



## Left univentricular pacing for cardiac resynchronization therapy using rate-adaptive atrioventricular delay

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### Abstract

**Objective** To evaluate left univentricular (LUV) pacing for cardiac resynchronization therapy (CRT) using a rate-adaptive atrioventricular delay (RAAVD) algorithm to track physiological atrioventricular delay (AVD). **Methods** A total of 72 patients with congestive heart failure (CHF) were randomized to RAAVD LUV pacing versus standard biventricular (BiV) pacing in a 1: 1 ratio. Echocardiography was used to optimize AVD for both groups. The effects of sequential BiV pacing and LUV pacing with optimized A-V (right atrio-LV) delay using an RAAVD algorithm were compared. The standard deviation (SD) of the S/R ratio in lead V1 at five heart rate (HR) segments ( $R_{S/R-SD5}$ ), defined as the “tracking index,” was used to evaluate the accuracy of the RAAVD algorithm for tracking physiological AVD. **Results** The QRS complex duration ( $132 \pm 9.8$  vs.  $138 \pm 10$  ms,  $P < 0.05$ ), the time required for optimization ( $21 \pm 5$  vs.  $50 \pm 8$  min,  $P < 0.001$ ), the mitral regurgitant area ( $1.9 \pm 1.1$  vs.  $2.5 \pm 1.3$  cm<sup>2</sup>,  $P < 0.05$ ), the interventricular mechanical delay time ( $60.7 \pm 13.3$  ms vs.  $68.3 \pm 14.2$  ms,  $P < 0.05$ ), and the average annual cost ( $13,200 \pm 1000$  vs.  $21,600 \pm 2000$  RMB,  $P < 0.001$ ) in the RAAVD LUV pacing group were significantly less than those in the standard BiV pacing group. The aortic valve velocity-time integral in the RAAVD LUV pacing group was greater than that in the standard BiV pacing group ( $22.7 \pm 2.2$  vs.  $21.4 \pm 2.1$  cm,  $P < 0.05$ ). The  $R_{S/R-SD5}$  was  $4.08 \pm 1.91$  in the RAAVD LUV pacing group, and was significantly negatively correlated with improved left ventricular ejection fraction (LVEF) ( $\Delta$ LVEF, Pearson's  $r = -0.427$ ,  $P = 0.009$ ), and positively correlated with New York Heart Association class (Spearman's  $r = 0.348$ ,  $P = 0.037$ ). **Conclusions** RAAVD LUV pacing is as effective as standard BiV pacing, can be more physiological than standard BiV pacing, and can decrease the average annual cost of CRT.

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**Keywords:** Cardiac resynchronization therapy; Congestive heart failure; Left univentricular pacing; Rate adaptive atrio-ventricular delay

## 1 Introduction

The cost for treatment of congestive heart failure (CHF) is relatively higher than that for other cardiovascular diseases.<sup>[1]</sup> Many CHF patients also have complete left bundle branch block (CLBBB),<sup>[2]</sup> which can result in systolic inter-

or intra-ventricular asynchrony, thereby compromising cardiac pump function.<sup>[3,4]</sup> Cardiac resynchronization therapy (CRT) which achieved by biventricular (BiV) pacing was developed to correct desynchronization of electrical and mechanical activation between the right ventricle (RV) and left ventricle (LV) that occurs in CHF patients with CLBBB.

CRT has been demonstrated to significantly improve cardiac function and clinical outcomes in patients with CHF.<sup>[5–7]</sup> However, one-third of CHF patients remain non-responsive to standard BiV pacing. Although many reasons have been suggested,<sup>[8]</sup> RV pacing with a changed activation sequence, attributed to the abnormal electrical and mechanical activation of the ventricles,<sup>[9,10]</sup> may play a role in the lack of response to CRT.

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The intrinsic atrioventricular delay (AVD) varies with the activity of the autonomic nervous system and heart rate (HR).<sup>[11–13]</sup> Accordingly, rate-adaptive AVD (RAAVD) was developed to mimic physiological AVD, and to dynamically coordinate the filling from atrium to ventricle.<sup>[14]</sup> However, use of a fixed, short AVD (100–120 ms) setting for biventricular capture in CRT,<sup>[15]</sup> which abolishes the physiological AVD of the AV node (AVN), can impede physiological conduction in the AVN, thereby counteracting the benefit of standard BiV pacing.<sup>[16,17]</sup>

Generally, right-sided conduction is normal in patients with CLBBB; therefore, there is no need for RV pacing in CRT.<sup>[18]</sup> Studies have shown that maintaining intrinsic AVN conduction, with simultaneous LV pacing and elimination of RV pacing, can improve acute hemodynamics more effectively than standard BiV pacing.<sup>[19–21]</sup> Thus, enabling fusion of intrinsic right bundle conduction with paced LV conduction, by tracking right-sided intrinsic AVD using an RAAVD algorithm, can be more physiological than standard BiV pacing, thereby increasing the response to CRT. This study evaluated the effect of LUV pacing for CRT using an RAAVD algorithm to track physiological AVD, in comparison with that for standard BiV pacing.

