Society of Echocardiography (10).

Two cardiologists performed manual QRSd measurements in the leads II, V1, or V6 on a 12-lead surface ECG (0.5-150 Hz, 25 mm/s, 10 mm/mV) (11). All baseline and follow-up clinical, electrocardiographic, and echocardiographic data were acquired and analyzed by two independent clinicians blinded to the study design and the patient data.

Echocardiographic response to CRT was defined as a reduction in LVESV >15% (8, 12). Clinical response was defined as an improvement (> or=1 score) in NYHA class at 6 months after CRT-D implantation.

Implantation techniques

All CRT-D implantations were performed using a left infraclavicular approach. The right ventricular (RV) lead was placed according to the operator's preference at either the RV septum or RV apex. RV septum was considered optimally implanted when they were oriented frontally and toward the left in a 40-45 left anterior oblique fluoroscopic projection. Leads assigned to the RV apex were advanced as far as possible toward the apex.

In group 1, LV lead placement was performed in a three-step process. First, the coronary venous anatomy was delineated using balloon occlusive CS venography. Then, LV lead was placed in lateral, posterior, or posterolateral veins. At each LV lead placement site, QRSd in the lead II, V1, or V6 on the 12-lead surface ECG was measured during BiV pacing. Finally, the LV lead was placed in the CS branch with the shortest BiV-paced QRSd. In group 2, this was performed according to the standard clinical practice without ECG guidance, preferentially in a lateral, posterior, or posterolateral vein.

The atrioventricular and interventricular delays were optimized using Doppler echocardiographic measurements of transmitral flow 1 week after implantation. Devices were programmed in DDD(R) mode (lower rate limit, 40) to achieve atrial synchronous BiV pacing.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov test was used to test the normality of data distribution. Continuous variables were expressed as mean±standard deviation and median (25^{th} percentile/75^{th} percentile), and categorical variables were expressed as counts (percentages). Comparisons of continuous paired variables were performed using Wilcoxon t-test, and comparisons of categorical variables between the groups were performed using χ^2 analysis.

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Table 1. Baseline characteristics of the overall study population

	Group 1 (n=40)	Group 2	*P* values
Age, years	64.45±8.88	65.65±9.22	0.297
Male, %	24 (60%)	26 (65%)	0.213
BMI, kg/m^2	27.46±3.96	27.50±3.26	0.969
Hypertension, %	16 (40%)	30 (75%)	0.003
Diabetes mellitus, %	17 (42.5%)	20 (50%)	0.501
Ischemic, n%	14 (35%)	18 (45%)	0.494
NYHA functional class	2.55±0.50	2.45±0.50	0.502
QRS duration, msn	158.85±13.93	154.110±13.50	0.210
β-blockers, n%	40 (100)	40 (100)	1.000
ACE inhibitors or ARBs, n%	40 (100)	36 (90)	0.116
Spironolactone	40 (100)	36 (90)	0.116

ACE - angiotensin-converting enzyme; ARBs - angiotensin receptor blockers; BMI - body mass index; NYHA - New York Heart Association

Table 2. Left and right ventricular lead positions in both randomized groups

	Group 1 (n=40)	Group 2 (n=40)	*P* value
Posterior	18	16	0.651
Posterolateral	20	18	0.654
Lateral	2	6	0.263
Apex	27	26	0.813
Septum	13	14	0.813

Simple and multiple regression analyses were used to identify variables predictive of a positive response to CRT, including gender, NYHA class, QRSd at baseline and at 6 months, the difference between two values (ΔQRS), LVEDV, LVESV, and baseline LVEF. Finally, the goodness-of-fit was assessed using Hosmer and Lemeshow test. A two-sided p value <.05 was considered significant.

Results

The demographic and clinical characteristics as well as baseline QRSd of all group 1 and group 2 patients are presented in Table 1. The mean patient age was 65.05±9.05 years; 62.5% patients were male (60% in group 1 vs 65% in group 2; p=0.213), and in 40% patients, ischemic heart disease was the primary cause of HF.

The number of patients with hypertension were significantly higher in group 2 than in group 1 (p=0.003). All patients underwent successful CRT-D implantation on the basis of standard clinical criteria. No deaths were reported during the 6-month follow-up period, and no patient was lost to follow-up. None of the patients experienced any appropriate or inappropriate ICD therapy.

