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ORIGINAL RESEARCH ARTICLE

Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing

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Abstract

Aims This multicentre observational study aimed to prospectively assess the efficacy of left bundle branch area pacing (LBBAP) in heart failure patients with left bundle branch block (LBBB) and compare the 6-month outcomes between LBBAP and biventricular pacing (BVP).

Methods and results Consecutive patients with LBBB and left ventricular ejection fraction (LVEF) ≤ 35% were prospectively recruited if they had undergone LBBAP as a primary or rescue strategy from three separate centres from March to December 2018. Patients who received BVP in 2018 were retrospectively selected by using 2 to 1 propensity score matching to minimize bias. Implant characteristics and echocardiographic parameters were assessed during the 6-month follow-up. LBBAP procedure succeeded in 81.1% (30/37) of patients, with selective LBBAP in 10 patients, and 3 of 20 patients combined non-selective LBBAP and LV lead pacing for further QRS narrowing. LBBAP resulted in significant QRS narrowing (from 178.2 ± 18.8 to 121.8 ± 10.8 ms, $P < 0.001$, paced QRS duration ≤ 130 ms in 27 patients) and improved LVEF (from 28.8 ± 4.5% to 44.3 ± 8.7%, $P < 0.001$) during the 6-month follow-up. The comparison between 27 patients with LBBAP alone and 54 of 130 matching patients with BVP showed that LBBAP delivered a greater reduction in the QRSd (58.0 vs. 12.5 ms, $P < 0.001$), a greater increase in LVEF (15.6% vs. 7.0%, $P < 0.001$), and greater echocardiographic (88.9% vs. 66.7%, $P = 0.035$) and super response (44.4% vs. 16.7%, $P = 0.007$) to cardiac resynchronization therapy.

Conclusions LBBAP could deliver cardiac resynchronization therapy in most patients with heart failure and LBBB, and might be a promising alternative resynchronization approach to BVP.

Keywords Left bundle branch area pacing; Cardiac resynchronization therapy; Heart failure; Left bundle branch block

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with reduced left ventricular ejection fraction (LVEF) and complete left bundle branch block (LBBB) by utilizing biventricular pacing (BVP). However, approximately 30% of patients do not respond to BVP.[1] His-bundle pacing (HBP) is a method of pacing that can maintain physiologic electromechanical synchrony by facilitating conduction through the native His−Purkinje system. HBP has been associated with improved cardiac function and fewer heart failure (HF) hospitalizations.[2] According to previous studies, HBP delivers better QRS narrowing and greater improvement in haemodynamic parameters than traditional BVP.[3–5] However, a number of clinical concerns remain regarding the application of HBP in patients with HF, including

technical challenges in His lead placement,[6] failed corrections of bundle branch blocks (BBB),[7] the risk of increased capture thresholds during later period, and high complications for lead revision.[8]

Left bundle branch area pacing (LBBAP) has emerged as an alternative choice to HBP by pacing the left bundle branch (LBB) region beyond the block site with a stable threshold and narrow QRS duration (QRSd) in patients with bradycardia.[9,10] Huang *et al*. first demonstrated that LBBAP could achieve complete correction of LBBB and improved cardiac function in patients with LBBB and HF in case reports.[11,12] Recently, an observational study summarized the effect of LBBAP in 11 patients with HF and LBBB and demonstrated the feasibility of LBBAP delivered CRT.[13] However, still few data are available on the application of LBBAP delivered CRT in patients with HF and LBBB, and there are no data on direct comparisons of echocardiographic and clinical responses with CRT between LBBAP and BVP. Therefore, the present study aimed to prospectively assess the implant, electrocardiogram (ECG) and pacing parameters, and echocardiographic and clinical response to LBBAP delivered CRT in patients with LBBB and HF. A preliminary comparison of the clinical response between LBBAP and BVP was also performed by using propensity score matching to minimize bias.

Methods

This was a prospective, observational, multicentre study including three clinical sites in China, and the Fuwai Hospital worked as the study coordinating site. The institutional review board of the Fuwai Hospital approved the study protocol of LBBAP and data analysis. All patients provided informed consent on receiving CRT therapy, while patients in LBBAP group had given written informed consent to the study and on an agreement of undergoing LBBAP or LBBAP combined with BVP as the unconventional pacing approach to achieve cardiac resynchronization before the enrolment at each participating site. All data were finally sent to the Fuwai Hospital for analysis.

