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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Research Article

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Abstract

Background

This study investigated the predictive value of preoperative QRS duration (ORSd) 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=18) and a no-responsiveness group (n=13). 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 these 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 were all significantly correlated with responsiveness to LBBAP. Multivariate binary logistic regression analysis showed that ORSd was an independent predictor of responsiveness to LBBAP. The maximum area under the ROC curve for QRSd was 0.827, 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 ORSd predicts the responsiveness of CHF patients with pacemaker indications to LBBAP.

Introduction

Chronic heart failure (CHF), characterized by impaired cardiac pump function[1], is the end-stage cardiac disease of a variety of cardiovascular disorders including coronary heart disease, dilated cardiomyopathy, hypertension, diabetes, and valvular diseases[2], 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 ageing population[3]. 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)[4]. 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[5–7]. 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[8].

However, 30% of patients who receive CRT do not respond to treatment[9]. 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[10]. Previous studies mainly investigated the predictors of response to BVP[11], but not to LBBAP, although patients with poor response to LBBAP treatment were still reported[12]. 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.

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, 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[13]: 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 patient's EKG with a paper speed of 25 mm/s and a calibration voltage of 10 mm/mV. Patient's ECG QRSd and LVAT before and after the procedure were recorded. The preoperative QRSd was measured from the starting point of the QRS complex to the end point of the QRS complex. Preoperative LVAT was measured as the distance from the starting point of the QRS complex to the vertical line of the apex of the QRS complex R (or R').

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), the American College of Cardiology Foundation (ACCF), and the 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, and 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) symptoms improvedwithin 12 months after the procedure, and cardiac function improved by 1 grade; 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. Measurement data are expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared using independent sample t test between two groups. The paired sample t test was used for pre- and post- operative data comparison. Count data is expressed as number (percentage) and compared using 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 the 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 Function (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, 5 having CRBBB, and 10 having no BBB. Among these 31 patients, 11 had ischemic cardiomyopathy, 6 had dilated cardiomyopathy, 18 had hypertension, 2 had diabetes, 4 had valvular disease, and 1 had pacemaker-related HF. All patients were successfully implanted with pacemakers in the left bundle branch area for pacing, including 5 single-chamber pacemakers, 24 dual-chamber pacemakers, and 2 cardiac resynchronization therapy cardioverter defibrillators (CRTDs) (Table 1).

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

Groups	No Responsiveness (n=15)	Responsiveness (n=16)	t/x2	P Value
Sex				1.000
male	10(50.0%)	10(50.0%)		
female	5(45.5%)	6(54.5%)		
Age	72.7±9.8	72.3±8.3	0.1281	0.8989
NYHA classification			3.053	0.245
II	8(51.7%)	6(42.9%)		
III	3(75.0%)	1(25.0%)		
IV	4(30.8%)	9(69.2%)		
underlying disease				0.458
ischemic cardiomyopathy	4(36.4%)	7(63.6%)		
Non ischemic cardiomyopathy	11(55%)	9(45%)		
Branch type			13.024	0.001
No BBB	9(90.0%)	1(10.0%)		
CRBBB	3(60.0%)	2(40.0%)		
CLBBB	3(18.8%)	13(81.2%)		
QRSd	121.2±36.4	165.8±26.8	-3.9026	0.0005
LVAT	55.9±24.1	83.9±31.6	-2.7593	0.0099
NTproBNP	1999.7±2783.5	4687.5±5631.8	-1.6662	0.1064
Cardiothoracic ratio	0.6±0.1	0.6±0.1	-0.8978	0.3767
LVEDD	54.8±8.8	58.3±8	-1.1625	0.2545
LVESD	40.6±8.5	45.8±9.3	-1.6088	0.1185
LVEF	48.5±10.5	44.2±10.6	1.1292	0.2681

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 ECG showing CLBBB was 93.8% (15/16), the response rate of patients with preoperative ECG showing CRBBB was 40% (2/5), and the response rate of patients with preoperative ECG 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 post-operative 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 group, QRSd and LVAT after operation were significantly increased compared with those before surgery (P<0.05), however, no significance differences were observed between before and after surgery in LVESD, LVEDD, LVEF (%), NT-proBNP, and cardiothoracic ratio (P>0.05) (Table 2).

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	**Post operation**	**t**	***P***	**Pre operation**	**Post operation**	**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

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 were all significantly correlated with the responsiveness to LBBAP (P<0.05) (Table 3). Following that, the multivariate binary logistic regression analysis showed that ORSd was an independent predictor of the responsiveness (OR=1.039, 95%CI: 1.001-1.078, P=0.042) (Table 4).

