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# Left Univentricular Pacing by Rate-Adaptive Atrioventricular Delay in Treatment of Chronic Heart Failure

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** Cardiac resynchronization therapy (CRT) is efficacious in the treatment of chronic heart failure (CHF); however, because it is non-physiological, some patients are unresponsive. The present study used rate-adaptive atrioventricular delay (RAAVD) to track the physiological atrioventricular delay and investigated the effects of left univentricular pacing on CRT.

**Material/Methods:** Patients with CHF fulfilling the indication of CRT Class I were categorized into a left univentricular pacing by RAAVD group and a standard biventricular pacing group. Preoperative and postoperative electrocardiography QRS duration, echocardiographic indicators, quality of life, cardiac function, and annual treatment cost were estimated. The standard deviation ($R_{S/R}$-SD5) of the S/R ratio in lead $V_1$ at 5 heart rate segments in the left univentricular pacing by RAAVD was calculated, and the accuracy of RAAVD in tracking the physiological AV delay was evaluated.

**Results:** The comparison between the left univentricular pacing by RAAVD group and the standard biventricular pacing group after operation showed a significantly reduced QRS duration (137±11 *vs.* 144±11 ms, *P*<0.05), increased AVVTI (21.84±2.25 *vs.* 20.45±2.12 cm, *P*<0.05), reduced IVMD (64.27±12.29 *vs.* 71.39±13.64 ms, *P*<0.05), decreased MRA (3.09±1.12 *vs.* 3.73±1.19 $cm^2$, *P*<0.05), and reduced average annual treatment cost (1.30±0.1 *vs.* 2.20±0.2 million Yuan, *P*<0.05). The $R_{S/R}$-SD5 in the left univentricular pacing by RAAVD group was negatively correlated with improvements in cardiac function (*r*=–0.394, *P*=0.031).

**Conclusions:** Left univentricular pacing by RAAVD has treatment effects similar to those of standard biventricular pacing, and is an economically and physiologically effective method for biventricular systolic resynchronization in the treatment of CHF.

**MeSH Keywords:** **Caridiac Resynchronization Therapy • Heart Failure • Left Ventricle • Pacing**

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## Background

Chronic congestive heart failure (CHF) is a severe and end-stage form of various cardiovascular diseases, with a high morbidity and mortality; the 5-year mortality is 30–50%, treatment is difficult, and the medical cost is high. Patients with CHF frequently present intracardiac electrical conduction anomaly, leading to non-synchronization in atrioventricular (AV), interventricular, and/or intraventricular movements, especially combined with left bundle branch block (LBBB), manifesting as non-synchronization in the left and right ventricles, which lead to contradictory movements of the ventricular septal as well as reduced cardiac output [1–3].

Cardiac resynchronization therapy (CRT) is effective in the treatment of chronic heart failure [4–8], improving cardiac function and quality of life, and reducing the rates of re-hospitalization and mortality. However, approximately 30% of patients do not respond to cardiac resynchronization therapy of standard biventricular pacing [9–11], which may be partially due to the short and fixed AV delay (AVD); the physiological AVD conduction is abandoned to ensure a 100% biventricular seizure [12]. In addition, right ventricular pacing leads to slow excitation and non-homogeneous inverse conduction in the His-Purkinje system in the right ventricle. This conduction affects ventricular structure and functions, systolic and diastolic synchronization, and deterioration of hemodynamics, resulting in new atrioventricular and intraventricular non-synchrony that reduces efficacy of CRT treatment [12–14].

In a physiological state, the interval of physiological AVD (PR interval) changes with that of the sympathetic tone and heart rate in order to coordinate the filling of the atrium to the ventricle [15]. When patients with chronic heart failure did not exhibit any atrioventricular block, their PR intervals were optimal AVDs [16]. The use of a pacemaker with rate-adaptive AVD (RAAVD) and initiation of this function can simulate the physiological AVD to achieve "physiological pacing." Furthermore, patients with chronic heart failure combined with LBBB commonly present normal right-sided His-Purkinje system conduction, and thus do not require right ventricular pacing [17]. Therefore, cardiac resynchronization therapy can be implemented when left univentricular pacing tracks the intrinsic physiological AV conduction interval on the right side through RAAVD and fuses with self-excitement.

The present study aimed to investigate the effects of left univentricular pacing in the treatment of chronic heart failure by tracking physiological AVD through RAAVD.

## Material and Methods

### Study subjects

A total of 60 cases with chronic heart failure admitted to the Cardiovascular Department of the First Affiliated Hospital of Kunming Medical University from May 2013 to May 2016 were enrolled. A series of 30 cases were categorized in each of the left univentricular pacings by RAAVD group (23 males and 7 females, average age 55.0±13.0 years) and the standard biventricular pacing group (22 males and 8 females, average age 54.0±14.0 years).