Table 3. Comparison of intraoperative biventricular-paced QRS durations between preferred and non-preferred coronary sinus branches for LV lead implantation in group 1

	Preferred CS branch (n=40)	Non-preferred CS branch (n=72)	*P* value
BiV-paced QRS duration, msn	139.45±10	157±10	<0.001

LV - left ventricular; CS - coronary sinus

There was no significant difference in the LV lead placement site between two groups. In both groups, a majority of the LV leads were positioned in the posterior and posterolateral veins (Table 2). In group 1, LV lead could be inserted into two of all target veins in 8 patients and into three of all target veins in 32 patients. In each vein, BiV-paced QRS width was measured on an intraoperative 12-lead surface ECG, and the shortest width was the preferred measurement. In total, 112 CS branches were tested to find the most suitable site in group 1. Three optimal CS branches with the shortest BiV-paced QRSd were given up due to the diaphragmatic stimulation. The mean BiV-paced QRS width was significantly different between the preferred LV lead placement sites and non-preferred sites in group 1 patients (139.45±10 msn vs 157±10 msn, p≤0.001) (Table 3).

As shown in Table 4, all variables of the patients in both groups, except ΔQRS in group 2, exhibited a significant improvement at 6 months compared with baseline. In group 1, BiV stimulation shortened the mean QRSd from 155.85±13.93 ms to 139.45±10.25 ms (p<0.001), whereas no significant shortening of QRSd was observed in group 2 (p=0.936).

Compared with group 2, group 1 had a greater proportion of echocardiographic responders (85% vs. 50%, p=0.02). There were significant differences in echocardiographic measure-

Table 4. QRS duration, New York Heart Association functional class, proBNP levels, and echocardiographic parameters at baseline and 6 months in both randomized groups

	Group 1			Group 2		
	Baseline	6 month	*P* value	Baseline	6 month	*P* value
QRS duration, msn	158.85±13.9	139.45±10.2	<0.001	154.1±13.5	154.1±13.4	0.936
NYHA functional class	2.55±0.5	1.65±0.73	<0.001	2.45±0.5	1.85±0.92	<0.001
proBNP levels, pg/mL	1355 (398-3372)	654 (180-2277)	<0.001	1290 (358-3612)	976 (168-2619)	0.001
LVEF, %	21.05±4.83	33.70±10.6	<0.001	20.55±5.02	26.35±7.47	<0.001
LVEDV, mL	234.5 (187- 262)	192 (123-225)	<0.001	239 (201-262)	205.5 (181-254)	<0.001
LVESV, mL	188.0 (132-202)	132 (67-168)	<0.001	191 (157-212)	142.5 (127-194)	<0.001

Values are median (25^{th}/75^{th} percentile) or n (%).
LVEF - left ventricular ejection fraction; LVEDV - left ventricular end-diastolic volume; LVESV - left ventricular end-systolic volume; NYHA - New York Heart Association; proBNP - brain natriuretic peptide

Table 5. QRS duration, New York Heart Association functional class, proBNP levels, and echocardiographic parameters at baseline and 6 months between both randomized groups

	Group 1	Group 2	*P* value
QRS duration, ms			
Baseline	158.85±13.93	154.1±13.5	0.210
6 months	139.45±10.25	154.1±13.4	<0.001
NYHA functional class			
Baseline	2.55±0.50	2.45±0.50	0.502
6 months	1.65±0.73	1.85±0.92	0.402
proBNP levels, pg/mL			
Baseline	1355 (398-3372)	1290 (358-3612)	0.821
6 months	654 (180-2277)	976 (168-2619)	0.590
LVEF, %			
Baseline	21.05±4.83	20.55±5.02	0.772
6 months	33.70±10.6	26.35±7.47	0.005
LVEDV, mL			
Baseline	234.5 (187-262)	239 (201-262)	0.464
6 months	192 (123-225)	205.5 (181-254)	0.037
LVESV, mL			
Baseline	188.0 (132-202)	191 (157-212)	0.878
6 months	132 (67-168)	142.5 (127-194)	0.018
Fluoroscopy time, min	20 (18-23)	17 (15.25-19)	<0.001

Values are median (25^{th}/75^{th} percentile) or n (%).
LVEF - left ventricular ejection fraction; LVEDV - left ventricular end-diastolic volume; LVESV - left ventricular end-systolic volume; NYHA - New York Heart Association; proBNP - brain natriuretic peptide

ments of LV volumes (LVEDV, p=0.037 and LVESV, p=0.018) and LVEF (p=0.005) between the groups. The changes in LVEDV, LVESV, and LVEF for both the groups at baseline and follow-up are shown in Table 5. The fluoroscopy time was significantly greater in group 1 than in group 2 (p≤0.001).

