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Preoperative QRS Duration Predicts the Responsiveness of Chronic Heart Failure Patients with Pacemaker Indications to Left Bundle Branch Area Pacing Treatment

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ABSTRACT

Background: This study investigated the predictive value of preoperative QRS duration (QRSd) in responsiveness of chronic heart failure (CHF) patients with pacemaker indications to the left bundle branch area pacing (LBBAP).

Methods: Thirty-one CHF patients with cardiac function categorized as NYHA class II or above and indications for pacemaker therapy who successfully underwent LBBAP treatment were enrolled in this study. Based on the 12-month postoperative responsiveness to treatment, patients were divided into a responsiveness group ($N = 16$) and a no-responsiveness group ($N = 15$). Data from all patients were collected for analysis. Multivariate binary logistic regression analysis was used to determine the independent factors associated with the responsiveness to LBBAP treatment.

Results: Among the 31 patients with LBBAP, 16 patients (51.6%) responded to the treatment, and 15 patients (48.4%) had no response. There were significant differences between the two groups with regard to complete left bundle branch block (CLBBB), preoperative QRSd, and preoperative left ventricular peak time (LVAT). Univariate logistic regression analysis showed that CLBBB, preoperative QRSd, and preoperative LVAT all were significantly correlated with responsiveness to LBBAP. Multivariate binary logistic regression analysis showed that QRSd was an independent predictor of responsiveness to LBBAP. The maximum area under the ROC curve for QRSd was 0.827 (95%C.I.:0.663-0.991), the maximum Youden index was 0.679, with the optimal cutoff point of QRSd ≥ 153 ms, a sensitivity of 81.3%, and a specificity of 86.7%.

Conclusion: Preoperative QRSd predicts the responsiveness of CHF patients with pacemaker indications to LBBAP.

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INTRODUCTION

Chronic heart failure (CHF), characterized by impaired cardiac pump function [Tan 2010], is the end-stage cardiac disease of a variety of cardiovascular disorders, including coronary heart disease, dilated cardiomyopathy, hypertension, diabetes, and valvular diseases [Ramani 2010], with variable clinical manifestations, including dyspnea, fatigue and fluid retention. CHF is significantly associated with high mortality, morbidity, and poor quality of life. Globally, the prevalence of CHF is increasing due to expansion of the aging population [Savarese 2017]. Currently, there is no cure for CHF except heart transplantation, which is not only technically challenging but also associated with considerable expenses. The objectives of primary treatment for CHF are to alleviate the clinical symptoms of CHF, delay the progression of CHF, and improve patient quality of life.

CHF patients often have extensive fibrosis of the cardiac tissue, which may interfere with the electrical conduction system. As such, one of the major complications linked to CHF is bradyarrhythmia, including sick sinus syndrome, atrioventricular block, and bundle branch block (BBB), the latter of which includes right bundle branch block (RBBB) and left bundle branch block (LBBB) [Sidhu 2020]. Bradycardia may further exacerbate CHF, thus increasing mortality and morbidity. Currently, right ventricular pacing (RVP) is a safe and effective treatment for bradycardia. However, long-term RVP can cause asynchrony of left and right ventricular contractions, thereby increasing the risk of atrial fibrillation and deteriorating HF [Lamas 1998; Lamas 2002; Toff 2005]. Compared with RVP, biventricular pulse pacing (BVP), which is based on cardiac resynchronization therapy (CRT) for patients with impaired cardiac function with a high pacing ratio, can reduce mortality and HF rehospitalization rates and improve patient quality of life [Curtis 2013]. However, 30% of patients who receive CRT do not respond to treatment [Naqvi 2018]. Left bundle branch area pacing (LBBAP), as an alternative to CRT, has lower and more stable pacing parameters and a shorter QRS duration (QRSd), which can increase the left ventricular ejection fraction (LVEF) and improve patient outcomes [Vijayaraman 2021]. Previous studies mainly investigated the predictors of response to BVP [Chung 2008], but not to LBBAP, although patients with poor response to LBBAP treatment were still reported [Li 2020]. Therefore, it is imperative to identify the factors that may be used to predict which patients will not respond to LBBAP treatment so that they may be managed more appropriately in the clinic.

