Showa Univ J Med Sci 29(2), 131～139, June 2017

Original

Usefulness of Intracardiac Local Ventricular Electrogram to Predict Responders in Patients Undergoing Cardiac Resynchronization Therapy

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Abstract: Cardiac resynchronization therapy (CRT) is a well-established, efficient strategy for medically-refractory congestive heart failure (HF) with ventricular conduction disturbances. However, about 30% of patients who undergo CRT do not receive any benefit. Therefore, we investigated the usefulness of the QRS-left ventricle (LV) interval for predicting responders during CRT implantation. This study included 66 patients who underwent CRT implantation. The definition of responder was a ≥15% reduction in LV end-systolic volume or ≥20% increase in LV ejection fraction. The QRS-LV interval was measured from the beginning of the body surface electrocardiogram QRS complex to the LV potential recorded by LV leads. We analyzed the correlations between the QRS-LV intervals and CRT responders, admission for HF and mortality. The patients were 67 ± 12 years old, and their mean LV ejection fraction was 26.3% ± 8.3%. During follow-up (27.2 ± 19.9 months), 27 patients were admitted for HF (40.1%), and 17 died (25.7%); the median QRS-LV interval was 103 ± 33 msec. Patients were divided into 2 groups: wide QRS-LV (> 103 msec), and narrow QRS-LV (< 103 msec). The wide QRS-LV group had a lower mortality rate than the narrow QRS-LV group (77% vs. 53%, $P < 0.05$). In patients with dilated cardiomyopathy, the QRS-LV interval was significantly wider in responders, compared to non-responders (112 ± 9.2 vs. 80.0 ± 10 msec, $P < 0.05$). The QRS-LV interval did not correlate with CRT responders or admission for HF. The mortality rate was lower in patients with wide QRS-LV intervals, compared to narrow QRS-LV intervals. Furthermore, a wide QRS-LV interval might be a predictor for CRT responders in patients with dilated cardiomyopathy.

Key words: cardiac resynchronization therapy, ventricular tachycardia, intracardiac electrocardiogram, heart failure

Introduction

Cardiac resynchronization therapy (CRT) is a well-established and efficient strategy for

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medically-refractory congestive heart failure (HF) in patients with wide QRS duration, and this therapy is associated with a reduction of symptoms, improvement of ejection fraction (EF), and decrease in hospitalization and mortality[1-4]. In particular, in patients with left bundle branch block (CLBBB) and wide QRS duration, CRT tends to be effective for left ventricular (LV) reverse remodeling[5]. This suggests that a LV electrical delay might be a factor in predicting CRT responders. However, about 30% of patients who undergo CRT do not receive any benefit from CRT[6,7] and responders cannot be predicted by QRS waveform and QRS duration alone. Furthermore, inadequate selection criteria for identifying potential responders, based on QRS duration, result in a high rate of non-responders. Therefore, this study investigated the relationship between such electrical delay at the LV leads and CRT responders.

Material and methods

Patients and study protocol

This study included 66 patients who underwent CRT implantation from June 2008 to August 2013. The mean follow-up period was 27.2 ± 19.9 months. Patients with advanced HF were New York Heart Association functional class II, III or IV, and had decreased LVEF (40% or less) and wide QRS complexes (> 120 msec). Patients with the following criteria were excluded: (1) patients who did not visit after hospital discharge; (2) history of cardiac surgery within 1 month after implantation; (3) acute myocardial infarction, unstable angina or stroke within 1 month; (4) acute HF; and (5) permanent atrial fibrillation.

Echocardiographic evaluation

Patients underwent echocardiography in the left lateral decubitus position. LVEF and LV end-systolic volume (LVESV) were assessed by the biplane Simpson's equation using the apical 4-chamber and 2-chamber views, before and 6 months after CRT implantation. Patients were classified as responders if their LVEF increased by at least 20%, and/or the LVESV decreased by at least 15% with respect to baseline (variations were considered as relative values). Patients were defined as non-responders if they did not reach both of the above pre-specified echocardiographic changes[8].