Group 1 patients had a shorter QRSd (139.45±10.25 ms vs. 154.1±13.4 ms, p<0.001) and a greater ΔQRS [-12.500 ms (–16.250 – 4.750) vs. 1.5 ms (–6.750 – 18.500), p≤0.001)] at 6 months compared with baseline. The mean NYHA functional class significantly improved in both groups, and no significant differences were found in the clinical response to CRT (85% vs. 70%, p=0.181). ProBNP levels significantly decreased in both groups at 6 months after CRT, and no significant difference was observed between the groups (p=0.590) (Table 5).

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Table 6. Simple and multivariate regression analyses to determine the effect of each variable on LV reverse remodeling at 6 months

	OR	95% CI	*P* value
Simple regression analysis			
Male	0.356	0.132-0.958	0.041
NYHA class	3.273	1.211-8.844	0.019
QRS duration at baseline	0.993	0.960-1.028	0.019
QRS duration at 6 months	0.954	0.920-0.990	0.011
ΔQRS	0.961	0.921-1.002	0.065
LVEDV	0.997	0.987-1.008	0.605
LVESV	0.996	0.984-1.007	0.441
LVEF	1.037	0.940-1.144	0.470
Multivariate regression analysis			
Male	0.183	0.0470-714	0.015
NYHA class	8.316	2.008-34.434	0.003
Baseline QRS	0.995	0.903-1.097	0.927
QRS duration at 6 months	0.964	0.889-1.045	0.372
ΔQRS	0.969	0.854-1.100	0.624
LVEDV	1.011	0.956-1.070	0.699
LVESV	0.985	0.922-1.052	0.644
LVEF	0.916	0.749-1.120	0.391

LVEF - left ventricular ejection fraction; LVEDV - left ventricular end-diastolic volume; LVESV - left ventricular end-systolic volume; NYHA - New York Heart Association; OR – odds ratio; CI – confidence interval
ΔQRS, (Baseline QRSd-QRSd at 6 months)

The univariate logistic regression analysis showed that gender, NYHA functional class, and QRSd at baseline and 6 months were significantly associated with response to CRT. On the multivariable logistic regression analysis, gender and NYHA functional class emerged as the independent predictors of response to CRT (Table 6).

Discussion

The present study showed the feasibility of ECG-guided LV lead placement during CRT-D implantation. Greater LV reverse remodeling was observed with guided LV lead implantation using the BiV-paced QRS width on surface ECG intraprocedurally.

CRT has been confirmed to be effective in patients with advanced CHF that is refractory to medical treatment; however, up to 30% of patients do not respond to it (13-17). Patient selection, lack of LV dyssynchrony, sub-optimal LV lead position, high myocardial scar burden, and sub-optimal device programming have been related to a nonresponse to CRT (18-20). In MIRACLE study, improvement in NYHA functional class was not observed in 32% of patients (21). In PROSPECT trial, based on the clinical improvement, 69% of CRT patients improved, 15% did not show any changes, and 16% showed clinical (8). Although, the rate of unresponsiveness to CRT in our study was close to that reported in the aforementioned studies in the control group, this ratio was lower (15%) in the surface ECG-guided group.

One of the main determinants of response to CRT is the LV lead position. The conventional LV lead placement strategy involves an anatomical approach, targeting a coronary venous branch situated on the posterolateral wall (22). Based on the contention of this strategy, in patients with LBBB, the posterolateral wall is typically the latest activated site of the ventricle. However, studies have shown a considerable variability in the ventricular activation pattern in LBBB, resulting in interindividual variability in the optimal pacing site (23-25). In our study, the final LV lead placement site did not differ between the two groups. In both groups, a majority of the LV leads were placed in the posterior and posterolateral coronary venous branches. However, a significant shortening of QRS width and a better echocardiographic response to resynchronization therapy was observed in our study population. These findings demonstrate that there is no standard and an appropriate CS side branch. LV lead placement site should be individually optimized due to the anatomic variability of CS, different degrees of scar tissue, and the location of CS and its side branches with respect to the anatomical location of LV.

Placing the LV lead away from scar and at or near the site of the latest mechanical activation is necessary for response to

CRT. Different strategies have been suggested to overcome the obstacles for efficient LV lead placement, such as multimodality cardiac imaging to assist in the preprocedural or intraprocedural recognition of the segment with maximum mechanical dyssynchrony or a site of late electrical activation distant from the scar and potential anatomical confinements (6, 26-29). Speckle-tracking echocardiography (STE)-derived strain imaging offers a detailed characterization of LV function and provides indices of mechanical dyssynchrony; in addition, STE systolic strain could be used to identify the area of scar (30). Nuclear image-guided approaches for CRT have been demonstrated to have a significant clinical value in evaluating LV myocardial viability and mechanical dyssynchrony, navigating the LV lead to the target coronary venous site, and recommending the optimal LV lead position (31). Delayed-enhancement CMR for evaluating scar prior to CRT-D implantation is being increasingly adopted as the standard care in many centers (26). Electrophysiological mapping (EPM) in CS branches is also feasible for guiding LV lead placement to the optimal, latest activated site during CRT (32).