## 2 Methods

### 2.1 Patients

A total of 72 patients with congestive heart failure (CHF) were randomized to RAAVD LUV pacing versus standard BiV pacing in a 1:1 ratio. The study was performed at the first affiliated hospital of Kunming Medical University from July 2013 to December 2015. All patients had the following Class IA indications for CRT:<sup>[7]</sup> (1) ischemic or non-ischemic cardiomyopathy; (2) New York Heart Association (NYHA) Class II, III, or ambulatory Class IV after optimal medical therapy for CHF; (3) sinus rhythm; (4) left ventricular ejection fraction (LVEF)  $\leq$  35%; and (5) CLBBB, with QRS complex  $>$  150 ms. Standard medical therapy for CHF was given to all enrolled patients, which included administration of  $\beta$ -receptor antagonists, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and spironolactone. Informed consent for CRT was obtained. Basic demographic information, preimplantation CHF parameters, relevant CHF medications, and pacing lead locations were collected at subject enrolment. This study was conducted in accordance with the declaration of Helsinki, and conducted with approval from the Ethics Committee of Kunming medical University. Written informed consent was obtained from all participants.

Patients were excluded from the study if they had (1) life

expectancy of less than one year, (2) cardiomyopathy due to reversible causes, (3) valvular disease, (4) hypertrophic obstructive cardiomyopathy, (5) second or third degree atrioventricular block, (6) atrial fibrillation, or a (7) PQ interval  $>$  0.22 s.

### 2.2 CRT pacing system and pacemaker implantation

A CRT pacing system, according to operator preference, was implanted after informed consent was obtained. The devices used in this study included a three-chamber pacemaker/defibrillator (CRT-P/D) (Synkra C2TR01CRT, C174AWK CRT-D, Maximo II CRT-D, Insync sentry 7298 CRT-D) and a dual-chamber pacemaker (Adapta ADDR1/ADDRS1/ADDR01, Sensia SED01/SEDR01, Relia RED01) (Medtronic; Minneapolis, MN, USA). Pacemaker implantation was performed according to a standard procedure. For a dual-chamber pacemaker, two J-type guidewires were inserted through the left subclavian vein into the inferior vena cava. The pacemaker pocket was formed through blunt fascial dissection. The peel-away introducer was advanced along a guidewire, and the electrode was advanced to the coronary sinus ostium, followed by balloon catheter placement for retrograde angiography. Then, LV conveyor systems were placed. Under X-ray guidance, a percutaneous transluminal coronary angioplasty guidewire was used to advance the LV electrode lead to a position in the left posterolateral cardiac vein where possible, or in an alternative posterior or lateral vein, and the right atrial electrode was placed in the right atrial appendage. The LV lead was placed for greatest spatial separation from the tip of the RV lead, with stable LV capture and without diaphragmatic capture at four times the threshold voltage. The LV electrode and right atrial electrode leads were connected to corresponding jacks on the pulse generator. For a three-chamber CRT-P/D, a RV lead was placed in the apex of the RV.

### 2.3 Measurement of QRS duration

The QRS duration was automatically measured by using a 12-lead ECG machine (Marquette; GE, USA) at a speed of 25 mm/s and a gain of 1 mv/10 mm) before and after CRT, optimized using current guidelines and RAAVD LUV pacing, respectively). The morphology of the QRS complex in lead V1, defined as the average amplitude of S and R waves, was used to characterize the degree of fusion between LV pacing and intrinsic excitation.<sup>[22,23]</sup> A Holter ECG was recorded at follow-up, and the ratio of the amplitude of S and R (S/R ratio) was calculated at a heart rate (HR) of 60, 70, 80, 90, and 100 beats/min. For each patient in the RAAVD LUV pacing group, QRS duration and the amplitude of S and R were measured and averaged for three

consecutive beats using software calipers, and the S/R ratio was calculated. In this study, we defined standard deviation (SD) of the S/R ratio in lead V1 at five segments of HR ( $R_{S/R}-SD5$ ) as the “tracking index,” which was used to evaluate the accuracy of the RAAVD algorithm for tracking physiological AVD at varying HRs.