This study explored the factors related to the responsiveness of CHF patients with pacemaker implantation indications for LBBAP therapy.

MATERIALS AND METHODS

Patient selection: This retrospective study recruited a total of 31 CHF patients with cardiac function categorized as New York Heart Function (NYHA) class II and above and pacemaker therapy indications (bradyarrhythmia), who successfully underwent LBBAP treatment in the Department of Cardiology at The First Affiliated Hospital of Bengbu Medical College between October 2018 and September 2020. The inclusion criteria were as follows: 1) indications for pacemaker therapy, 2) CHF [McDonagh 2021], and 3) symptoms after receiving standard anti-heart failure drugs for 3 months before surgery. Patients who had one of the following conditions were excluded from this study: 1) no indication for pacemaker therapy, 2) incomplete follow-up data, 3) follow-up time of less than 12 months, and 4) malignant tumors and severe liver and kidney failure. Demographic and baseline clinical characteristics of all patients, including gender, age, history of underlying diseases, medications, preoperative electrocardiogram, chest X-ray, cardiac color Doppler ultrasound, and blood levels of NT-proBNP, were collected from the hospital database.

LBBAP procedure: All patients were prophylactically administrated antibiotics 30 minutes before surgery and underwent local anesthesia with 1% lidocaine. The left axillary vein or the left subclavian vein was punctured under the guidance of digital subtraction angiography (DSA) and implanted with an 8F tear-away sheath. A C315 His sheath (Medtronic) was inserted through the tear-away introducer sheath, and A 3830 pacing electrode lead (Medtronic) was then inserted through the His sheath. First, the potential of the His bundle was measured, the His bundle was connected to the apex of the heart, and then the electrode was moved forward and downward along this line by 10-20 mm. Under 5V pacing, the intracardiac electrogram showed a W-shape. The C315 sheath was then adjusted to be perpendicular to the septum, the 3830 electrode was placed under the left ventricular endocardium surface, and the 3830 electrode lead was connected to the pulse generator. Surgical success criteria were described previously [Huang 2019]: 1) the pacing electrocardiogram showed an incomplete RBBB pattern, 2) there was a selective LBBAP or an increase in the output voltage, the left ventricular peak time (LVAT) was suddenly shortened by ≥10 ms, and 3) the pacing parameters were stable.

Follow up: In accordance with the requirements of pacemaker program control, the program control was performed once at 1, 3, 6 and 12 months in the first year post-operation and once every year thereafter. Program control examination included pacing threshold, perception, and impedance. Electrocardiogram (EKG), chest X-ray, cardiac color Doppler ultrasound (UCG), and determination of blood levels of NT-proBNP were performed 12 months after the LBBAP procedure. Any symptoms and medications related to HF were collected and used to determine the state of cardiac function.

EKG analysis: A standard 12-lead EKG machine was used to trace the patient's EKG with a paper speed of 25 mm/s and a calibration voltage of 10 mm/mV. The patient's ECG QRSd and LVAT before and after the procedure were recorded. The pre- and postoperative post-QRSd was measured manually from the starting point of the earliest QRS complex to the end point of the latest QRS complex, based on the 12-lead EKG reading. Pre- and postoperative LVAT was measured manually on the ECG leads V4~V6 as the distance from the starting point of the earliest QRS complex to the vertical line of the apex of the latest QRS complex R (or R'). If there was an R' wave, it should be measured to the R' peak; if the R peak was a notch, it should be measured to the second peak of the notch.

Echocardiography: Echocardiography was performed by a professional physician, using GE VIVID 7 Doppler echocardiography (probe frequency: 3.4~5.0 MHz) to measure the left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) and LVEF before and 12 months after the procedure.