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

Parameters	Univariate analysis		
	OR	95% C.I.	P
Sex	0.833	0.191~3.644	0.809
Age	0.995	0.918~1.078	0.895
NYHA Class II		0~0	0.225
NYHA ClassIII	0.444	0.037~5.406	0.525
NYHA ClassIV	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

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

Parameters	Multivariate analysis		
	OR	95% C.I.	P value
QRSd	1.039	1.001~1.078	0.042
LVAT	1.003	0.966~1.042	0.869

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 performed to identify factors that may predict the responsiveness to BVP, few studies were specifically 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[8, 14]. However, some CHF patients with bradyarrhythmia showed no or poor response to treatment[9]. On the other hand, BVP is expensive and technically challenging. As an alternative, LBBAP can also 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[15]. As a result, LBBAP can also increase LVEF and improve patient quality of life[16]. 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[12]. This discrepancy might be attributed to the differences in patient selection criteria and the sample size in these two studies.

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[13,17–19]. 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 that they were not influential factors for the responsiveness to LBBAP treatment in CHF patients. Previously, LBBAP was shown to shorten the QRS duration of ECG in patients with CLBBB, reduce LVAT[15, 20], 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 ECG and prolong LVAT in patients without BBB. However, we observed that there were significant differences in pre- and post-operative QRSd between these two groups. We further found that in the responsiveness group, the QRSd was significantly decreased after operation, while in the no-responsiveness group, the QRSd was significantly increased. We noticed that 13 of the 16 patients with LBBB responded to the treatment, and only 3 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[15, 20]. In contrast, there were 10 CHF patients with no BBB before surgery, and the no-responsiveness group had 9 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[11], but a number of variables were identified in another study[21]. 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. For, 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.

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.

Abbreviations

AHA: American Heart Association; ACCF: American College of Cardiology Foundation; BBB: bundle branch block; BVP: biventricular pulse pacing; CHF: chronic heart failure; CRT: cardiac resynchronization therapy; CRTD: cardiac resynchronization therapy cardioverter defibrillator; CLBBB: complete left bundle branch block; CRBBB: complete right bundle branch block; DSA: digital subtraction angiography; EKG: Electrocardiogram; HRS: Heart Rhythm Society; LBBAP: left bundle branch area pacing;

LVAT: left ventricular peak time; LBBB: left bundle branch block; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Function; QRSd: QRS duration; RBBB: right bundle branch block; RVP: right ventricular pacing; UCG: cardiac color Doppler ultrasound.

Declarations

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) before performance 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.

Consent for publication

All data published here are under the consent for publication.

Availability of data and material

The datasets generated and analyzed in the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TPC and XG designed topics of the subject study, analyzed and interpreted data of the work. YXF and YCY acquired data of the work and prepared charts and tables of the paper. TPC and NJZ Wrote a draft of the work and approved finally the manuscript.

All authors reviewed the manuscript.

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Figures

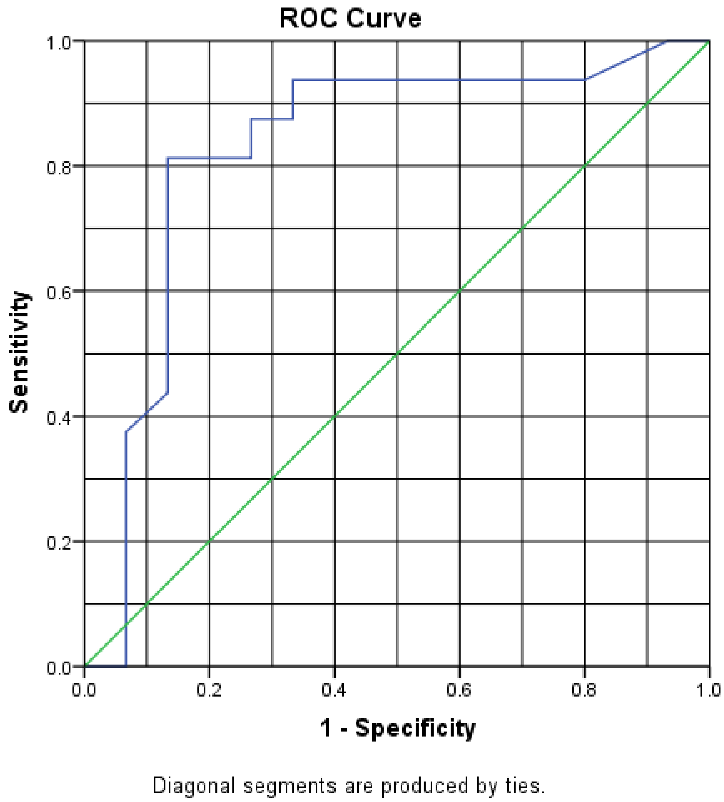

Figure 1

Determination of QRSd as a predictor of the responsiveness to LBBAP with ROC curve.