ORIGINAL ARTICLE

Notched QRS Complex in Lateral Leads as a Novel Predictor of Response to Cardiac Resynchronization Therapy

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Backgrounds: Notched QRS (nQRS) may be an indicator of ventricular delay. There are very few studies investigating the value of nQRS. The aim of the study was to identify the predictive value of nQRS for response to cardiac resynchronization therapy (CRT).

Methods: Eighty-two patients with heart failure (HF) and widened QRS (≥ 120 ms) were implanted with a CRT device. nQRS was defined as presence of ≥ 2 R waves, or ≥ 1 notch in the R wave or S wave in ≥ 2 contiguous leads. Response to CRT was defined as percentage of left ventricular end-systolic volume (LVESV) reduction after 6 months CRT ($\Delta\text{LVESV}\%$) $\geq 15\%$.

Results: nQRS was presented in 62 (76%) patients, 16 of whom had nQRS in anterior leads, 47 in inferior leads, and 42 in lateral leads. The rate of CRT response (65% vs 50%, $P = 0.29$) and $\Delta\text{LVESV}\%$ ($21.7 \pm 31.7\%$ vs $7.9 \pm 25.4\%$, $P = 0.09$) were not different between patients with and without nQRS. But the rate of CRT response was higher in patients with nQRS in lateral leads (nQRS-L) than in those without nQRS-L (76% vs 45%, $P = 0.006$). $\Delta\text{LVESV}\%$ was greater in patients with nQRS-L than in those without nQRS-L ($25.2 \pm 34.3\%$ vs $10.1 \pm 24.5\%$, $P = 0.004$). After adjusting for potential confounders including QRS duration, presence of nQRS-L still predicted positive CRT response (OR = 4.04, $P = 0.009$).

Conclusions: nQRS-L may be a novel predictor of response to CRT in patients with HF and widened QRS. Large-scale studies are needed to confirm this prognostic value of nQRS-L.

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notch; QRS complex; cardiac resynchronization therapy; response

INTRODUCTION

During the past 10 years, the benefits of cardiac resynchronization therapy (CRT) for patients with reduced left ventricular systolic function and prolonged QRS have been well established.^{1–4} CRT has been confirmed to improve left ventricular systolic function, reverse left ventricular remodeling, improve clinical symptoms as well as reduce mortality.^{1–4} However, even using

the well-recognized criteria to select patients for CRT,⁵ the rate of CRT response is just about 60–70%,^{6–8} which varies when using different response criteria.⁸ Therefore, determination of predictors of response to CRT is of important clinical significance.

Numerous echocardiographic parameters of ventricular dyssynchrony have been explored, but none has emerged as a predictor of response to CRT in a multicenter study.⁶ QRS duration

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has been used to select patients for CRT since early 2000s, while many studies have focused on the potential value of QRS duration in predicting CRT response. However, the performance of QRS duration to predict CRT response in heart failure patients with widened QRS duration is unimpressive, because the results of these studies have been conflicting.^{9–11} QRS morphology seems to be able to identify patients who benefit from CRT, as shown by a recent study, which documented that no clinical benefit was observed in patients with right bundle-branch block (RBBB) or intraventricular conduction delay (IVCD).¹² Another recent study found that greater longest baseline left ventricular activation time and smaller scar volume on electrocardiogram (ECG) combined with wavefront fusion on the paced ECG, anticipate higher probability of reverse remodeling.¹³

QRS complex notch is frequently seen in bundle branch block, which may be due to nonuniform depolarization of the ventricles. There are very few studies investigating the value of QRS complex notch up to now. One study found that there was an association between QRS notch and interventricular delay.¹⁴ The value for notched QRS (nQRS) to predict CRT response has not been investigated. We postulated that nQRS is an indicator of ventricular delay and associated with good response to CRT. Accordingly, the aim of the study was to determine the predictive value of nQRS for response to CRT in patients with heart failure and widened QRS.