#### *Inclusion criteria*

(1) Patients who fulfilled the indications of CRT Class I [18]: cardiac function category of the New York Heart Association (NYHA) was still at grade II–IV, after the patients received adequate anti-heart failure medication, patients with sinus rhythm, patients with LBBB, patients with QRS duration >150 ms, patients with left ventricular ejection fraction (LVEF) ≤35%; (2) patients with abnormal functions of intrinsic AV conduction; (3) patients with normal function of right bundle branch conduction; (4) patients with expected survival >1 year.

#### *Exclusion criteria*

(1) Patients with AV block; (2) patients with the expected survival <1 year; (3) patients with potentially reversible cardiomyopathy; (4) patients with surgically uncorrected valvular disease; (5) patients with hypertrophic obstructive cardiomyopathy; (6) patients with right bundle branch block (RBBB); (7) patients who cannot continue the follow-up.

This study was reviewed and approved by the Clinical Trials Review and the Management Committee of the First Affiliated Hospital of Kunming Medical University. The study complied with the Declaration of Helsinki and informed consent was obtained from all participants.

#### *Establishment of a pacing system*

The system used in the present study was a pacemaker with RAAVD, for left univentricular pacing by a 3-chamber instrument to close the function of the right ventricular electrode, or by inserting the left ventricular electrode into the right ventricular jack of a dual-chamber pacemaker.

#### *Available pacemaker manufacturers and models*

The 3-chamber pacemakers were from Medtronic (USA): Synacra C2TR01 CRT, C174AWK CRT-D, Maximo II CRT-D, InsyncSentry 7298 CRT-D, and dual-chamber pacemakers were





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AdaptaADDRL1/ADDRS01/ADDR01, Sensia SED01\SEDR01, Relia RED01, and D394TRG.

5596CRT-P and V-350CRT-D were from St. Jude (USA).

Stratos LV and Lumax 300HF-T were obtained from Biotronik (Germany).

The pacing systems were implanted according to the current standard method, and various parameters were measured.

*The implantation of the 3-chamber pacemaker*

The atrial electrode was placed in the right atrial appendage, the right ventricular electrode was placed in the apex of the right ventricle, and the left ventricular electrode was placed into the lateral veins or posterolateral veins after retrograde angiography of coronary sinus.

*The implantation of dual-chamber pacemaker*

The left ventricular electrode was inserted into the right ventricular jack of the dual-chamber pacemaker, except for the non-implantation of the right ventricular electrode. The others were implanted similar to that of the 3-chamber pacemaker.

**Program-controlled optimization of the pacing systems**

*Optimization of the interval in the standard biventricular pacing group*

Program-controlled pacing is known as biventricular pacing. If the function of the sinus node was normal, the titration of AVD used atrial sensing A-V interval (SAV); if the percentage of atrial pacing was >50%, then the atrial pacing A-V interval (PAV) was used. If AVVTI and LVEF were the largest, reference E and A peaks were separated, MRA was the smallest, and QRS duration on the ECG was the narrowest; consequently, the corresponding A-V and V-V intervals were optimized.

*Interval optimization of the left univentricular pacing by RAAVD group*

The 3-chamber pacemaker was programmed into the left univentricular pacing, the program-controlled device was adjusted, luminal signed channel was displayed, and the ventricular delay was gradually prolonged until the intracardiac electrogram showed atrial sensing–ventricular sensing (AS-VS). For a 3-chamber pacemaker that closed the pacing function of the right ventricular pacing electrode, the AS-VS interval – atrial sense compensation (ASC) at optimization (ASC was the time from the start of the right atrial intracardiac electrogram A-wave to atrial sensing [AS]) was used as the AVD of the baseline. In the case of a dual-chamber pacemaker, AS-VS interval was the right atrium – left ventricular interval, which cannot represent the physiological AVD; thus, the PR interval at optimization was used to replace the AS-VS interval for "titration". The AVD was shortened by 10-ms steps (equivalent to left ventricular first), and echocardiographic measurement was performed after 5 min of program control at each timepoint. The corresponding AVD was optimized when AVVTI and LVEF were the largest, reference E and A peaks were separated, MRA was the smallest, and ECG QRS duration was the narrowest. The parameters of RAVVD were set according to the formula: SAV of the initial rate=optimized AVD + (PR interval of the initial rate – PR interval at optimization), SAV of the terminating rate=optimized AVD – (PR interval at optimization – PR interval of the terminating rate). The application of the dual-chamber pacemaker did not set the SAV of the termination rate; however, the variation of RAAVD should be set: PR interval of the terminating rate – PR interval of the initial rate. The other settings were similar to those of the 3-chamber pacemaker. After obtaining the optimal SAV, the optimal PAV (PAV=SAV+ASC) can be calculated. The individual AV intervals were programmed into the pacemaker and the function of RAAVD was opened to direct the left AVD to always track the right AV physiological PR interval to achieve biventricular systolic resynchronization.