Measurements

We measured the QRS-LV interval during sinus rhythm. The QRS-LV interval was defined as the distance measured from the beginning of the QRS complex, recorded by the body surface electrocardiogram (ECG), to the first large positive or negative peak of the LV potential, recorded by the LV leads during CRT implantation (Fig. 1). We calculated the median QRS-LV interval and divided the patients into 2 groups, based on this measurement: wide QRS-LV group (QRS-LV interval > 103 msec), and narrow QRS-LV group (QRS-LV interval < 103 msec). Furthermore, we evaluated the implantable cardioverter-defibrillator therapy after implantation using the device reports. The assessment of shock therapy and anti-tachycardia pacing therapy was also evaluated using the device reports. Two electrophysiologists measured the ECG and echocardiographic data.

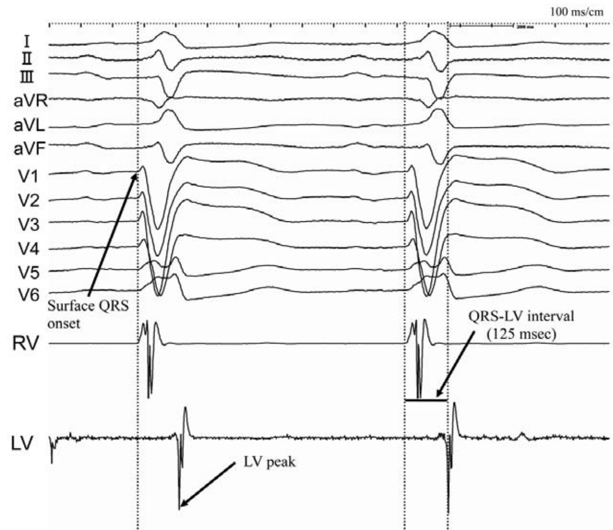

Fig. 1. QRS-LV interval (msec)
Example of QRS-LV interval measurements. The calipers are aligned with the onset of QRS and the peak of the left ventricular electrogram. The QRS-LV interval was calculated as 125 msec for this patient.

CRT-defibrillator (CRT-D) implantation and definitions

The decision to implant CRT-Ds was based on the American College of Cardiology / American Heart Association / Heart Rhythm Society guidelines for device-based therapy of cardiac rhythm abnormalities and the guidelines for non-pharmacotherapy of cardiac arrhythmias published by the Japanese Circulation Society[9, 10]. LV pacing was performed with a lead into a branch of the coronary sinus (n = 66). The LV lead was implanted transvenously via the coronary sinus tributaries and placed preferably to stimulate the lateral or postero-lateral LV wall.

Statistical analysis

Data are presented as mean ± standard deviation. Differences in baseline characteristics between the 2 groups were analyzed using unpaired t tests. Paired t tests were used to compare continuous data within the subgroups during follow-up. P values < 0.05 were considered statistically significant. The authors had full access to and take full responsibility for the integrity of the data.

Results

Patient characteristics

We investigated and analyzed a total of 66 patients which received CRT. Baseline characteristics are summarized in Table 1. There were 56 men and 10 women, and their mean age was 67 ± 12 years. The mean LVEF before CRT was 26.3% ± 8.3%. Twenty patients (30%) had dilated cardiomyopathy (DCM). Medical therapies included beta-blockers (70%), diuretics (89%), angiotensin receptor blockers / angiotensin converting-enzyme inhibitors (67%), and amiodarone (21 %). QRS morphology and ECG findings are summarized in Table 2. Twenty-six patients had CLBBB. The mean QRS duration was 148 ± 26 msec, the mean QRS-LV interval was 103 ± 33 msec, and the median QRS-LV interval was 103 msec.