#### 2.4 Determination of PR interval at start and stop rate

A Holter ECG was recorded before CRT, and the HR and PR interval were used as dependent and independent variables, respectively, to establish a linear regression model. The start and stop rates were defined as the lower limit rate (LLR) and upper tracking rate (UTR), respectively. If the PR interval at the start and stop rates was not recorded by the Holter ECG, it could be calculated by using the linear regression model; the regression equation was defined as follows: PR interval =  $a \times \text{HR} + b$ , where  $b$  is constant,  $a$  is the partial regression coefficient, and HR is LLR or UTR.

#### 2.5 Measurement of cardiac ultrasound indicators

A Vivid7 Color Doppler System (GE Medical, Milwaukee, WI, USA) was used to measure echocardiographic indicators. The results were analyzed at a core laboratory by a single experienced observer blinded to the study. First, left ventricular end-diastolic diameter was measured directly from the 2-dimensional parasternal long-axis view or from M-mode recordings, using the leading-edge technique. Second, Doppler sample volume was located at the level of the mitral ostium in an apical 4-chamber view. Third, LV outflow tract blood flow spectrum was analyzed by locating the sample volume below the level of the aortic valve in an apical 5-chamber view. LVEF was calculated using Simpson’s rule (biplane method of disks at end-diastole and end-systole in orthogonal apical 2- and 4-chamber views). For each patient, the following echocardiographic parameters were measured before and after CRT: (1) mitral regurgitant area (MRA), (2) LVEF, (3) aortic valve velocity-time integral (AVVTI), (4) interventricular mechanical delay (IVMD) time, (5) E/A procedure duration, and (6) SD of time intervals of 12 LV segments ( $Ts-SD12$ ). Each parameter was measured three times, and an average value was calculated.

#### 2.6 Exercise tolerance

The 6-minute walk test distance was measured, and used to evaluate the improvement of exercise capacity.

#### 2.7 A-V and V-V delay optimization in standard BiV pacing

A device programmer (CareLink model 2090; Medtronic)

was used to interrogate and program the device. A-V and V-V delay were optimized at rest with the patient in the left lateral position after pacemaker implantation, according to current guidelines. Sensed A-V interval (SAV) was used when the function of the sinus node was normal. First, BiV pacing mode (RV + LV) was programmed, and then the AVD was titrated in 10-ms steps. The atrio-LV delay was programmed first. The optimal AVD in standard BiV pacing was defined as the shortest AVD that could ensure the longest duration of ventricular filling, the largest stroke volume, the largest AVVTI, and minimization of mitral regurgitation (MR), with no truncation of the transmural A wave, while ensuring paced ventricular activation.<sup>[24]</sup> The optimal V-V delay was confirmed when the largest AVVTI was achieved.<sup>[25]</sup> Cardiac function indicators were measured 5 minutes after each A-V and V-V delay optimization.

#### 2.8 AVD and V-R delay optimization in the RAAVD LUV pacing group

Atrial sense compensation (ASC) was measured as the time from onset of the A wave to atrial sense (AS) in the right atrial (RA) intracardiac electrogram (IEGM). In this study, the optimal interval between the RV and LV was defined as the V-R delay in the LUV pacing group. Prolonging AVD until ventricular sense (VS) showed on the IEGM, with AS-VS interval – ASC as the baseline interval, and progressive shortening by 10-ms steps. The optimal AVD (i.e., left-sided AVD) was that which achieved the maximal increase in AVVTI. Optimal V-R delay can be calculated as PR interval at optimization – (optimal AVD + ASC).

#### 2.9 Programing steps for LUV pacing with RAAVD

Set start (60 beats/min) and stop rate (UTR). Set SAV for start and stop rate: start/stop rate SAV = PR interval at start/stop rate – (Optimal V-R delay + ASC) = {PR interval at start/stop rate – [PR interval at optimization – (optimal AVD + ASC)]} – ASC = Optimal AVD + (PR interval at start/stop rate – PR interval at optimization). Set PAV for start/stop rate (PAV = SAV for start/stop rate + ASC). The AVD was titrated until ventricular sensing (VS) was displayed on the marker channel of the programmer. LV-only pacing mode was programmed and RAAVD was set to ON. Echocardiographic evaluation of cardiac function was performed five minutes after programing. The times required for optimization in both groups were compared.

#### 2.10 Estimation of device longevity

Device longevity was estimated for standard BiV and LUV pacing groups. The average cost of CRT was based on

the cost of the pacemaker system and device longevity. Efficacy of CRT was compared for LUV pacing with an RAAVD algorithm and standard BiV pacing.