**Clinical follow-up**

The time of enrolling in the study was considered as the starting point, and all the patients underwent clinical follow-up at 1, 3, 6, and 12 months. Consequently, the patients were followed up once every 12 months until the end of the study. The data were based on the last follow-up.

**Evaluation indicators**

*Echocardiography*

Vivid E9 Doppler echocardiography (GE, USA) with M5S and 4V probes was used, with the emission frequency of 2.5 MHZ. The echocardiography examination was performed by the same echocardiologist, who was blinded to the study groups. The following indicators before and after the CRT operations of left univentricular pacing by RAAVD, as well as standard biventricular pacing, were measured in the patients: left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), right atrial diameter (RAD), mitral regurgitation area (MRA), left ventricular ejection fraction (LVEF), aortic valvular velocity time integral (AVVTI), atrioventricular synchronous index: EA peak distance (E/A pd), interventricular synchronous index: interventricular mechanical delay (IVMD), and left ventricle synchronous index: standard deviation of Ts of 12 LV segments (Ts-SD12).





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*Electrocardiogram*

The preoperative and postoperative follow-up of the included patients was performed by the same electrocardiologist, who was blinded to the study groups. Twelve-lead (25 mm/s and 10 mm/mV) and 24-h ambulatory electrocardiograms (25 mm/s and 10mm/mV) were obtained from the patients. QRS duration and PR interval of different heart rates were measured; the changes in the heart rate were measured as the independent variable (x) and changes of PR interval as the dependent variable (y) to establish the regression equation of the heart rate and PR interval changes in each patient: y=a+bx (a was the constant term, b was normalized partial regression coefficient). The PR intervals of the lower limit frequency (LLR: default as 60 bpm) and upper tracking frequency (UTR: default as 130 bpm) of the pacemaker cannot be acquired by the 24-h ambulatory electrocardiogram; the regression equation of PR interval derived from the heart rate was established with the heart rate as the independent variable and PR interval as the dependent variable: PR=a+bx (LLR or UTR) (b was the constant item and indicated the normalized partial regression coefficient). Thus, LLR and UTR corresponding to the PR intervals could be calculated for the start and end frequencies of RAAVD. In the left univentricular pacing by RAAVD group, $V_1$ lead R and S waves at the 5 heart rate segments, including 60, 70, 80, 90, and 100 beats/min (bpm) were collected and the amplitude measured. In this study, the standard deviation ($R_{S/R}$-SD5) of the S/R ratio of $V_1$ lead in the 5 heart rate segments was defined as the "tracking index", which was used to evaluate the accuracy of the RAAVD algorithm for monitoring the physiological AVD and the change of the degree of fusion between left univentricular pacing excitement and self-excitement, as well as analyzing the correction with cardiac function improvement, which is the variation of left ventricular ejection fraction (ΔLVEF). The ΔLVEF was defined as the difference of LVEF values between the latest follow-up and the time-point before the operation.

*Clinical evaluation index*

To assess cardiac function, we used the 6-min walk test (6-MWT), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the NYHA classification. Adverse events during follow-up, including re-hospitalization due to heart failure or death of the subjects, were recorded. The medical expenses essential for the mechanical treatment of chronic heart failure for the patients in the study group were also accurately recorded.

**Statistical analysis**

Statistical analyses were carried out using the SPSS 19.00 package. Continuous data of normal distribution are represented as mean ± standard deviation, and categorical data are represented as percentage and were analyzed by the $\chi^2$ test. Continuous data with normal distribution were analyzed with the 2 independent samples *t* test, and continuous data of the paired design with normal distribution were analyzed with the paired *t* test. The correlation between heart rate and PR interval was analyzed by linear regression, and $R_{S/R}$-SD5 and ΔLVEF were analyzed by Pearson's correlation analysis. $P<0.05$ was considered as a statistically significant difference.

## Results

In the 60 included patients, 30 completed the left univentricular pacing by the RAAVD, and 30 completed the conventional dual-chamber pacing. The mean duration of follow-up after the operation was 7.86±3.67 months in both groups. Among these, 1 patient who was implanted with a dual-chamber pacemaker to implement biventricular resynchronization through left univentricular pacing by RAAVD died due to cerebrovascular events. Two patients who received cardiac resynchronization therapy through standard biventricular pacing died due to end-stage heart failure and malignant arrhythmias. The remaining patients did not present any complications such as blood pneumothorax and capsular infection after implantation of the pacemaker.

**Comparison of baseline indicators**

The preoperative baseline data for the 60 patients enrolled in the study are summarized in Table 1. No statistically significant differences in age, sex, causes of disease, NYHA classification, PR interval, QRS duration, or echocardiographic parameters were observed in the baseline data between the left univentricular pacing by RAAVD group and the standard biventricular pacing group ($P>0.05$) (Table 1).