Table 1. Patient baseline characteristics (n = 66)

Age, mean ± SD, y	67 ± 12
Gender Male	56
Female	10
Cause	
Ischemic heart disease	29 (44%)
Dilated cardiomyopathy	20 (30%)
Other cardiomyopathy	17 (26%)
NYHA II	12 (18%)
III	51 (77%)
IV	3 (5%)
LVEF, mean ± SD, (%)	26 ± 8
Pharmacological treatment	
Beta blocker	43 (70%)
ACE I or ARB	36 (67%)
Diuretics	54 (89%)
Statin	25 (41%)
Amiodarone	14 (21%)

Values are n (%), unless otherwise indicated.
SD, standard deviation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Patient electrocardiogram findings (n = 66)

QRS morphology	
CLBBB	26 (39%)
CRBBB	9 (14%)
Intraventricular conduction delay	21 (32%)
RV pacing	10 (15%)
PQ interval, mean ± SD, msec	204 ± 44
QRS duration, mean ± SD, msec	148 ± 26
QT interval, mean ± SD, msec	446 ± 54
QRS-LV interval, mean ± SD, msec	103 ± 33
Atrial fibrillation	19 (29%)

Values are n (%), unless otherwise indicated.
CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; RV, right ventricular; LV, left ventricular.

Comparison of ECG and clinical characteristics between the 2 groups

The median QRS-LV interval was 103 msec, so we divided patients into 2 groups: wide QRS-LV (QRS-LV > 103 msec) and narrow QRS-LV (QRS-LV < 103 msec). Table 3 shows the comparison of ECG and clinical characteristics between the wide and narrow QRS-LV groups. Thirty-two patients did not have follow-up echocardiography at 6 months due to death or dropout. This included 18 patients from the narrow QRS-LV group and 14 patients from the wide QRS-LV group. Ten of these 32 patients died (9 from the narrow QRS-LV group and one from the wide QRS-LV group) and the remaining 22 patients were dropouts. Therefore the final analysis included 15 patients in the wide QRS-LV group and 19 in the narrow QRS-LV group. CLBBB morphology was more frequent in the wide QRS-LV group, compared to the narrow QRS-LV group (63% vs. 34%, respectively; $P = 0.08$). There were no significant differences for ventricular tachycardia events, or CRT responders or non-responders between the 2 groups.

Comparison of mortality and responders between the 2 groups

Fig. 2 shows the Kaplan–Meier estimates of the percentage of patients remaining free from readmission for HF and all-cause mortality. The X-axis shows the duration of follow-up (days) after CRT. The readmission free rate for HF was 60% in the wide QRS-LV group, and 24% in the narrow QRS-LV group during the follow-up period. Freedom from all-cause mortality was 77% in the wide QRS-LV group, and 53% in the narrow QRS-LV group (log rank test, $P = 0.04$).

Table 3. Characteristics of patients in the narrow and wide QRS-LV interval groups

	Narrow QRS-LV (< 103 msec) (n = 15)	Wide QRS-LV (> 103 msec) (n = 19)	*P* value
QRS morphology			
CLBBB	5 (34%)	12 (63%)	0.08
CRBBB	2 (13%)	1 (5%)	0.40
Intraventricular conduction delay	8 (53%)	2 (11%)	0.005
RV pacing	0 (0%)	4 (21%)	0.002
PQ interval, mean ± SD, msec	194 ± 42	203 ± 44	0.90
QRS duration, mean ± SD, msec	132 ± 25	158 ± 18	0.006
QT interval, mean ± SD, msec	443 ± 62	462 ± 51	0.30
Ventricular tachycardia event	2 (13%)	4 (21%)	0.50
Responder	6 (40%)	11 (58%)	0.22
Non-responder	9 (60%)	8 (42%)	0.22

Values are n (%), unless otherwise indicated. Thirty-two patients were not included in the final analysis due to death or dropout (18 patients from the narrow QRS-LV group, and 14 from the wide QRS-LV group). Of these 32 patients, 10 died, including 9 from the narrow QRS-LV group (heart failure [7], sudden death [1], ventricular tachycardia [1]), and 1 from the wide QRS-LV group (cancer); 22 patients dropped out of the study.
LV, left ventricular; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; RV, right ventricular; SD, standard deviation.