Patient selection

Permanent LBBAP was attempted in patients who failed or were eligible for BVP according to the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines from March to December 2018. All operators are experienced in BVP-CRT implantation and have performed 50 LBBAP implantation procedures. All patients included in the study had HF symptoms, LVEF $\leq$ 35% with LBBB, and had received at least 4 months of guideline-directed medical therapy. LBBAP was performed as two strategies: rescue LBBAP was performed in patients with unsuccessful coronary sinus (CS) LV lead placement, and primary LBBAP was attempted as the first option in place of the CS-LV lead. In order to evaluate the clinical effects of LBBAP against BVP, patients who received BVP because of LBBB and LVEF $\leq$ 35% in 2018 were selected by using 2 to 1 propensity score matching to minimize bias based on gender, baseline QRS morphology and duration, and LVEF and LV end-diastolic diameter (LVEDD).

Procedures

LBBAP was performed using the SelectSecure system (model 3830 lead, 69 cm; C315 His sheath, Medtronic, Inc., Minneapolis, MN) as previously described.[9,14] Briefly, the 3830 pacing lead was delivered through the C315 His sheath in the right anterior oblique 30° fluoroscopy view. Unipolar pacing mapping at 2.0 V/0.4 ms was used to identify the ideal pacing site with the following criteria: (i) The paced QRS complex in lead V1 had a duration of less than 145 ms or/and presented with a 'W' morphology with a notch at the nadir or at the rising branch; and (ii) R-wave sensing of the tip was at least 5.0 mV. Subsequently, the 3830 lead was screwed clockwise with approximately 5 to 6 rotations, and unipolar pacing was performed frequently to assess the paced QRS morphology, QRSd, pacing impedance, and R-wave amplitude. Generally, the paced QRS complex in lead V1 would display right bundle branch block pattern, and the QRSd would narrow significantly when the tip of the lead reached the LBB area. The stimulus to the peak of the left ventricular activation time in leads V5 to V6 was tested, and the lead screwing was stopped when the stimulus to the peak of the left ventricular activation time was shortened significantly and remained stable at different outputs ($>$ 5.0 V/0.4 and 2.0 V/0.4 ms). The lead depth in the interventricular septum was checked by ring capture testing and fluoroscopy views in the left anterior oblique 45° position. Unipolar and bipolar pacing tests were performed, and the LBB potential was evaluated on an intracardiac electrogram. During the procedure, fluoroscopic and cinematographic imaging were set to 4 frames per second for fluoroscopy and 7.5 frames per second for cinematographic images. Rescue LBBAP was performed in patients with unsuccessful CS-LV lead implantation. In the primary LBBAP procedure, the CS-LV lead was implanted following LBBAP lead placement for backup of resynchronization therapy during the initial study period due concerns regarding the long-term effect of LBBAP. During the later phase, the implantation of the CS-LV lead was abandoned if a QRSd $\leq$ 130 ms was achieved by LBBAP in the primary procedure.

Traditional cardiac resynchronization therapy procedure

The CS was cannulated from left auxiliary or subclavian vein. The selection of the LV lead was based on the decision of the

implanting physician, and the LV lead was positioned preferably in the lateral or posterolateral vein, sometimes in the anterolateral vein. The right atrial and right ventricular leads were positioned in the appendage of the right atrium and the right ventricular septum or apex.

Device connection and programming

The lead-to-device connection configurations that were used in LBBAP are presented in a schematic diagram (*Figure 1*). In patients with sinus rhythm, the LBBAP lead was usually connected to the LV port for the rescue LBBAP procedure for implantation of a CRT-defibrillator (CRT-D) (*Figure 1A, 1B,* and *1I*) or a CRT-pacemaker (CRT-P) (*Figure 1C*). In the primary LBBAP procedure, if the CS-LV lead was routinely implanted and connected to the LV port, the LBBAP lead was connected to the right ventricular (RV) pace-sense port while the pace-sense port of the spliced defibrillator lead (DF1) was capped in patients with CRT-D (*Figure 1D* and *1J*) or to the RV port in patients with CRT-P (*Figure 1E*). In patients with persistent atrial fibrillation, the LBBAP lead was connected to the atrial port for implantation of CRT-P or CRT-D (*Figure 1F, 1G, 1H,* and *1K*).