**Comparison of electrocardiogram and echocardiographic parameters in the 2 modes**

The QRS duration was narrowed after the operation in the left univentricular pacing by RAAVD groups as compared to that before the operation (137±11 *vs.* 187±21 ms, $P<0.001$); it was also narrowed after the operation in the standard biventricular pacing group (144±11 *vs.* 182±20 ms, $P<0.001$). Moreover, the postoperative QRS duration in the left univentricular pacing by RAAVD group was narrower than in the standard biventricular pacing group (137±11 *vs.* 144±11 ms, $P<0.05$) (Figure 1).

Regarding the echocardiographic parameters, postoperative LVEF and AVVTI increased significantly in the left univentricular pacing by RAAVD group and the standard biventricular pacing group ($P<0.001$) (Table 2). Postoperative LVEDD, MRA, IVMD, and Ts-SD12 were reduced after the operation





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**Table 1.** Comparison of postoperative baseline data between the RAAVD left univentricular pacing group and the standard biventricular pacing group.

| Indicators | Standard biventricular pacing group (n=30) | RAAVD left univentricular pacing group (n=30) | *P*-value |
|---|---|---|---|
| Age (years, $\bar{\chi}$±s) | 54±14 | 55±13 | 0.775 |
| Mal [case (%)] | 22 (73.3) | 23 (76.7) | 0.766 |
| Causes [case (%)] | | | |
| Dilated cardiomyopathy | 26 (86.7) | 25 (83.3) | 0.718 |
| Ischemic cardiomyopathy | 4 (13.3) | 5 (16.7) | 0.718 |
| Classification (class) | 3.10±0.49 | 3.21±0.54 | 0.412 |
| II class [case (%)] | 2 (6.67) | 1 (3.33) | 0.554 |
| III class [case (%)] | 23 (76.67) | 22 (71.33) | 0.766 |
| IV class [case (%)] | 5 (16.67) | 7 (21.33) | 0.519 |
| QRS duration (ms) | 180.00±19.00 | 188.00±21.00 | 0.127 |
| LVEDD (mm) | 79.10±11.50 | 73.90±10.10 | 0.067 |
| LAD (mm) | 42.4±8.2 | 44.6±8.4 | 0.090 |
| LVEF (%) | 27.00±4.00 | 29.00±5.00 | 0.092 |
| MRA ($cm^2$) | 4.50±1.30 | 3.90±1.10 | 0.059 |
| AVVTI (cm) | 15.80±2.10 | 16.40±2.30 | 0.295 |
| E/Apd (ms) | 200.00±58.00 | 221.00±64.00 | 0.188 |
| IVMD (ms) | 78.30±13.80 | 82.60±14.40 | 0.242 |
| Ts-SD12 (ms) | 118.00±26.00 | 127.00±29.00 | 0.211 |
| MLHFQ (score) | 35.47±21.03 | 37.86±15.79 | 0.621 |
| 6-MWT (m) | 348.00±58.00 | 336.00±51.00 | 0.398 |

ICM – ischemiccardiomyopathy; DCM – dilated cardiomyopathy; NYHA : New York Heart function Association; QRS duration – duration of QRS wave; 6-MWT – 6-min walk test; MLHF – Minnesota living with heart failure questionnaire; LVEDD – left ventricular end diastolic diameter; LVEF – left ventricular ejection fraction; MRA – mitral regurgitation area; E/Apd – EA peak distance; AVVTI – aortic valvular velocity time integral; Ts-SD12 – the standard deviation of Ts of 12 LV segments; IVMD – interventricular mechanical delay.

(*P*<0.05) (Table 2). Conversely, preoperative and postoperative E/A pd did not differ significantly between the 2 groups. Postoperative AVVTI was increased in the left univentricular pacing by RAAVD group as compared to that in the standard biventricular pacing group (21.84±2.25 *vs.* 20.45±2.12 cm, *P*<0.05), whereas MRA and IVMD were reduced (3.09±1.12 *vs.* 3.73±1.19 $cm^2$, *P*<0.05; 64.27±12.29 *vs.* 71.39±13.64 ms, *P*<0.05, respectively). The other echocardiographic parameters did not differ significantly after the operation between the 2 groups (Table 2; Figures 2, 3).

### Comparison of clinical evaluation indicators

During clinical follow-up, NYHA classification, 6WMT, and MLHFQ, after implanting the pacemaker in the study participants, were found to improve before the operation in both the left univentricular pacing by RAAVD group and the standard biventricular pacing group. No statistically significant difference was observed in clinical indicators between in the 2 groups after the operation; the annual treatment cost was significantly reduced for the former group compared to the latter group (1.30±0.1 *vs.* 2.20±0.2 million Yuan, *P*<0.05).