Diagnosis of complete left bundle branch block (CLBBB) and complete right bundle branch block (CRBBB): CLBBB and CRBBB were diagnosed based on the criteria jointly developed by the American Heart Association (AHA), American College of Cardiology Foundation (ACCF), and American Heart Rhythm Society (HRS) in 2009. Briefly, CLBBB was diagnosed based on the following criteria: 1) a QRS wave time limit ≥ 120 ms; 2) lead V1 had no R wave, QS type, or rS type; and 3) R waves in lead I and V6 were broadened and accompanied by a notch or frustration without q wave. CRBBB was diagnosed based on the following criteria:1) a QRS complex time limit was ≥ 120ms; 2) the QRS in lead V1 or V2 was rsR' or M type; and 3) S waves in leads I, V5, and V6 were widened with a notch. No BBB was diagnosed if the QRS wave time limit was < 120 ms.

Definition of responsiveness: Responsiveness to LBBAP treatment was defined as patients having two of the following four criteria: 1) the follow-up New York Heart Association function class decreased by more than 1 class in 12 months after operation; 2) the cardiothoracic ratio decreased by more than 0.1 within 12 months after the procedure; 3) LVEF increased by more than 5% within 12 months after the procedure as revealed by UCG examination; and 4) the circulating levels of NT-proBNP decreased by more than 50%. Failure to meet the above criteria was defined as no-responsiveness.

Statistical analysis: All statistical analyses were performed using SPSS 21 software. Continuous variables are expressed as mean ± standard deviation ($\bar{x}$±s) and compared using independent sample t test between two groups. The paired sample t test was used for pre- and postoperative data comparison. Categorical variables are expressed as number (percentage) and compared using the Chi-square test or Fisher's exact probability method between two groups. Multivariate binary logistic regression was used to identify the factors that were associated with the postoperative responsiveness to LBBAP treatment. A P value ≤ 0.05 indicated a significant difference.

RESULTS

Comparison of demographic and baseline clinical characteristics of patients between two groups: This study recruited 31 CHF patients with New York Heart Association (NYHA) class II or higher with pacemaker implantation indications, including 20 males and 11 females (age: 72.5±8.9 years), with 16 having CLBBB, five having CRBBB, and 10 having no BBB. Among these 31 patients, 11 had ischemic cardiomyopathy, six had dilated cardiomyopathy, 18 had hypertension, two had diabetes, four had valvular disease, and one had pacemaker-related HF. All patients were successfully implanted with pacemakers in the left bundle branch area for pacing, including five single-chamber pacemakers, 24 dual-chamber pacemakers, and two cardiac resynchronization therapy cardioverter defibrillators (CRTDs). (Table 1)

Among these 31 follow-up patients, 16 patients (51.6%) responded to the treatment, and 15 patients (48.4%) had no response. Among those 16 responsive patients, the response rate of patients with preoperative EKG showing CLBBB was 93.8% (15/16), the response rate of patients with preoperative EKG showing CRBBB was 40% (2/5), and the response rate of patients with preoperative EKG who had no BBB was 10% (1/10). There were significant differences between the responsiveness and no-responsiveness groups, preoperative QRSd, and preoperative LVAT ($P < 0.05$), but no significant differences with regard to age, gender, ischemic and non-ischemic cardiomyopathy, preoperative NT-proBNP levels and preoperative cardiothoracic ratio, LVEDD, LVESD, and LVEF ($P > 0.05$) (Table 1).