If LBBAP could achieve perfect correction of the LBBB, the V-V delay was programmed to a maximum of 80 ms for introducing LBBAP alone, and the output of the RV or LV lead was set to 0.5 V/0.1 ms to avoid RV or LV pacing. If the paced QRSd was not less than 140 ms with LBBAP alone during the primary procedure, sequential pacing combined with LBBAP and CS-LV lead pacing was then programmed with appropriate and LV-RV (V-V) interval for further QRS narrowing. In patients with sinus rhythm, the atrial-ventricular (A-V) delay was adjusted for ECG optimization.

In patients with BVP, the optimization of the A-V and V-V intervals was routinely adjusted by the implanting physician to optimize QRSd narrowing. For some patients with unsatisfactory QRS shortening, echocardiographic optimization based on the maximal aortic velocity-time integral was used to adjust the A-V and V-V delays.[15]

ECG, echocardiographic evaluation and follow up

All patients were followed-up in the device clinic at 3-month interval. At each visit, the use of the loop diuretics and digitalis might be decreased gradually if a patient was presented with significantly reduced HF symptoms. The dosages of beta blockers, spironolactone, and ACEI/ARB or ARNI would not change during the first 6-month follow-up. R-wave amplitudes, capture thresholds, lead impedance, percentage of ventricular pacing, and 12-lead ECG were recorded at baseline and follow-up. Lead-related complications were routinely tracked. QRSd was measured on lead V1 at implant and at follow-up. Echocardiography was performed at baseline and 6 months after the procedure at each site by an experienced fixed operator. LVEF was calculated from the apical two-chamber and four-chamber views by two-dimensional transthoracic echocardiography using biplane Simpson's method.[16] The original images were all transferred to the core laboratory (Fuwai Hospital) for analysis by an experienced operator who was blinded to all clinical data. The New York Heart Association (NYHA) functional class and plasma NT-proBNP levels were evaluated at each visit. Rehospitalization because of HF and mortality were all tracked during follow-up.