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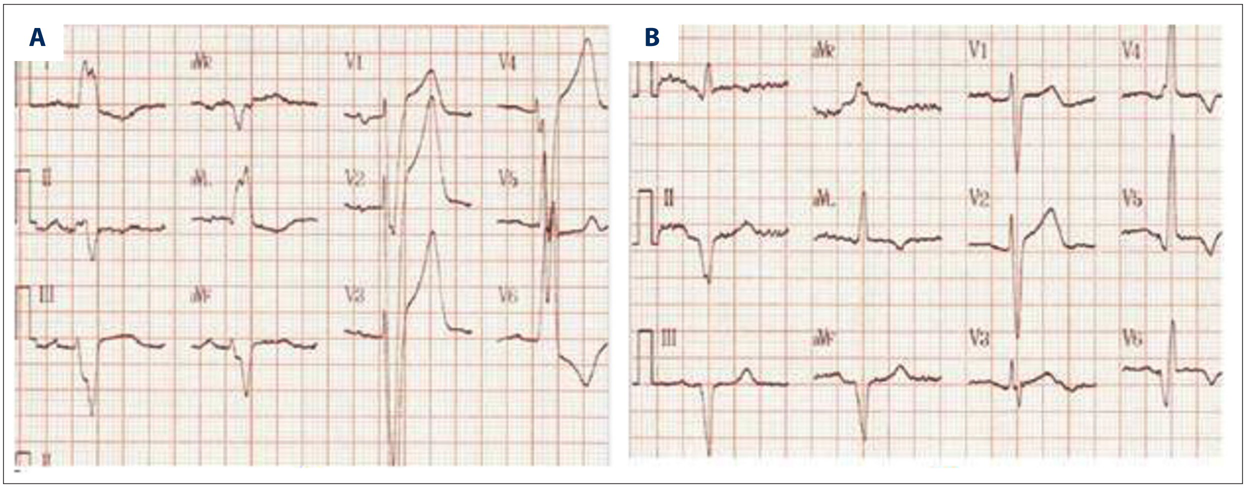


**Figure 1.** QRS duration was significantly narrowed for the case with chronic heart failure implanted with a dual-chamber pacemaker (Medtronic Relia RED01) to implement biventricular resynchronization through rate-adapted atrioventricular delay. (**A**) CLBBB before the operation and QRS duration was 200 ms; (**B**) Postoperative optimized QRS duration was 137 ms.

**Table 2.** Comparison of various indicators between the RAAVD, left univentricular pacing group, and the standard biventricular pacing group ($n$=30, $\bar{\chi}\pm s$).

| Indicators | The standard biventricular pacing group | | The RAAVD left univentricular pacing group | |
|---|---|---|---|---|
| | Before the operation | After the operation | Before the operation | After the operation |
| QRSduration (ms) | 182±20 | 144±11** | 187±21 | 137±11**,# |
| LVEF (%) | 29.21±5.01 | 34.27±3.32** | 27.61±4.20 | 35.2±3.98** |
| LVEDD (mm) | 73.96±10.83 | 68.30±10.91* | 79.11±11.53 | 67.27±10.93** |
| MRA ($cm^2$) | 4.53±1.31 | 3.73±1.19* | 4.08±1.15 | 3.09±1.12**,# |
| AVVTI (cm) | 15.81±2.13 | 20.45±2.12** | 16.43±2.31 | 21.84±2.25**,# |
| IVMD (ms) | 76.31±13.82 | 71.39±13.64 | 82.64±14.74 | 64.27±12.29**,# |
| E/Apd (ms) | 211.12±58.23 | 217.32±52.41 | 215.09±64.12 | 212.06±56.42 |
| Ts-SD12 (ms) | 118.37±23.51 | 97.19±26.97** | 122.06±22.23 | 95.29±25.59** |
| 6-MWT (m) | 355±60 | 495±63** | 348±57 | 502±62** |
| MLHFQ (score) | 37.86±15.79 | 27.96±10.77** | 35.47±21.03 | 25.71±15.93* |
| NYHA (class) | 3.10±0.49 | 1.875±0.64** | 3.21±0.54 | 1.75±0.46** |
| Annual treatment cost (million Yuan) | 2.20±0.20 | | 1.30±0.10# | |

LVEDD – left ventricular end diastolic diameter; LVEF – left ventricular ejection fraction; MRA – mitral regurgitation area; AVVTI – aortic valvular velocity time integral; IVMD – interventricular mechanical delay; E/Apd – EA peak distance; Ts-SD12 – standard deviation ofTs of 12 LV segments; 6-MWT – 6-minwalk test; NYHA – New York Heart function Association; Compared to those before the operation, * P<0.05 and ** P<0.001; Compared to those after the operation in the standard biventricular pacing group, # P<0.05.

### "Tracking Index" in the evaluation of the tracking circumstances of left univentricular pacing by RAAVD

According to the QRS wave morphologies of the 24-h dynamic electrocardiogram at different heart rate segments in the left univentricular pacing by RAAVD group (Figure 4), the S/R ratio of $V_1$ lead in each heart rate segment was calculated as 4.23±1.89 after measuring the R and S waves of $V_1$ lead in different heart rate segments, as well as the amplitude. These estimations indicated that the "tracking index ($R_{S/R}$-SD5)" in the left univentricular pacing by RAAVD group was 1.89 and was negatively correlated with ΔLVEF ($r$=–0.394, $P$=0.031) (Figure 4).