In an effort to improve the response to CRT, it has been extensively published in literature that multimodality cardiac imaging may play a decisive role in this matter. However, we are so far from the routine use in clinical practice. ECG (with respect to paced QRS narrowing) may present a simple and economic approach for guiding LV lead placement to an optimal anatomical position. The quality of electrical resynchronization and the degree of correction of electromechanical abnormalities could be reflected in the changes in QRSd produced by CRT. It may also be an indirect method of identifying a region near scar or an area of poor conduction. In this case, a narrower CRT-paced QRSd indicated electrically viable tissue. Besides, a wider LV-paced QRS implied proximity to a region of scar in which resynchronization is less likely to occur and electric signals are slowly conducted (33).

During CRT-D implantation, it is recommended that the LV lead be positioned to minimize both the LV- and BiV-paced QRS widths, especially if there are multiple coronary veins, multiple locations within a vein, or multiple pacing configurations from which to choose (33, 34) To the best of our knowledge, ours is the first study to use BiV-paced QRS width on the surface ECG to optimize LV lead placement. Lecoq et al. (2) also attempted to minimize the QRS width during CRT-D implantation, but unlike ours, the LV lead was positioned in the standard lateral or posterolateral vein and the RV lead was then implanted at RVOT, the septum, the anterior wall, or the apex according to the result of intraoperative BiV pace mapping by considering the shortest BiV-paced QRSd. Liang et al. (32) showed that targeting the LV lead at the latest activated site determined using electrophysiological mapping (EPM) in CS branches improves response to CRT. They used the LV lead as a mapping bipolar electrode, and EPM was successfully performed in 85 of 91 CS branches during CRT (32).

The technique used in this study is safe, requiring reasonable fluoroscopy times. The fluoroscopy time was significantly greater in group 1 than in group 2. All procedures were completed without any complications. Echocardiography and other imaging techniques are challenging to apply in the catheter laboratory and often require a separate pre-operative assessment. In contrast, our method has the advantages of being inexpensive, easily accessible, and applicable. In addition, identifying the LV lead target segments prior to implantation using multimodality imaging techniques alone may not always be effective. Bakos et al. (35) assessed the feasibility of using an integrated bullseye model for presenting data from cardiac computed tomography (CT) and magnetic resonance imaging (MRI) in combination with echocardiography to evaluate segmental mechanical delay for guiding optimal LV lead placement in CRT. STE helped determine the LV segment with the latest mechanical activation. Cardiac CT scan was utilized to anatomically assess CS and its branches. Cardiac MRI was used to evaluate the viability. There was no matching coronary vein in the segment with the latest mechanical delay in 47% of the patients, which indicated the significance of only detecting delays in areas of coronary vein anatomy (35).

In most studies, any two of these methods were used to guide LV lead placement to the latest activated vein remote from scar (26-28). We did not need any additional imaging modalities to guide the lead placement.

ΔQRS after CRT-D implantation is associated with favorable clinical and echocardiographic responses. A meta-analysis by Korantzopoulos et al. (36) showed that QRS narrowing was a positive predictor of response to CRT. Their subgroup analysis showed that QRSd change was more pronounced in studies having a follow-up period of ≤6 months. They did not find any significant differences between studies measuring postimplantation QRSd after a certain follow-up period and those measuring QRSd immediately after CRT-D implantation (36). In our study, surface ECG-guided CRT patients had a shorter QRSd and a greater ΔQRS at 6 months compared with baseline. Our analysis showed that QRSd at 6 months was significantly associated with echocardiographic response to CRT.

Study limitations

This was a single-center study with a small number of patients. Patients with non-LBBB morphology or atrial fibrillation or various comorbidities were excluded. LV lead was inserted into all the available collateral branches to determine the optimal site with the shortest BiV-paced QRSd. Thus, this method can increase the procedure and fluoroscopy times. Also, our method is heavily dependent on the operator' experience. Moreover, to obtain the shortest BiV-paced QRSd, instead of the LV lead, the newly-developed guidewire could be used to enable pacing and sensing at the distal tip before final LV lead implantation (37).

Conclusion

The present study demonstrates that a surface ECG can be used in patients with multiple target veins to guide LV lead place-

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ment to the region with shortest BiV-paced QRSd. It is a safe, feasible, and economic approach for CRT-D implantation.

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