METHODS

Patients Selection

The prospective, observational study involved consecutive patients referred to our department for CRT implantation from January 2008 to January 2011. The inclusion criteria were as follows: (1) congestive heart failure patients remained symptomatic in New York Heart Association class (NYHA) III or stable class IV, despite optimal pharmacological therapy; (2) left ventricular ejection fraction $\leq 40\%$; (3) left ventricular diastolic diameter ≥ 56 mm; and (4) QRS duration ≥ 120 ms. The exclusion criteria were: (1) RBBB (a terminal R wave in lead V_1 , and a wide S waves in leads I and V_6)¹⁵ or RBBB type IVCD ($R/S > 1$ in leads V_1

and V_2); (2) pacemaker implantation; (3) expected longevity < 1 year; (4) severe renal dysfunction (serum creatinine > 3 mg/dL); (5) atrial fibrillation or flutter; and (6) age < 18 years. The study was approved by Biomedical Research Ethics Committee of Zhongshan Hospital and in accordance with the Declaration of Helsinki. Because this was an observational study and all examinations included in the study were commonly performed for all patients in our department, the need for written informed consent was waived by the ethical review board.

CRT Device Implantation and Follow-Up

All patients were implanted with a biventricular cardiac pacemaker (Frontier, St. Jude Medical, St. Paul, MN, USA or InSync III, Medtronic, Minneapolis, MN, USA). Left ventricular pacing was obtained transvenously using a unipolar lead generally in the lateral or posterolateral cardiac vein. But in a few patients in whom placement of left ventricular lead in the both veins was difficult, the lead was implanted in middle or great cardiac vein. The right ventricular and right atrial leads were placed in right ventricular apex and right appendage, respectively. CRT devices were commonly programmed with an atrioventricular sensed delay of 100 ms and paced delay of 130 ms. The VV offset was programmed at 0 m second. AV and VV optimization was performed in nonresponsive patients with refractory heart failure or worsening functional status during follow-up (1, 3, 6 months). Standard antiheart failure medications were given to the patients.

ECG

Standard 12-lead ECG (filter 0.16–100 or 0.16–150 Hz, 25 mm/s, 10 mm/mV) were performed in all patients before CRT implantation. The ECGs were analyzed by two blinded cardiologists (WP and WZ) for the presence of nQRS and fragmented (fQRS). In rare instances of disagreement, the ECG was reviewed by two reviewers and a consensus decision reached. The QRS complexes included in the studies were the supraventricular beats but not the ventricular premature beats or pacing beats. In order to avoid the effect of heart rate on intraventricular conduction, the interval between the QRS complexes for analysis should be large than 600 ms. nQRS was defined as presence of ≥ 2 R

Figure 1. Four types of notched QRS complex in lateral leads. Because we just included left bundle branch block or left bundle branch block type intraventricular conduction delay patients, the QRS complexes in all lateral leads (I, aVL, V₆) presented as R or RsR' configurations. nQRS was defined as presence of ≥ 2 R waves, or ≥ 1 notch in the R wave in ≥ 2 contiguous leads. Type 1 A had two notch in the peak of the R wave. Type 1 B had a small spike in the peak of the R wave. Type 2 had a notch in the downstroke and type 3 had a notch in the upstroke of the R wave, while A denoted a large notch (height of the notch ≥ 0.05 mv) and B a small notch (height of the notch < 0.05 mv). Type 4A had RsR' configurations and 4B had more than 2 R waves (fragmented QRS).

waves, or ≥ 1 notch in the R wave or S wave in ≥ 2 contiguous leads defined as follows: anterior (V1-V5), lateral (I, aVL, V₆), and inferior (II, III, aVF). Figure 1 shows four types of nQRS in lateral leads (nQRS-L). QRS complexes without any notch in ≥ 2 contiguous leads were defined as smooth QRS (sQRS). Patients having nQRS-L, whether having single or multiple nQRS territories, were assigned to nQRS-L subgroup for subgroup analysis, and the others patients were assigned to sQRS-L group. Presence of > 2 R waves, > 2 notches in the R wave, or > 2 notches in the downstroke or upstroke of the S wave in 2 contiguous leads was defined as fQRS.¹⁶