Comparison of pre- and postoperative parameters of patients within the group: In the responsiveness group, QRSd, LVESD, LVEDD, LVEF, NT-proBNP levels, and cardiothoracic ratio after surgery were significantly improved compared with those before surgery ($P < 0.05$), but LVAT showed no significant improvement. In the no-responsiveness

Table 1. Comparison of demographic and baseline clinical data of patients between two groups

Groups	No responsiveness (*N* = 15)	Responsiveness (*N* = 16)
Sex		
Male (n, %)	10 (50%)	10 (50%)
Female (n, %)	5 (45.5%)	6 (54.5%)
Age ({QUOTE $\bar{x}$ }±s)	72.7±9.8	72.3±8.3
NYHA classification		
II (n, %)	8 (51.7%)	6 (42.9%)
III (n, %)	3 (75.0%)	1 (25.0%)
IV (n, %)	4 (30.8%)	9 (69.2%)
Underlying disease		
Ischemic cardiomyopathy (n, %)	4 (36.4%)	7 (63.6%)
Non ischemic cardiomyopathy (n, %)	11 (55%)	9 (45%)
Branch type		
No BBB (n, %)	9 (90.0%)	1 (10.0%)
CRBBB (n, %)	3 (60.0%)	2 (40.0%)
CLBBB (n, %)	3 (18.8%)	13 (81.2%)
QRSd (ms) ($\bar{x}$±s)	121.2±36.4	165.8±26.8
LVAT (ms) ($\bar{x}$±s)	55.9±24.1	83.9±31.6
NTproBNP (pg/ml) ($\bar{x}$±s)	1999.7±2783.5	4687.5±5631.8
Cardiothoracic ratio ($\bar{x}$±s)	0.6±0.1	0.6±0.1
LVEDD (mm) ($\bar{x}$±s)	54.8±8.8	58.3±8
LVESD (mm) ($\bar{x}$±s)	40.6±8.5	45.8±9.3
LVEF (±s)	48.5±10.5	44.2±10.6
ACE-i/ARB	12 (80.0%)	13 (81.3%)
Beta-blocker	0 (0.0%)	0 (0.0%)
MRA	11 (73.3%)	12 (75.0%)

group, QRSd and LVAT after operation were significantly increased compared with those before surgery (P < 0.05), however, no significant differences were observed between before and after surgery in LVESD, LVEDD, LVEF (%), NT-proBNP, and cardiothoracic ratio (*P* > 0.05). (Table 2)

Determination of factors associated with responsiveness to LBBAP: We first used the single-factor binary logistic regression analysis to determine the factors that were associated with the responsiveness to LBBAP treatment. The preoperative QRSd and preoperative LVAT all were significantly correlated with the responsiveness to LBBAP (*P* < 0.05). (Table 3) Following that, the multivariate binary logistic regression analysis showed that QRSd was an independent predictor of the responsiveness (OR=1.039, 95%CI%1.001-1.078, *P* = 0.042). (Table 4)

Determination of the optimal predictive value of QRSd for responsiveness to LBBAP: We next calculated the Youden index to determine the optimal predictive value of QRSd for responsiveness to LBBAP and found that when QRSd was ≥ 153 ms, the maximum Youden index was 0.679, which was below the ROC curve. The maximum area was 0.827 (95% CI: 0.663-0.991), with a sensitivity of 81.3% and a specificity of 86.7%. These findings suggest that those with a greater QRSd had better the responsiveness to LBBAP. (Figure 1)

DISCUSSION

It is well known that there is a wide variation in clinical responses to BVP in CHF patients. While studies have been

Table 2. Comparison of pre- and post-operative parameters of patients within each group

	No responsiveness group (N = 15)				Responsiveness group (N = 16)			
	Pre-operation ($\bar{x}$±s)	Post-operation ($\bar{x}$±s)	t	*P*	Pre-operation ($\bar{x}$±s)	Post-operation ($\bar{x}$±s)	t	*P*
QRSd (ms)	121.2±36.4	141.7±26.6	-3.24	0.006[a]	165.8±26.8	124.9±20.8	7.88	0.000[a]
LVAT (ms)	55.9±24.1	76.9±22.6	-4.14	0.001[a]	83.9±31.6	70.8±17.5	1.38	0.189
NTproBNP	1999.7±2783.5	1639±1640.6	0.94	0.362	4687.5±5631.8	917.5±1246.3	3.16	0.006[a]
Cardiothoracic ratio	0.6±0.1	0.6±0.1	1.12	0.282	0.6±0.1	0.6±0.1	4.64	0.000[a]
LVEDD (mm)	54.8±8.8	53.9±8.4	0.94	0.365	58.3±8	52.6±6	4.09	0.001[a]
LVESD (mm)	40.6±8.5	39.8±8.1	0.90	0.384	45.8±9.3	38.9±5.8	4.17	0.001[a]
LVEF (%)	48.5±10.5	50.8±9.3	-1.19	0.255	44.2±10.6	51.3±5.4	-3.60	0.003[a]