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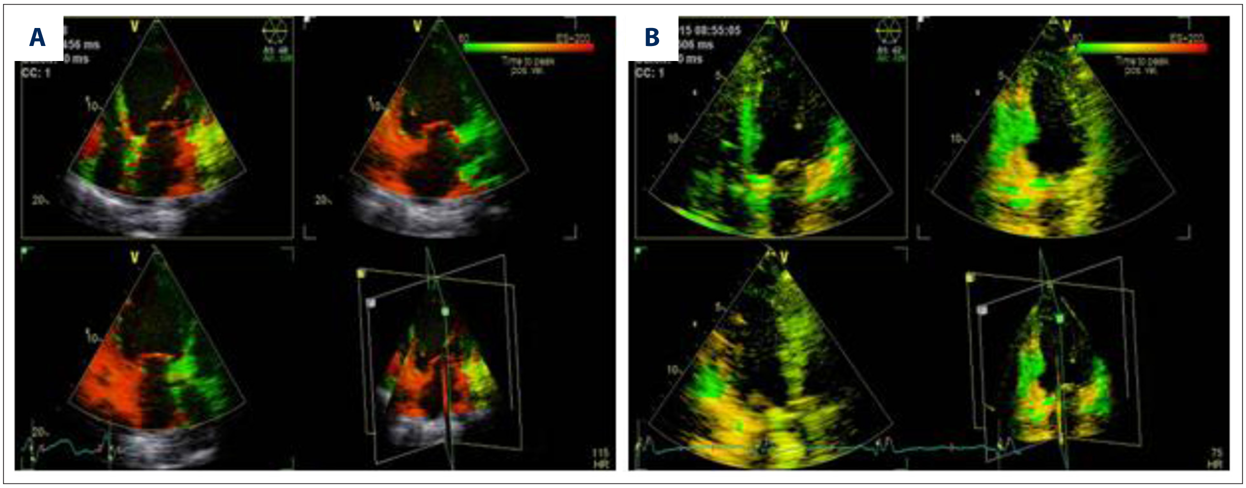


**Figure 2.** Echocardiographic synchronous imaging showed a significant improvement in postoperative synchronization in the 1 case with chronic heart failure implanted with a dual-chamber pacemaker (Medtronic Relia RED01) to implement biventricular resynchronization through rate-adapted atrioventricular delay. (**A**) Preoperative ventricular septum, inferior wall delayed in the lateral wall. (**B**) Postoperative left ventricular synchronization was good.