Echocardiography

Echocardiography were performed with a commercially available GE vidvid 7 (GE Healthcare, Milwaukee, WI, USA) and a 1.7–3.4 MZ probe. Left ventricular end-diastolic, systolic volumes (LVESV) and left ventricular ejection fraction were measured with Simpson's method. We calculated the percentage of LVESV reduction after 6 months CRT (Δ LVESV%) using the following formula: Δ LVESV% = [(LVESV before - LVESV after)/LVESV before] * 100%. Response to CRT was defined as LVESV % $\geq 15\%$.^{6, 17, 18}

Statistical Analysis

Continuous variables and categorical variables were presented as mean value $\pm$ SD and %, respectively. The data between groups were compared with unpaired Student's *t*-test or Mann-Whitney test for continuous variables and chi-square or Fisher's exact tests for categorical variables. A forward stepwise multivariate logistic regression was conducted to determine the independent predictors of response to CRT. A criterion of $P < 0.05$ for entry and a $P \geq 0.10$ for removal was imposed in this procedure. We also performed the multivariate logistic regression to adjust the correlation between nQRS-L and CRT response. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with SPSS 13.0 software (SPSS, Inc, Chicago, IL, USA).

RESULTS

Baseline Characteristics

There were 86 patients enrolled in this study at baseline. Two of them died with in 6 months after CRT implantation, and two were lost to follow-up.

Table 1. Comparisons of Baseline Characteristics and CRT Response between Patients with nQRS and sQRS

	Total (N = 82)	nQRS (N = 62)	sQRS (N = 20)	P
Age (years)	62.6 ± 11.8	63.2 ± 11.7	61.0 ± 12.1	0.48
Male (n, %)	65 (79%)	46 (74%)	19 (95%)	0.06
Ischemic heart disease (n, %)	5 (6%)	4 (6%)	1 (5%)	1.00
Hypertension (n, %)	9 (11%)	7 (11%)	2 (10%)	1.00
Diabetes (n, %)	10 (12%)	9 (14%)	1 (5%)	0.44
NYHA class III/IV (n, %)	67/15 (82%/18%)	53/9 (85%/15%)	14/6 (70%/30%)	0.18
LVEF (%)	30.5 ± 7.6	29.9 ± 7.8	32.3 ± 6.7	0.22
LVESV (mL)	213.7 ± 125.7	213.8 ± 117.0	213.1 ± 152.8	0.98
LVEDV (mL)	309.5 ± 161.0	305.9 ± 145.6	320.7 ± 205.5	0.72
Mitral regurgitation (grades)	1.8 ± 0.8	1.9 ± 0.8	1.7 ± 0.9	0.46
NT-proBNP (pg/mL)	2563 (550–14,780)	2502 (499–1360)	3855 (550–16,189)	0.44
QRS duration (ms)	164.5 ± 25.6	170.9 ± 23.5	144.6 ± 21.3	0.00
IVCD/CLBBB (n, %)	15/67 (18%/82%)	9/53 (15%/85%)	6/14 (30%/70%)	0.18
LV lead placement (n, %)				0.57
Lateral or posterolateral vein	69 (84%)	52 (84%)	17 (85%)	
Middle cardiac vein	10 (12%)	7 (11%)	3 (15%)	
Great cardiac vein	3 (4%)	3 (5%)	0 (10%)	
Serum creatine (mmol/L)	94.7 ± 24.6	93.7 ± 24.9	97.7 ± 23.7	0.54
Hemoglobin (g/L)	133.3 ± 15.4	132.8 ± 15.2	134.5 ± 16.2	0.69
Medication (n, %)				
ACEI/ARB	77 (91%)	59 (95%)	18 (90%)	0.59
Diuretics	82 (100%)	62 (100%)	20 (100%)	1.00
Beta blocker	73 (89%)	56 (90%)	17 (86%)	0.68
Digoxin	78 (92%)	60 (98%)	18 (90%)	1.00
Nitrates	23 (27%)	16 (26%)	7 (35%)	0.57
Antiarrhythmic drugs (n, %)	9 (11%)	7 (11%)	2 (10%)	1.00
CRT response (n, %)	50 (61%)	40 (65%)	10 (50%)	0.29
ΔLVESV%	21.2 ± 31.5%	21.1 ± 31.7%	7.9 ± 25.4%	0.09