### 2.11 Data analysis

All data were analyzed with SPSS 17.0 software. Baseline characteristics are expressed as mean and SD for continuous variables, and percentages for categorical variables. The chi-square test was used to analyze dichotomous variables. The means in the two groups were compared with a *t*-test if the data showed a normal distribution; if not, the Mann-Whitney U test was used. A linear regression model was used to analyze the correlation between PR interval and HR. Correlations between  $R_{S/R}$ -SD5 and improved LVEF ( $\Delta$ LVEF), and between  $R_{S/R}$ -SD5 and New York Heart Association (NYHA) class, were determined by Pearson and Spearman coefficients, respectively. A 2-tailed *P* value < 0.05 was considered statistically significant.

## 3 Results

### 3.1 Patient demographics

The preimplant characteristics of the 72 patients enrolled in the study are shown in Table 1. The baseline (pre-CRT) age, sex, exercise tolerance, PR intervals, NYHA class, and cardiac ultrasound indicators were not significantly different between RAAVD LUV pacing and standard BiV pacing groups ( $P > 0.05$ ).

### 3.2 Follow-up results

After a mean follow-up duration of 13 months, the estimated device longevity in the RAAVD LUV pacing group ( $6.9 \pm 0.3$  years) was significantly longer than that in the standard BiV pacing group ( $3.7 \pm 0.2$  years,  $P < 0.001$ ). The QRS duration ( $132 \pm 9.8$  vs.  $138 \pm 10$  ms,  $P < 0.05$ ), the time required for optimization ( $21 \pm 5$  vs.  $50 \pm 8$  min,  $P < 0.001$ ), the MRA ( $1.9 \pm 1.1$  vs.  $2.5 \pm 1.3$  cm<sup>2</sup>,  $P < 0.05$ ), the IVMD time ( $60.7 \pm 13.3$  vs.  $68.3 \pm 14.2$  ms,  $P < 0.05$ ), and the average annual cost ( $13,200 \pm 1,000$  vs.  $21,600 \pm 2,000$  RMB,  $P < 0.001$ ) were significantly lesser in the RAAVD LUV pacing group than in the standard BiV pacing group. The AVVTI in the RAAVD LUV pacing group was greater than that in the standard BiV pacing group ( $22.70 \pm 2.20$  vs.  $21.40 \pm 2.10$  cm,  $P < 0.05$ ). The other variables were not significantly different between the groups ( $P > 0.05$ ). Three patients in the RAAVD LUV pacing group and 4 in the standard BiV pacing group died ( $P > 0.05$ ) (Table 2). Figures 1-4 show a patient in the RAAVD LUV pacing group who received a dual-chamber pacemaker (Relia RED01).

**Table 1. Baseline characteristics.**

Variables	Standard BiV pacing group (n = 36)	RAAVD LUV pacing group (n = 36)	<i>P</i> value
Age, yrs	54 ± 13	55 ± 14	0.754
Male	27 (75%)	28 (77.8%)	0.781
Etiology			
DCM	30 (83.3%)	31 (86.1%)	0.743
ICM	6 (16.7%)	5 (13.9%)	0.743
NYHA Class	3.11 ± 0.57	3.19 ± 0.58	0.557
II	4 (11.11%)	3 (8.33%)	0.5
III	24 (66.67%)	23 (63.9%)	0.804
IV	8 (22.2%)	10 (27.8%)	0.586
PR interval, ms	162 ± 12	166 ± 12	0.162
QRS complex duration, ms	178 ± 19	182 ± 20	0.388
LADD, mm	42.1 ± 8.2	44.2 ± 8.6	0.293
LVDD, mm	74.6 ± 10.2	76.2 ± 10.5	0.514
LVEF, %	0.28 ± 0.06	0.27 ± 0.06	0.292
MRA, cm <sup>2</sup>	4.7 ± 1.3	4.3 ± 1.2	0.179
AVVTI, cm	15.7 ± 2.2	16.1 ± 2.2	0.443
E/A Pd, ms	207 ± 59	218 ± 62	0.443
IVMD, ms	77.5 ± 13.2	80.4 ± 13.4	0.358
Ts-SD12, ms	108 ± 19	114 ± 20	0.196
6MWT, m	350 ± 53	344 ± 51	0.626

Data were presented as mean ± SD or *n* (%). AVVTI: aortic velocity-time integral; BiV: biventricular; DCM: dilated cardiomyopathy; E/A Pd: E/A procedure duration; LADD: left atrial diastolic diameter; LUV: left univentricular; LVDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; ICM: ischemic cardiomyopathy; IVMD: Interventricular mechanical delay time; MRA: area of the mitral regurgitation; NYHA: New York Heart Association; RAAVD: rate adaptive atrio-ventricular delay; Ts-SD12: Standard deviation of time intervals of the 12 LV segments; 6MWT: 6- minute walk test.