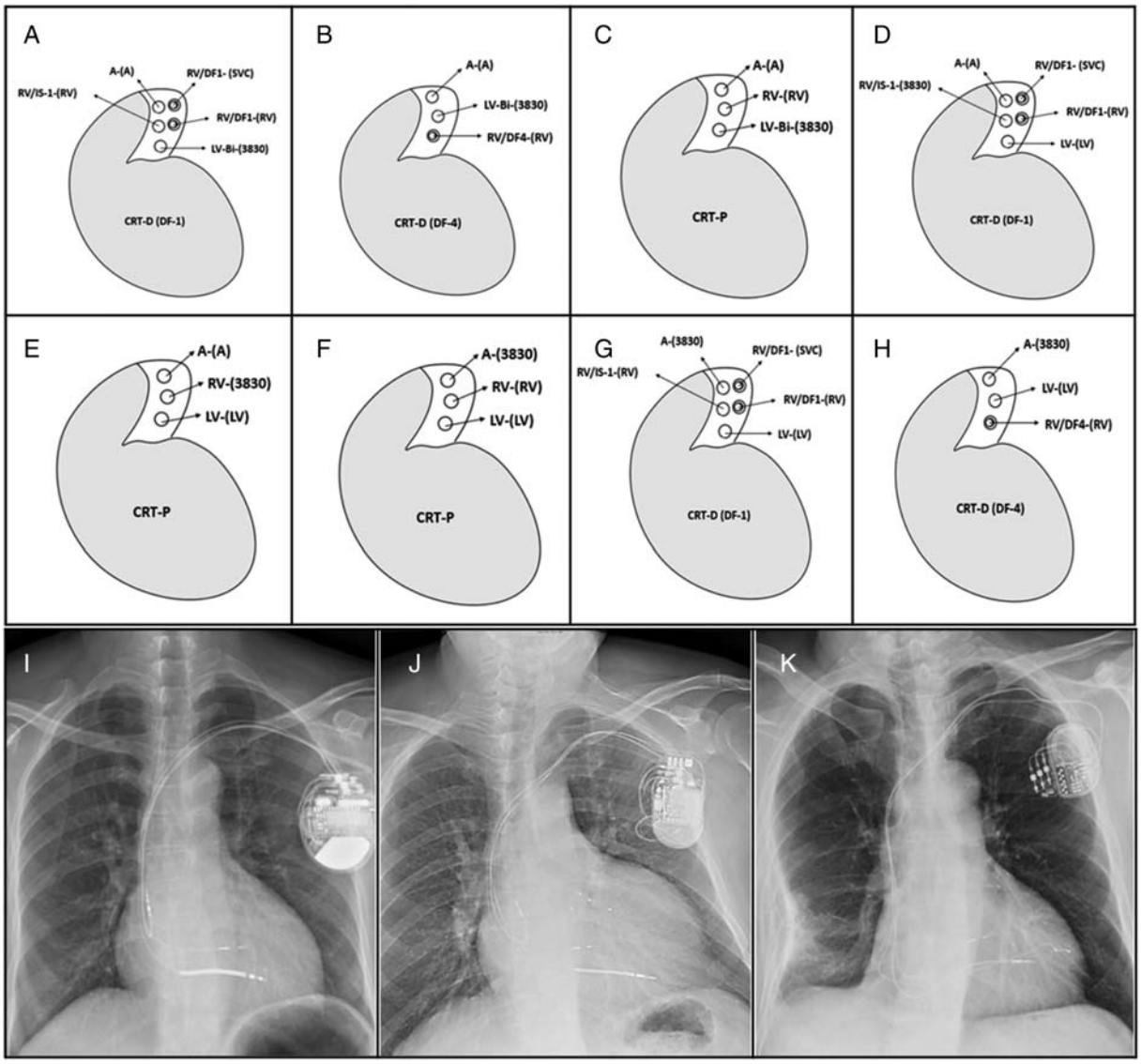
Definitions

The evidence for LBB capture followed the criteria published previously[10,17]: (i) Paced QRS morphology that presents with a right bundle branch block pattern; and (ii) a stimulus-peak LVAT that shortens abruptly with increasing output or remains short and constant at different test outputs. Successful LBBAP was defined as meeting both the criteria previously mentioned (*Figure 2B* and *2C*). Given successful LBBAP, if a discrete local component separate from the stimulus artefact to the beginning of QRS was presented on intracardiac electrogram at unipolar pacing, then selective LBBP was considered (*Figure 2D*, arrow). If none of the three criteria could be met, LV septal capture was considered. An echocardiographic response was defined as a $\geq$ 5% absolute improvement in the LVEF between baseline and follow-up echocardiograms. A super response was defined as an increase in the LVEF to $\geq$ 50% between the 6-month follow-up and baseline. The definition of clinical response was an improvement in the NYHA functional class by at least one class.

Statistical methods

We performed statistical analyses with SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA). Propensity score matching (1:2) based on gender, baseline QRS morphology and duration, and LVEF and LVEDD was used for the selection of patients receiving BVP by STATA 14.0 (StataCorp, College Station, TX, USA). The intra-observer variability of the measurements in this study was assessed by Bland–Altman plot analysis at the beginning of the analysis and interpretation of the data. Continuous variables are presented as the mean ± SD and compared with two tailed Student's *t*-tests and paired samples *t*-tests. Categorical data are presented as number and percentages and were compared using the chi-squared test. A multivariable logistic regression analysis was performed including all patients with LBBAP and BVP before matching to validate the propensity score matching

Figure 1 Schematic diagram of the lead-to-device connection configurations. CRT-D: cardiac resynchronization therapy defibrillator; CRT-P: cardiac resynchronization therapy pacemaker.



results. All statistical were two tailed; a *P* value of < 0.05 was considered significant.

Results

Baseline characteristics

The LBBAP procedure was attempted for a total of 37 consecutive patients at three centres during the study period. As shown in *Table 1*, 12 patients underwent rescue LBBAP, while 25 patients underwent primary LBBAP procedures. The mean age of the entire patient cohort was 56.8 ± 10.1 years (58.1% male), and the mean LVEF was 29.3 ± 5.9%. The majority of study patients had dilated cardiomyopathy (80.6%), while 19.4% had ischaemic cardiomyopathy. Most characteristics were comparable between patients with primary and rescue LBBAP. All patients received at least 4 months of guideline-directed medical therapy.