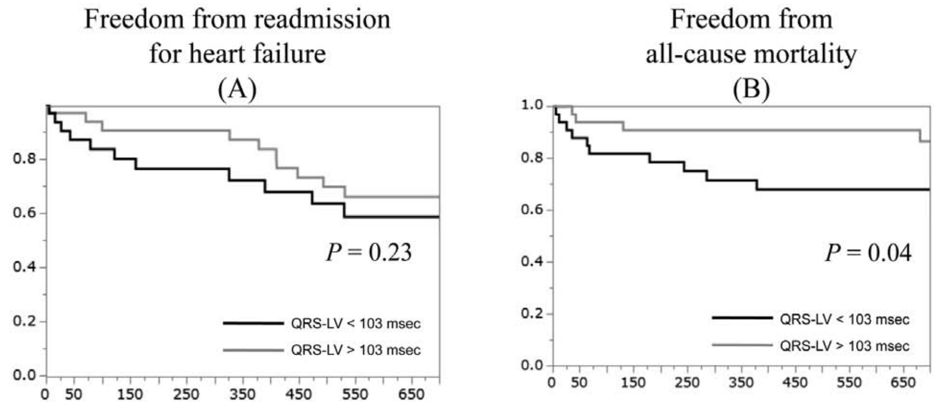

Fig. 2. Kaplan–Meier estimates of the percentage of patients remaining free from readmission for heart failure (A) and all-cause mortality (B) for the wide and narrow QRS-LV interval groups. The X-axis shows follow-up in days, after cardiac resynchronization therapy-defibrillator implantation.

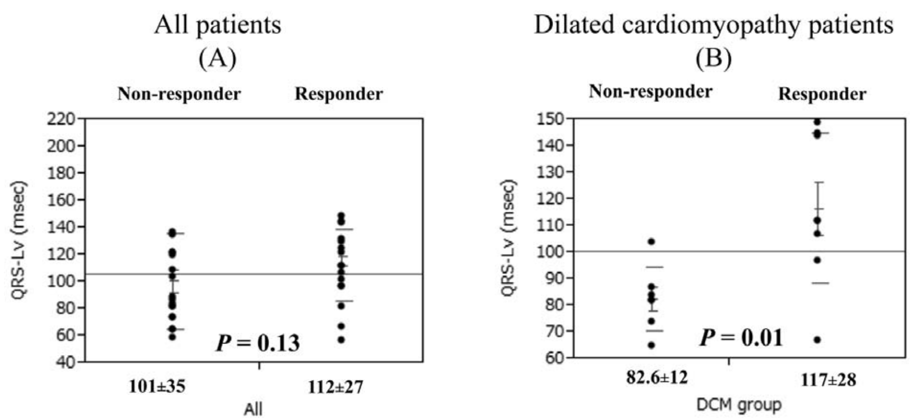

Fig. 3. Scatter plot of the QRS-LV interval between cardiac resynchronization therapy responders and non-responders in all patients (A) and in dilated cardiomyopathy (DCM) patients (B).

Fig. 3 shows the relationship between QRS-LV interval and CRT responders for all patients and patients with DCM. In patients with DCM, CRT responders had a significantly wider QRS-LV interval, compared to the non-responders (117 ± 28 msec vs. 83 ± 35 msec, respectively; $P = 0.01$). In the DCM patients, 9 had CLBBB (45%), two had CRBBB (10%), 8 had intraventricular conduction delay (40%), and 1 had RV pacing (5%).

Discussion

Main findings

The most important finding of this study is that freedom from all-cause mortality was higher in patients with a wide QRS-LV interval (QRS-LV interval > 103 msec), compared to a narrow QRS-LV interval. In patients with DCM, CRT responders had a significantly wider QRS-LV interval than non-responders. Furthermore, CLBBB morphology was more frequent in the wide QRS-LV group, compared to the narrow QRS-LV group.