$R_{S/R}$ -SD5 was  $4.08 \pm 1.91$  in the RAAVD LUV pacing group, and was significantly negatively correlated with improved LVEF ( $\Delta$ LVEF) (Pearson's  $r = -0.427$ ,  $P = 0.009$ ), and positively correlated with NYHA class (Spearman's  $r = 0.348$ ,  $P = 0.037$ ) (Figure 5).

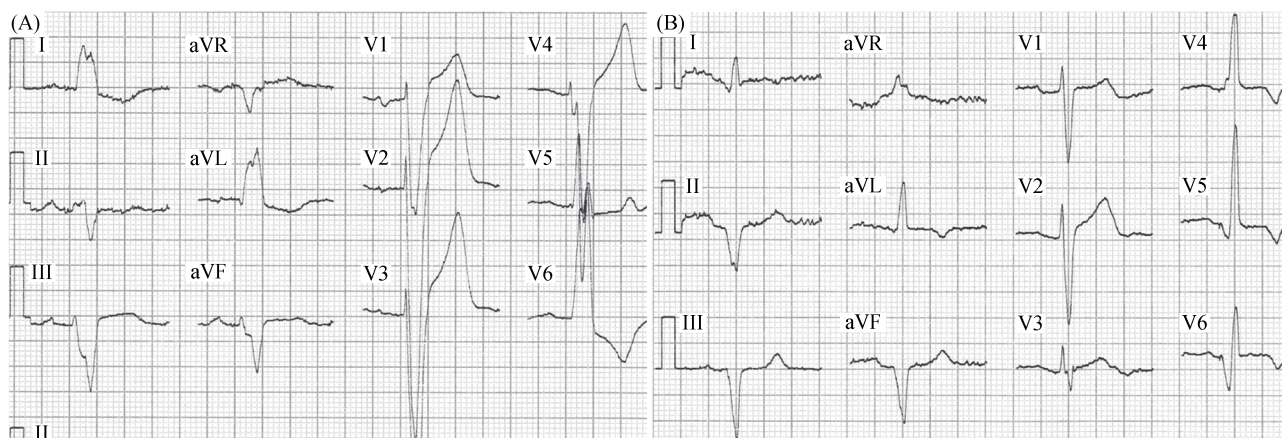
## 4 Discussion

Physiological AVD dynamically varies according to exercise and sympathetic tone changes, and plays a key role in optimal atrial contribution to ventricular filling. A previous study reported reduction in optimal AVD with physiological exercise in patients with CHF who underwent CRT. Furthermore, BiV pacing with a programmable RAAVD translated into a 10% improvement in exercise capacity.<sup>[26]</sup> This

**Table 2. Comparison between standard BiV and RAAVD LUV pacing group.**

Variables	Standard BiV pacing group (n = 36)	RAAVD LUV pacing group (n = 36)	P value
Average follow-up time, month	13.3 ± 8.6	13.7 ± 8.4	0.842
Time consuming for optimization, min	50 ± 8	21 ± 5	< 0.001
Device longevity, yrs	3.7 ± 0.2	6.9 ± 0.3	< 0.001
Optimized AVD, ms	110.3 ± 8.1	128.1 ± 9.8	< 0.001
NYHA class	2.56 ± 0.73	2.47 ± 0.70	0.422
II	21 (58.3%)	24 (66.7%)	0.465
III	10 (27.8%)	9 (25%)	0.789
IV	5 (13.9%)	3 (8.3%)	0.355
V-V/R delay, ms	23.9 ± 7.7	19.6 ± 7.3	0.018
QRS complex duration, ms	138 ± 10	132 ± 9.8	0.012
LADD, mm	38.3 ± 6.6	36.1 ± 6.2	0.149
LVDD, mm	65.8 ± 9.2	62.2 ± 8.8	0.094
LVEF, %	0.39 ± 0.06	0.41 ± 0.09	0.234
MRA, cm <sup>2</sup>	2.5 ± 1.3	1.9 ± 1.1	0.038
AVVTI, cm	21.4 ± 2.1	22.7 ± 2.2	0.012
E/A Pd, ms	198 ± 67	186 ± 60	0.426
IVMD, ms	68.3 ± 14.2	60.7 ± 13.3	0.022
Ts-SD12, ms	92 ± 26	81 ± 24	0.066
6MWT, m	563 ± 81	597 ± 85	0.087
Average annual cost, 10000 RMB	2.16 ± 0.2	1.32 ± 0.1	< 0.001
Hospital readmission	11 (30.56%)	10 (27.78%)	0.795
Mortality	4 (11.11%)	3 (8.33%)	0.5

Data were presented as mean ± SD or n (%). AVD: atrioventricular delay; AVVTI: Aortic velocity-time integral; BiV: biventricular; E/A Pd: E/A procedure duration; LADD: left atrial diameter; LUV: left univentricular; LVDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; IVMD: Interventricular mechanical delay time; MRA: area of the mitral regurgitation; NYHA: New York Heart Association; RAAVD: rate adaptive atrio-ventricular delay; Ts-SD12: standard deviation of time intervals of the 12 LV segments; 6MWT: 6-minute walk test.