nQRS = notched QRS; sQRS = smooth QRS; NYHA = New York heart association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; IVCD = intraventricular conduction delay; CLBBB = complete left bundle branch block; ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor antagonists; CRT = cardiac resynchronization therapy; ΔLVESV% = the percentage of LVESV reduction after 6 months CRT.

And thus, a total of 82 patients were included in the analysis. The mean age of the patients was 62.6 ± 11.8 years, and 79% of them were male, 6% patients had ischemia heart disease, 82% had left bundle branch block (LBBB), and 18% had LBBB type intraventricular conduction delay. The mean left ventricular ejection fraction was 30.5 ± 7.6%, LVESV was 213.7 ± 125.7 mL, LVEDV was 309.5 ± 161.0 mL, and QRS duration was 164.5 ± 25.6 ms. Other characteristics are given in Table 1.

Detections of nQRS and fQRS

nQRS was presented in 62 (76%) patients, 16 of whom had nQRS in anterior leads, 47 in inferior leads, and 42 in lateral leads, while fQRS just occurred in 14 patients (17%, $P < 0.01$ as compared with nQRS). Twenty-five (40%) patients of them had single nQRS territory while 37 (60%) had multiple territories. There was a 93% (77/82)

concordance for the detection of nQRS, 98% (80/82) concordance for nQRS-L, and 98% (80/82) concordance for fQRS.

Relation between nQRS and fQRS to CRT Response

Patients with nQRS had longer QRS duration (170.9 ± 23.5 ms vs 144.6 ± 21.3 ms, $P < 0.01$) than those with sQRS. Other baseline characteristics were similar between the both groups (Table 1). The rate of CRT response was not significantly different between patients with nQRS and sQRS (65% vs 50%, $P = 0.29$). The ΔLVESV% in patients with nQRS was also not different from that in sQRS patients (21.7 ± 31.7% vs 7.9 ± 25.4%, $P = 0.09$). There were no significant difference in the rate of CRT response (57% vs 63%, $P = 0.77$) and ΔLVESV% (19.5 ± 21.9 vs 17.5 ± 32.3; $P = 0.83$) between patients with and without fQRS.

Subgroup Analysis

The rate of CRT response and Δ LVESV% were not significantly different between patients with IVCD and LBBB (response rate: 53% vs 63%, $P = 0.56$; Δ LVESV%: $19.2 \pm 31.6\%$ vs $11.7 \pm 26.3\%$; $P = 0.39$), or between female and male patients (response rate: 65% vs 60%, $P = 0.79$; Δ LVESV%: $26.2 \pm 31.9\%$ vs $15.7 \pm 30.2\%$, $P = 0.21$). We then further examined the relation between presence of nQRS in anterior, inferior, or lateral leads and CRT response. The rate of CRT response and Δ LVESV% were not significantly different between patients with and without nQRS in anterior leads (response rate: 63% vs 61%, $P = 1.00$; Δ LVESV%: $26.8 \pm 25.7\%$ vs $15.7 \pm 31.6\%$, $P = 0.20$) or in inferior leads (response rate: 64% vs 57%, $P = 0.65$; Δ LVESV%: $16.6 \pm 28.3\%$ vs $18.8 \pm 32.7\%$, $P = 0.75$).