[a]P < 0.05, vs. pre-operation

Table 3. Univariate logistic regression analysis of factors related to LBBAP responsiveness

Parameters	Univariate analysis		
	OR	95% CI	*P*
Sex	0.833	0.191~3.644	0.809
Age	0.995	0.918~1.078	0.895
NYHA Class II	-	-	0.225
NYHA Class III	0.444	0.037~5.406	0.525
NYHA Class IV	3.000	0.616~14.617	0.174
Ischemic cardiomyopathy	2.139	0.472~9.699	0.324
Cardiothoracic ratio	109.858	0.004~3110991.252	0.369
NT-proBNP	1.000	1~1	0.138
LVEDD	1.055	0.962~1.158	0.253
LVESD	1.072	0.981~1.171	0.125
LVEF	0.960	0.894~1.031	0.261
QRSd	1.041	1.012~1.071	0.005
LVAT	1.035	1.006~1.066	0.019

performed to identify factors that may predict the responsiveness to BVP, few studies specifically were aimed to uncover the factors that may predict the responsiveness to LBBAP, another treatment to correct cardiac arrhythmias, such as bradycardia. In the present study, we examined a number of factors that might potentially affect the responsiveness to LBBAP treatment in CHF patients with CRBBB, CLBBB, or no BBB, respectively, and revealed that only QRSd was an independent predictor. Our study further suggests that the optimal cutoff point of QRSd for predicting the responsiveness to LBBAP is ≥153 ms, with a sensitivity of 81.3% and a specificity of 86.7%. Previous studies have shown that BVP can effectively shorten QRSd, increase heart rate and LVEF, and improve the clinical symptoms of CHF patients [Curtis 2013;Wu 2021]. However, some CHF patients with bradyarrhythmia showed no or poor response to treatment [Naqvi 2018]. On the other hand, BVP is expensive and technically challenging. As an alternative, LBBAP also can shorten the QRS duration of CLBBB patients and slightly increase the QRSd of patients with no BBB. Compared with RVP, LBBAP pacing parameters are more stable, and the QRSd is shorter [Chen 2019]. As a result, LBBAP also can increase LVEF and improve patient quality of life [Huang 2017]. In the present study, 16 patients (51.6%) responded to the treatment, and 15 (48.4%) had no response, which was higher than previously reported [Li 2020]. This discrepancy might be attributed to the differences in patient selection criteria and the sample size in these two studies.

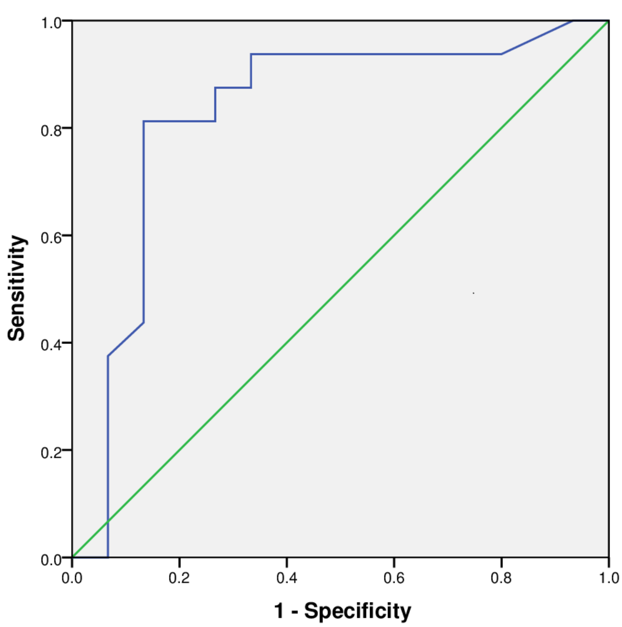

Figure 1. ROC curve of the optimal predictive value of QRSd for responsiveness to LBBAP