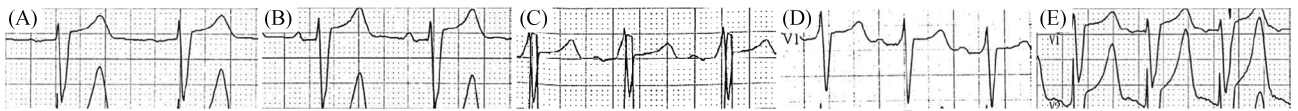


**Figure 1. The comparison between QRS complex pre- and post-operation.** A patient with CHF was implanted with a dual-chamber pacemaker (Relia RED01, Medtronic, Inc., Minneapolis, MN, USA). (A): Pre-CRT (CLBBB, QRS duration was 200 ms under intrinsic atrioventricular conduction); (B): post-LUV pacing with RAAVD (QRS duration was 137 ms). CHF: congestive heart failure; CRT: cardiac resynchronization therapy; LUV: left univentricular; RAAVD: rate adaptive atrio-ventricular delay;  $R_{SR}$ -SD5 (Tracking index)

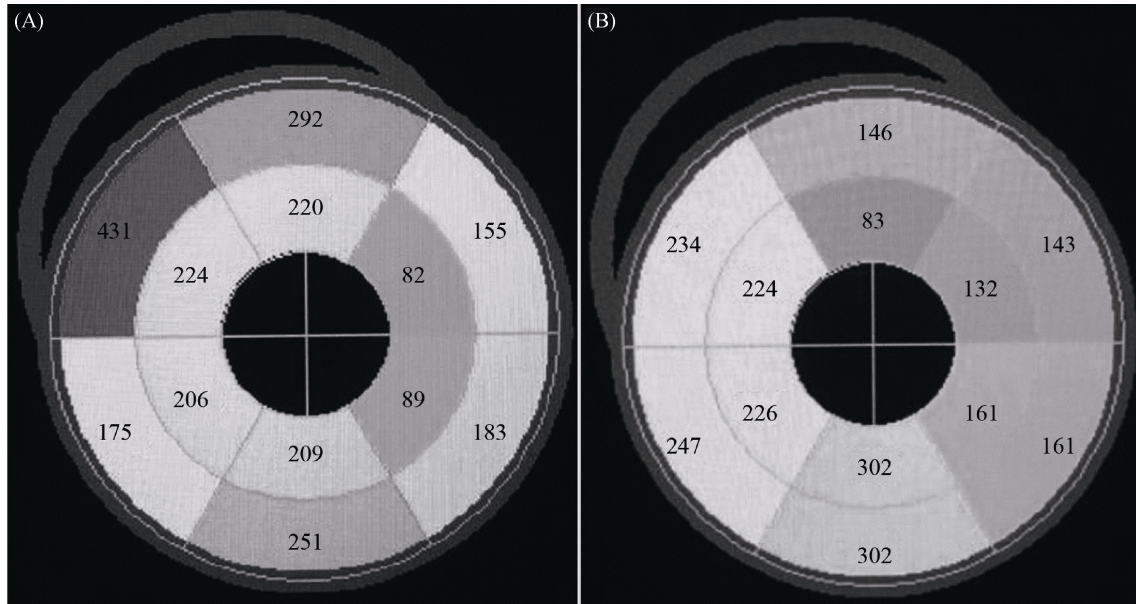
indicated that programming a fixed and short AVD for CRT, which abolishes the physiological AVD of the AVN, impaired physiological AV conduction. In this study, we de-

veloped an algorithm to preserve the physiological AVD of the AVN, and to achieve CRT with LUV pacing. Left-sided AVD automatically tracks physiological AVD by using an