Relation between nQRS-L and CRT Response

Patients with nQRS-L were older (65.2 ± 10.8 vs 60.0 ± 12.3 years, $P = 0.045$) and more likely to be female (10% vs 31%, $P = 0.03$), and had longer QRS duration (172.7 ± 20.3 ms vs 155.8 ± 27.8 ms, $P < 0.01$) and lower percentage of IVCD (7% vs 30%, $P = 0.01$) as compared with sQRS-L patients. Other baseline characteristics were comparable between the both groups (Table 2). The rate of CRT response was significantly higher in patients with nQRS-L than in those with sQRS-L (76% vs 45%, $P = 0.006$), and Δ LVESV% was greater in patients with nQRS-L than in those with sQRS-L ($25.2 \pm 34.3\%$ vs $10.1 \pm 24.5\%$, $P = 0.004$). Stepwise multivariate regression, including nQRS-L, intraventricular conduction delay, left ventricular ejection fraction, LVESV, QRS duration, age, and sex as independent variables, showed that only nQRS-L (OR = 3.91, $P = 0.005$) was a predictor of CRT response. Even after adjusting for QRS duration, presence of nQRS-L still predicted positive CRT response (OR = 3.74, $P = 0.009$); when adjusting for QRS duration, IVCD, and sex, this trend (OR = 4.04, $P = 0.009$) still existed.

DISCUSSION

The primary finding of the present study was that nQRS-L may be a novel predictor of response to CRT in patients with heart failure

and widened QRS. Patients with nQRS-L had a response rate of 76%, while response rate in those with sQRS-L was just 45%. Even adjusting for QRS duration, IVCD, and sex, nQRS-L still excellently predicted response to CRT. nQRS and fQRS in any continuous leads failed to predict outcome. Since nQRS-L can be easily and conveniently detected by common ECG, the findings of our study may have important clinical implications.

Although QRS notch is frequently seen in patients with cardiac structural changes or intra-ventricular conduction delay, we have not been concerned about its values until recently. In narrow QRS complexes (<120 ms), an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of more than one R' wave in ≥ 2 contiguous leads is defined as fQRS.¹⁹ In wide QRS complexes (≥ 120 ms), fQRS is defined as the presence of >2 R waves, >2 notches in the R wave, or >2 notches in the downstroke or upstroke of the S wave in ≥ 2 contiguous leads.¹⁶ fQRS, whether narrow or wide, has been confirmed to represent myocardial scar and predict poor prognosis.^{16,19} fQRS may be an indicator of local conduction delay and has been showed to be associated with intraventricular systolic dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS, indicating that fQRS might be useful in identifying patients who could benefit from CRT.²⁰ However, a recent study failed to confirm the predictive value of fQRS in CRT.²¹ In the present study, we defined nQRS as the presence of ≥ 2 R waves, or ≥ 1 notch in the R wave or S wave in ≥ 2 contiguous leads. We found that nQRS was more frequently seen than fQRS in heart failure patients with widened QRS, and the predictive value of nQRS was much stronger.

Normal ventricular depolarization includes three phases: depolarization of interventricular septum (phase 1), depolarization of free wall of right ventricle (phase 2), and depolarization of free wall of left ventricular (phase 3).²² Phases 2 and 3 normally occur simultaneously and are in almost opposite directions. As a result, only the net vector is registered on the surface ECG and the QRS configuration is often smooth.¹⁹ In patients with LBBB, the phase 3 is delayed and left ventricular depolarization generates a higher voltage potential on the surface ECG, due to the absence of the opposing effect of simultaneous right ventricular depolarization. This effect will lead to prolongation

Table 2. Comparisons of Baseline Characteristics and CRT Response between Patients with nQRS-L and sQRS-L