CRT responders and non-responders

CRT is a rapidly evolving therapeutic modality for patients with severe HF and intraventricular conduction delays. Furthermore, Gold *et al*[11)] reported that ventricular tachycardia was lower in patients whose LVESV decreased by at least 15% after CRT, compared to those whose LVESV did not decrease by 15%. These results suggest that effectiveness of CRT could be assessed by LVEF improvement and LVESV reduction. However, when defining CRT responders as those with an increased LVEF of at least 20% , and / or a decrease in LVESV of at least 15%, with respect to baseline, about 30% of patients fail to show improvement in clinical symptoms[12, 13)], and 40%–50% of patients have no improvement in LV function on echocardiography[14, 15)], Moreover, sophisticated echocardiographic studies have failed to predict appropriate candidates for CRT[16)]. Bonakdar *et al*[17)] described that not only baseline QRS duration but also QRS narrowing immediately after CRT can predict long-term response. In addition, acute hemodynamic improvement post-implant might predict long-term responders[17)].

In our study, patients in the wide QRS-LV group had wider QRS durations, compared to the narrow QRS-LV group. However, the QRS-LV interval on local ventricular ECG was not clearly associated with responders.

Association of QRS-LV interval and CRT responders

One important benefit of CRT is to achieve more synchronicity in the electrically-delayed LV area[18)]. CLBBB and QRS duration have been used to determine the adaption of CRT, however, some patients with prolonged QRS duration receive few benefits from CRT. Furthermore, optimal LV lead pacing sites are controversial. Butter *et al*[19)] reported that the lateral position was associated with a better outcome. The MADIT-CRT trial suggested that apical leads were associated with worse outcomes, rather than non-lateral leads, however, other studies have shown that apical leads can be optimal pacing sites[20–22)]. Anatomical position, CLBBB and QRS duration cannot determine an adequate LV lead position. In our study, DCM patients had a higher CRT response rate than all other patients, regardless of CLBBB. QRS duration shows total ventricular excitement, whereas the electrical potential of the LV leads indicate delay potential in the local LV area. Therefore, the QRS-LV interval might be useful for finding the delayed LV area, allowing us to determine the adequate LV pacing point. Furthermore, patients who were CRT responders were likely to have LV reverse remodeling. The study by Gold *et al*[23)] supports this suggestion. To ensure a good response to CRT, it is desirable to have an indicator that reflects the degree of delayed LV activation at the pacing site. The QRS-LV interval is such an index. The QRS onset is the earliest ventricular activation which usually starts in the septum. Thus the QRS-LV interval reflects the time that it takes for the ventricular depolarization wave front to reach the LV electrode site, and thus synchronization would occur with pacing at that site. It is intriguing to speculate that this could be utilized during the implant procedure to determine an area of late activation by repositioning the LV electrode and examining the QRS-LV value at different locations.

Association of QRS-LV interval and mortality

Previous studies reported that patients with CLBBB and a wide QRS duration (150 msec or greater) had lower risks of mortality and all-cause mortality, and cardiovascular and HF readmission, than those with QRS durations of 120–149 msec. CLBBB plus wide QRS duration was a predictor of a better CRT outcome[5, 17]. The relationship between the degree of electrical LV activation delay and QRS was strong[13], suggesting that QRS-LV could be an electrical LV delay indicator, and that the QRS-LV interval may reflect the effectiveness of CRT. Therefore, in our study, the wide QRS-LV group had a lower mortality than the narrow QRS-LV group.

Study limitations

The study has several limitations. First, the number of patients was relatively small. However, we believe that this study is an adequate evaluation as there was a significant difference between the wide and narrow QRS-LV interval groups. Second, this study was a retrospective observational analysis of prospectively assessed data evaluating QRS-LV interval. Further prospective studies will be required to ascertain the relationship between the QRS-LV interval and CRT responders.

Conclusions

The wide QRS-LV group (> 103 msec) had a lower mortality rate than the narrow QRS-LV group. In patients with DCM, the QRS-LV interval was significantly wider in the CRT responder group, compared to the non-responder group. Therefore, a wide QRS-LV interval might be associated with a favorable outcome.

Conflict of interest

The authors have declared no conflict of interest.

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[Received January 5, 2017 : Accepted January 18, 2017]