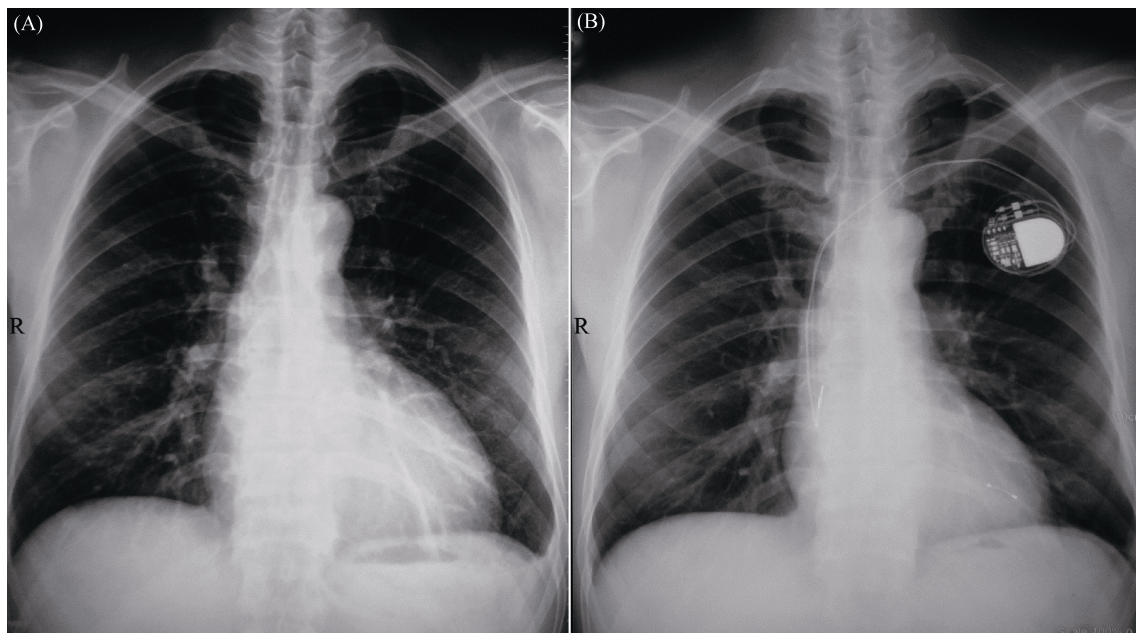




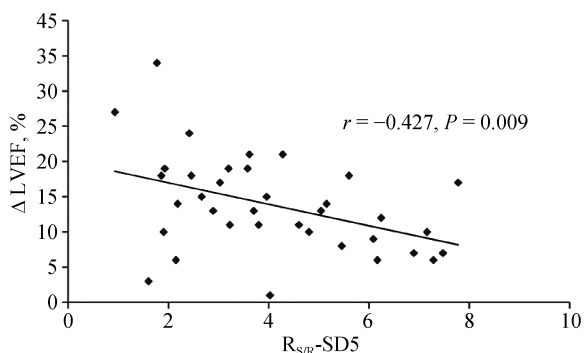
**Figure 2. QRS complex morphology at 5 different HR.** (A): At average HR of 60 bpm, S/R ratio was 3.29; (B): at average HR of 70 beats/min, S/R ratio was 3.55; (C): at average HR of 80 beats/min, S/R ratio was 1.25; (D): at average HR of 90 beats/min, S/R ratio was 2.18; (E): at average HR of 100 beats/min, S/R ratio was 2.2. S/R ratio of five segments of HR was  $2.49 \pm 0.93$ , tracking index  $[R_{S/R-SD5}]$  was 0.93 for this patient. HR: heart rate.



**Figure 3. The comparison between Ts-SD12 pre- and post-RAAVD LUV pacing.** Bull eye view of real-time three-dimensional echocardiography showed that Ts-SD12 improved 12 months post-RAAVD LUV pacing. (A): Ts-SD12 was 92 ms pre- RAAVD LUV pacing; (B): Ts-SD12 was 70 ms 12 months post-RAAVD LUV pacing. LUV: left univentricular; RAAVD: rate adaptive atrio-ventricular delay.



**Figure 4. Chest X-ray pre- and one year post-PM implantation.** (A): Pre-PM implantation, chest X-ray showed LV dilated. CTR was 56%, LVDD: 69 mm. (B): 12 months post-PM implantation, great reduction in ventricular size, the CTR decreased from 0.56 to 0.49, LVDD decreased from 69 mm to 53 mm. CRT: cardiac resynchronization therapy; CTR: cardiothoracic ratio; LV: left ventricular; LVDD: left ventricular diastolic diameter; PM: pacemaker.