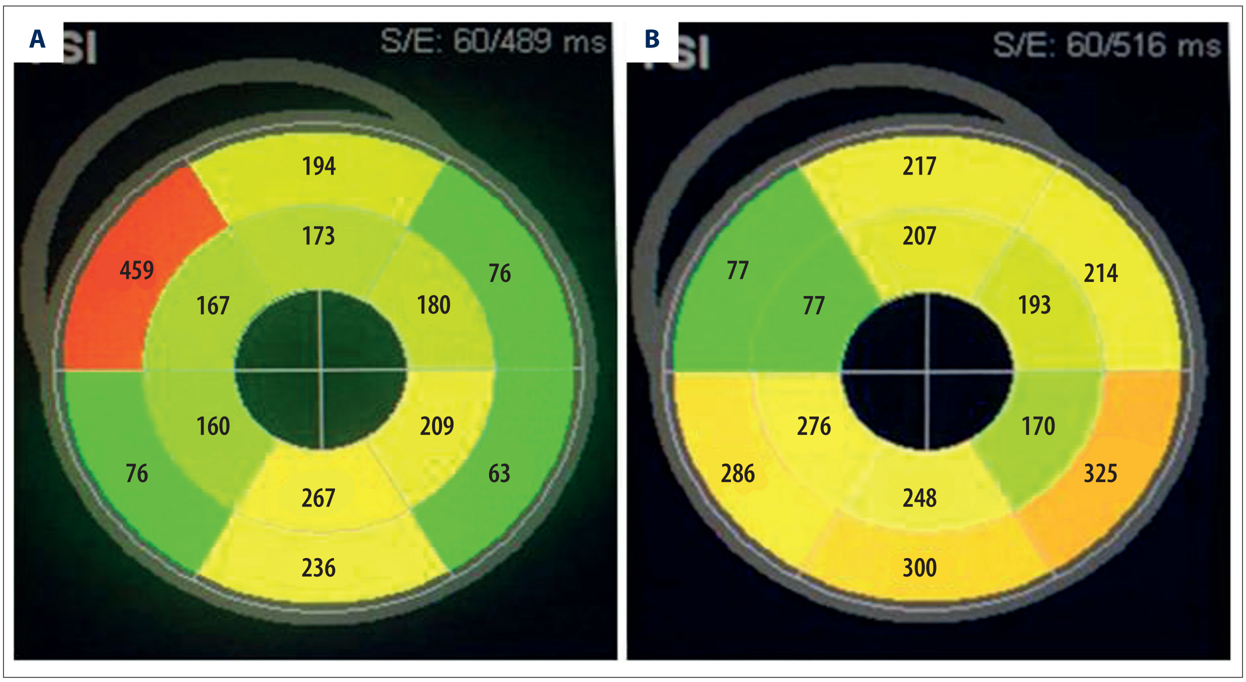


**Figure 3.** The "bulls-eye" diagram, reflecting left ventricular synchronization by real-time 3-dimensional echocardiography for the patients with chronic heart failure who had a dual-chamber pacemaker (Medtronic Relia RED01) implanted to implement biventricular resynchronization through rate-adapted atrioventricular delay, which suggested that the standard deviation of time to peak in 12 segments of left ventricle (Ts-SD12) was decreased, and intraventricular synchronization was significantly improved. (**A**) Preoperative TS-SD12 was 150 ms. (**B**) Postoperative TS-SD12 was 77 ms.

## Discussion

The present study found that QRS duration, LVEF, AVVTI, LVEDD, MRA, IVMD, Ts-SD12, and clinical indicators such as 6MWT and NYHA cardiac classification after the left univentricular pacing by RAAVD operation were improved significantly (*P*<0.001) as compared to the efficacies of the standard biventricular pacing in the treatment of chronic heart failure. Moreover, the post-operative QRS duration, AVVTI, MRA, and IVMD in the left univentricular pacing by RAAVD group were improved compared to those in the standard biventricular pacing group (*P*<0.05). "Tracking index" was used to assess the accuracy of the RAAVD





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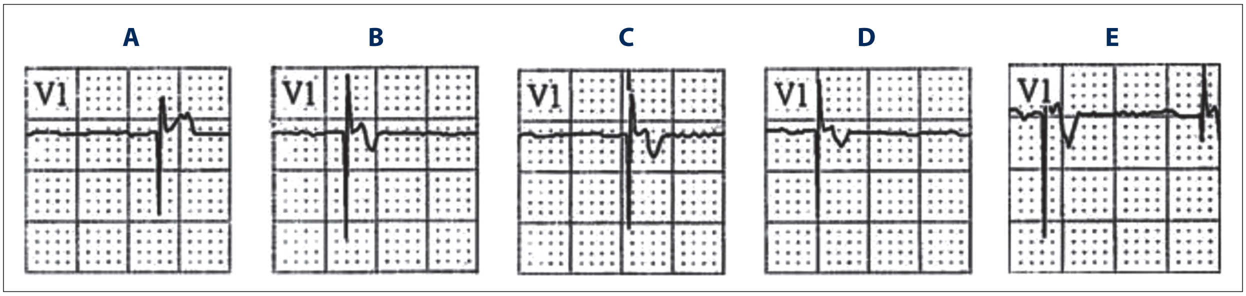


**Figure 4.** QRS wave morphologies at 5 different heart rate segments for 1 patient implanted with a dual-chamber pacemaker with rate-adaptive atrioventricular delay (RAAV) (Relia RED01, Medtronic, Inc., Minneapolis, MN, USA) in the left univentricular pacing by the rate-adaptive atrioventricular delay group. (**A**) Average heart rate of 60 bpm, S/R ratio of 1.25; (**B**) Average heart rate of 70 bpm S/R ratio of 2.00; (**C**) Average heart rate of 80 bpm, S/R ratio of 2.00; (**D**) Average heart rate of 90 bpm, S/R ratio of 1.88; (**E**) Average heart rate of 100 bpm, S/R ratio of 2.5. The 5 heart rate segments $V_1$ lead S/R ratio was 1.93±0.45; therefore, the tracking index ($R_{S/R}$-SD5) was 0.45.

algorithm in tracking the physiological AVD, as well as the degree of fusion between left univentricular pacing excitement and self-excitement, which was negatively correlated with improvement of LVEF.