	sQRS-L (N = 40)	nQRS-L (N = 42)	P
Age (years)	60.0 ± 12.3	65.2 ± 10.8	0.045
Male (%)	36 (90%)	29 (69%)	0.03
Ischemic heart disease (n, %)	3 (8%)	2 (5%)	0.67
Hypertension (n, %)	4 (10%)	5 (12%)	1.00
Diabetes (n, %)	3 (8%)	7 (17%)	0.31
NYHA III/IV (n, %)	32 (80%)/8 (20%)	35 (83%)/7 (17%)	0.78
LVEF (%)	31.2 ± 8.2	29.8 ± 6.9	0.38
LVESV (mL)	213.7 ± 143.9	213.6 ± 107.2	1.00
LVEDV (mL)	313.5 ± 181.5	305.7 ± 140.7	0.83
Mitral regurgitation (grades)	1.9 ± 0.8	1.8 ± 0.8	0.48
NT-proBNP (pg/mL)	3855 (550–16,189)	2855 (451–8051)	0.08
QRS duration (ms)	155.8 ± 27.8	172.7 ± 20.3	0.00
IVCD/CLBBB (n, %)	12/28 (30%/70%)	3/39 (7%/93%)	0.01
LV lead placement (n, %)			0.71
Lateral or posterolateral vein	34 (85%)	35 (83%)	/
Middle cardiac vein	4 (10%)	6 (14%)	/
Great cardiac vein	2 (5%)	1 (2%)	/
Serum creatine (mmol/L)	96.3 ± 20.1	93.2 ± 20.3	0.56
Hemoglobin (g/L)	132.7 ± 14.1	133.9 ± 16.6	0.72
Medication (n, %)			
ACEI	37 (93%)	40 (95%)	0.67
Diuretics	40 (100%)	42 (100%)	1.00
Beta-blocker	35 (88%)	38 (91%)	0.74
Digoxin	39 (98%)	39 (93%)	0.62
Nitrates	12 (30%)	11 (26%)	1.00
Antiarrhythmic drugs (n, %)	3 (8%)	6 (14%)	0.48
CRT response (n, %)	18 (45%)	32 (76%)	0.006
ΔLVESV%	10.1 ± 24.5%	25.2 ± 34.3%	0.004

nQRS-L = notched QRS in lateral leads; sQRS-L = smooth QRS in lateral leads. Other abbreviations as in Table 1.

of QRS duration as well as an additional R wave or a notch in QRS complex, which is frequently seen in these patients. This phenomenon is more obvious in lateral leads because the left ventricular posterolateral wall is generally depolarized last in complete LBBB. In a small part of patients with complete LBBB, there is no QRS notch in lateral leads. It may due to the time delay between left ventricular lateral wall and right ventricle depolarization is short. Rodriguez et al.²³ identified two patterns of LBBB activation based on endocardial matching: first one—initial activation of LV in mid-septal in the vicinity of posterior fascicular bundle resulting in slow activation of LV via left bundle block, and second one—initial activation in the high septum which results in conduction through the whole ventricular tissues. Regarding the first pattern, it would be more physiologic, 12-lead ECG still would demonstrate LBBB but smooth QRS, and there would be less mechanical dyssynchrony. Second pattern would result in more prolonged QRS, more notches on LBBB, and more mechanical dyssynchrony. So CRT works better when there

is notched QRS—smooth QRS has relatively less mechanical dyssynchrony and notched QRS has more mechanical dyssynchrony.

Several limitations existed in the present study. First, the scale of the study was small. Large-scale studies are needed to confirm the results of our study. Similarly, because of the small scale of the study, we cannot check whether “concordance” between left ventricular lead and nQRS-L predicted CRT response. Second, we did not include patients with RBBB or RBBB type IVCD and the etiology of heart failure was mostly nonischemic cardiomyopathy. Thus, the results of our study may not be applied to these patients. The baseline left ventricular ejection fraction was 30.5%, which was greater than previous studies.^{1–4} Future studies are needed to confirm this prognostic value of nQRS-L in patients with a lower left ventricular ejection fraction. Third, nQRS-L can be classified to at least four types as we described, which type of nQRS-L was best for clinical applications was not investigated due to small sample size. Future studies should better

define the difference between different types of nQRS-L.

CONCLUSION

nQRS-L may be a novel predictor of response to CRT in patients with heart failure and widened QRS. However, because the scale of the study was small and the etiology of heart failure in the patients was mostly nonischemic cardiomyopathy, large-scale studies are needed to confirm this prognostic value of nQRS-L.

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