**Figure 5. Correlation between  $R_{S/R}$ -SD5 and improved LVEF.** Correlation of SD of S/R ratio in lead V1 at five segments of HR ( $R_{S/R}$ -SD5) with improved LVEF ( $\Delta$ LVEF) in RAAVD LUV pacing group.  $R_{S/R}$ -SD5 significantly negative correlated with improved LVEF ( $r = -0.427$ ,  $P = 0.009$ ). HR: heart rate; LVEF: left ventricular ejection fraction; LUV: left univentricular; RAAVD: rate adaptive atrio-ventricular delay;  $R_{S/R}$ -SD5: standard deviation of the R/S ratio in lead V1 at five heart rate segments.

RAAVD algorithm to allow fusion, with intrinsic conduction from the normal right bundle branch. Therefore, RAAVD LUV pacing algorithms may be more physiological than those of standard BiV pacing. Furthermore, RAAVD LUV pacing eliminates RV pacing, thereby decreasing the risk of heart failure and atrial fibrillation.<sup>[27,28]</sup> Moreover, RAAVD LUV pacing increases device longevity, as it is not necessary to pace the RV. This decreases the average annual cost of CRT.

RV pacing is a component of standard BiV pacing, in which RV activation is delayed more than in physiological activation. This results in a longer QRS duration, which is associated with mechanical dyssynchrony, decreased cardiac function, and higher mortality.<sup>[29]</sup> Our results showed that RAAVD LUV pacing can shorten the QRS duration more than with standard BiV pacing. This indicated that RAAVD algorithms can accurately track physiological AVD and enable fusion of intrinsic right bundle conduction with paced LV conduction. Thus, the changes in fusion and QRS duration that result from fixed AVD and varying intrinsic conduction would be resolved. This may explain the results of previous studies showing that fusion was not established in LUV pacing with fixed AVD, and that LUV pacing is not superior to BiV pacing.<sup>[30,31]</sup>

Interval optimization plays a key role in improving hemodynamic effects in standard BiV pacing; however, it is time-consuming and difficult to achieve individualization and dynamic optimization.<sup>[32,33]</sup> In LUV pacing with RAAVD, the intrinsic AVD is physiologic and optimal, and there is no need for dynamic optimization. Moreover, left-sided AVD automatically tracks physiological AVD by

using an RAAV algorithm. Therefore, RAAVD LUV pacing can achieve dynamic optimization of AVD. Adaptation to physiological alterations during exercise and sympathetic tone changes thereby restore the optimal atrial contribution to ventricular filling. Theoretically, the efficacy of dynamic optimization in LUV pacing is determined by the accuracy of the RAAVD algorithm, which tracks physiological AVD under varying HR. The midpoint (average) between the maximum (R-wave) and minimum (S-wave) amplitude of the QRS complex in lead V1 [(R-V1 + S-V1)/2] has been previously used to characterize the degree of fusion between LUV-paced and intrinsic excitations. Furthermore, with progressive shortening of the programmed AV interval, the QRS (mainly in lead V1) changes from an LBBB- ( $S/R > 1$ ) to an RBBB-like ( $S/R < 1$ ) morphology at the shortest AV interval under LUV pacing.<sup>[22,23]</sup> This indicates that deviation of the S/R ratio may sensitively indicate the degree of fusion at varying HRs, and can evaluate the accuracy of an RAAVD algorithm. This study is the first to describe a tracking index ( $R_{S/R}$ -SD5) for use in evaluating the accuracy of an RAAVD algorithm for tracking physiological AVD at varying HRs in LUV pacing. The results of our study showed a significantly negative correlation between  $R_{S/R}$ -SD5 and improved LVEF ( $\Delta$ LVEF), indicating that  $R_{S/R}$ -SD5 may be a valuable predictor of response to CRT in LUV pacing. Recent studies have shown that an adaptive CRT LUV pacing algorithm may improve the response to CRT by 12%.<sup>[34,35]</sup> The accuracy of physiologic AVD tracking and the comparison between adaptive CRT and an RAAVD LUV pacing algorithm require further investigation.

In summary, RAAVD LUV pacing can preserve the physiological AV conduction of the AVN, and can restore physiological activation of the RV. The result is more physiological and beneficial than standard BiV pacing, thereby improving the response to CRT. However, several variables did not show differences between the two groups, which may be due to the relatively small sample size and short follow-up. Therefore, a randomized, multicenter, double-blind, controlled clinical study is needed to confirm our findings. The novel algorithms for tracking physiological AVD in LUV pacing will contribute to research and development of new pacemakers. This may even challenge the requirement for 100% BiV pacing in traditional CRT.<sup>[36]</sup>

In Conclusion, LUV pacing achieved CRT by using an RAAVD algorithm. This preserved the physiological AV conduction of the AVN, and was more physiological than standard BiV pacing, at least as effective as standard BiV pacing, and decreased the average annual cost of CRT.

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