Some previous studies have shown that effective fusion with self-excitement was not observed while using the left univentricular pacing, and the efficacy was not superior to that of standard biventricular pacing [19,20]. This phenomenon may be attributed to the use of left univentricular pacing through a fixed atrioventricular delay; on the other hand, the present study used a 3-chamber or dual-chamber pacemaker with RAAVD functions. Moreover, this study established parameters such as the variation of RAAVD according to the functional relationship between the heart rate of the patients and the variation of PR intervals. In a physiological environment, the supraventricular excitement rapidly and evenly passed down to activate the bilateral ventricles through the atrioventricular node and the His-Purkinje system. The physiological AVD showed a dynamic modification, with altered movements, sympathetic tone, and heart rate [15,21]. For patients with chronic heart failure combined with complete LBBB, this feature was physiologically relevant for retaining the inintrinsic AVD, preventing right ventricular pacing, restoring the intraventricular physiological exciting order of the right ventricle, dynamically tracking the right physiological PR interval by left univentricular pacing through RAAVD functions, and implementing the biventricular resynchronization by the ventricular fusion waves formed by self-excitement passed down from the right His-Purkinje system [22]. The results of our study further demonstrated that clinical symptoms, electrocardiogram, echocardiography, and cardiac function indicators improved significantly after left univentricular pacing by RAAVD, which were not inferior to those in patients in the standard biventricular pacing group. Also, some indicators were found to be superior to the latter group. However, the improvements in cardiac synchrony and hemodynamics revealed that QRS duration in the left univentricular pacing by RAAVD group was shortened compared to that in the standard biventricular pacing group. This altered duration appeared to be the right ventricular apex pacing of the standard biventricular pacing due to the excited slow conduction of the reverse His-Purkinje system among myocardial cells, thereby prolonging the exciting time in the right ventricle more than the self-excitement of the left univentricular pacing passed down by the right His-Purkinje system [22]. Previous studies have demonstrated that longer QRS duration is associated with a higher the proportion of non-synchronization, worse the cardiac functions, and higher mortality [23,24], suggesting that use of the left univentricular pacing by RAAVD may be better in long-term follow-up than standard biventricular pacing. Since the right ventricular electrode does not require pacing, the right ventricular electrode cannot be implanted or paced (retention of the functions of sensing and defibrillation). The cost of the medical equipment can be reduced for patients who have not had right ventricular electrodes implanted. Patients who have had the right ventricular electrodes implanted without pacing could potentiate the reduction of power consumption and prolong the service life, both of which can reduce study the medical costs to patients.

Previous studies have evaluated the degree of fusion between left univentricular pacing and intrinsic self-conduction through the average amplitude of R and S waves in lead $V_1$, which was (R+S)/2 [25,26]. This indicator was based on the left univentricular pacing through fixed AVD, and therefore was not suitable for left univentricular pacing in the application of AVD in the rate-adaptive AV algorithm. Thus, an indicator for the evaluation of the accuracy of left univentricular pacing in dynamically tracking the physiological AV is lacking. The present study was based on previous reports postulating that the left univentricular pacing delay conducted titration from more than (equivalent to the inherent LBBB or right ventricular first) to shorter than (equivalent to the left ventricular first or right bundle branch block) its AV. The changes in the amplitude of



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R and S waves in lead $V_1$ (S/R ratio) were from >1 to <1, suggesting that the dispersion of S/R ratio in lead $V_1$ at different heart rates can reflect the degree of fusion between heart rate changes in left univentricular pacing excitement and the inherent conduction through the RAAVD algorithm. This indicator was defined as the "tracking index" for the evaluation of the accuracy of RAAVD algorithm in dynamically tracking the physiological AVD. The application of $R_{S/R}$-SD5 in lead $V_1$ at 5 different heart rate segments found that $R_{S/R}$-SD5 was negatively correlated with ΔLVEF ($r$=–0.394, $P$=0.031), suggesting that $R_{S/R}$-SD5 can be used as an indicator for evaluating the accuracy of left univentricular pacing in tracking the physiological AVD and predicting the improvements in cardiac functions of patients with chronic heart failure after the implantation of a pacemaker. In recent years, 3-chamber pacemakers based on the algorithm of left univentricular pacing adaptive CRT have been used clinically. Studies showed that the application of this algorithm could improve the response rate by 12% compared to the traditional CRT [27,28]. Thus, the comparison of the accuracy and clinical efficacy of these 2 left univentricular pacing algorithms in tracking the physiological AVD is essential in subsequent studies.

### Limitations

The limitations of the present study include the use of dual-chamber pacemakers that cannot sense high-frequency ventricular events of ventricular tachycardia and ventricular fibrillation and cannot achieve defibrillation due to the absence of the right ventricular electrode. Thus, the use of dual-chamber pacemakers through the algorithm is not suitable for patients with ventricular tachycardia and/or ventricular fibrillation. For such patients, 3-chamber pacemakers (CRT-D) can be implanted, which utilizes the application of the algorithm implementing cardiac resynchronization therapy through left univentricular pacing. Although the pacing function of the implanted right ventricular electrode was closed, the sensing and defibrillation functions of the right ventricular electrode were retained. Thus, defibrillation could be enabled in the 3-chamber pacemaker, as necessary, in the event of closing of the pacing function of the implanted right ventricular electrode.

## Conclusions

The left univentricular pacing by RAAVD is physiologically relevant by considering the conduction of intrinsic AV node that can significantly improve the clinical symptoms, electrocardiogram, echocardiography, and cardiac function indicators; the efficacy is similar to the standard biventricular pacing. Moreover, some indicators are superior to the latter and can reduce the medical expense to patients. Left univentricular pacing by RAAVD can achieve an economical and physiological biventricular systolic resynchronization therapy for chronic heart failure patients.

### Conflict of interest

The authors declare that they have no actual or potential conflicts of interest.

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