Table 4. Multivariate logistic regression analysis of factors related to LBBAP responsiveness

Parameters	Multivariate analysis		
	OR	95% CI	*P*
QRSd	1.039	1.001~1.078	0.042
LVAT	1.003	0.966~1.042	0.869

LBBAP paces the main branch of LBB, and LV is first tissue to be excited by the Purkinje fiber network. When the LBB is captured by pacing, an incomplete RBBB appears and the LVAT is suddenly shortened to between 65 and 80 ms in EKG [Huang 2019; Chen 2019; Zhang 2019; Su 2020]. In this study, patients in both groups had a successful LBBAP procedure. However, there were no significant differences between these two groups with regard to demographic and baseline clinical characteristics, indicating they were not influential factors for the responsiveness to LBBAP treatment in CHF patients. Previously, LBBAP was shown to shorten the QRS duration of EKG in patients with CLBBB, reduce LVAT [Chen 2019; Cai 2020], improve the synchrony of the left ventricle, ameliorate the symptoms of CHF patients, and reverse ventricular remodeling. On the contrary, LBBAP can increase the QRS duration of EKG and prolong LVAT in patients without BBB. However, we observed that there were significant differences in pre- and postoperative QRSd between the two groups. We further found that in the responsiveness group, the QRSd significantly was decreased after operation, while in the no-responsiveness group, the QRSd significantly was increased. We noticed that 13 of the 16 patients with LBBB responded to the treatment and only three did not, which was probably the primary reason for shortened QRSd and decreased LVAT after LBBAP treatment in the responsiveness group, consistent with previous reports [Chen 2019; Cai 2020]. In contrast, there were 10 CHF patients with no BBB before surgery, and the no-responsiveness group had nine CHF patients, which was probably the main reason why there was an increase in QRSd and prolonged LVAT after LBBAP treatment. This could be the main reason for the lack of response to LBBAP treatment.

Studies have yielded conflicting results regarding the predictors for the response to CRT. For example, the PROSPECT Trial did not uncover any independent parameters related to the responsiveness to CRT [Chung 2008], but a number of variables were identified in another study [Loutfi 2016]. In contrast, few studies were performed to examine the variables predictive of response to LBBAP, although LBBAP is a viable alternative treatment to the traditional CRT. In this study, although univariate binary logistic regression analysis revealed that preoperative QRSd, preoperative LVAT, and CLBBB were all significantly correlated with the responsiveness to LBBAP treatment, QRSd was the only independent predictor for the responsiveness as suggested by multivariate binary logistic regression analysis. When the QRSd exceeded 153 ms, CHF patients had a better response to LBBAP treatment. Therefore, we determined that the optimal cutoff value of QRSd was ≥153 ms, with a sensitivity of 81.3% and a specificity of 86.7%.

Some limitations of this study should be noted. First, this was a single-center retrospective study. Therefore, there could have been potential sampling bias. Also, our study had a limited sample size. Thus, the conclusions from this study need to be further corroborated by prospective studies with large cohorts in the future.

CONCLUSION

In summary, our data suggest that QRSd can be used as an easy and reliable indicator of LBBAP therapy for CHF patients with bradyarrhythmias to improve cardiac function, and that QRSd can be used to guide treatment.

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Ethics approval and consent to participate: The protocol for the study was approved by the ethics committee of the First Affiliated Hospital of Bengbu Medical College (Approval No. 2019109) prior to the initiation of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from each patient before enrollment in the study.

Patient consent: Informed consent was obtained from patients to publish the data concerning this study.

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