Implant outcomes of left bundle branch area pacing

LBBAP was achieved in 30 of 37 patients (81.1%), including 9 of 12 patients (75%) receiving rescue procedures and 21 of 25 patients (84%) receiving primary LBBAP procedures. As shown in *Table 2*, full correction of the LBBB with a QRSd $\leq$ 130 ms was achieved in 18 of 21 patients with

Figure 2 Pacing electrocardiogram characteristics and the location of the pacing lead for left bundle branch area pacing. Intrinsic rhythm of LBBB (A); LVAT remains stable for different pacing outputs (B and C); The transition from NS-LBBP to S-LBBP (discrete component in the intracardiac EGM, red arrow, D). The location of the LBB pacing lead on CT scan and 3D echocardiogram (E and F). LBB pacing with intrinsic RBB conduction. When the SAV was 110 ms, the best QRS morphology and duration were achieved (F). LBBB, left bundle branch block; LVAT, left ventricular activation time; NS-LBBP, non-selective left bundle branch pacing; S-LBBP, selective left bundle branch pacing; EGM, electrogram; CT, computed tomography; LBB, left bundle branch; RBB, right bundle branch.

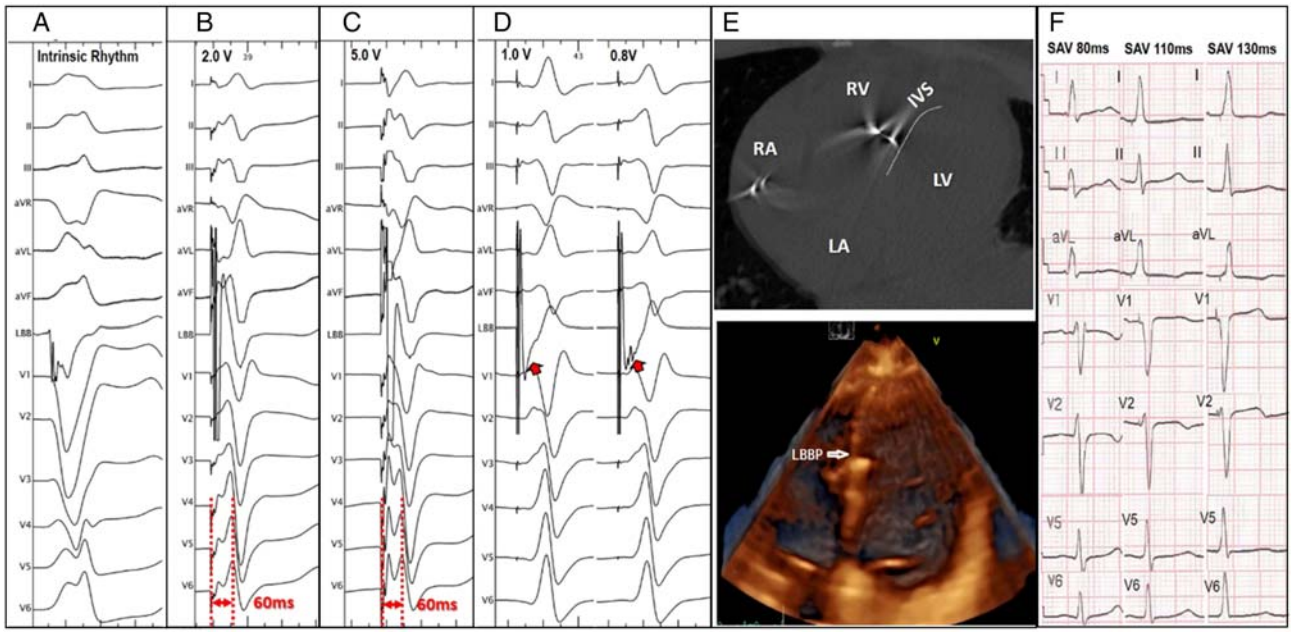


Table 1 Baseline characteristics of patients attempted for left bundle branch area pacing

Variables	Total (*N* = 37)	Primary LBBAP (*N* = 25)	Rescue LBBAP (*N* = 12)
Age, years	56.8 ± 10.1	55.9 ± 10.0	59.2 ± 10.2
Male, *n* (%)	22(59.5)	15(60.0)	7(58.3)
NYHA	3.1 ± 0.7	3.0 ± 0.7	3.3 ± 0.5
NYHA II, *n* (%)	6(16.2)	5(22.7)	1(8.3)
NYHA III, *n* (%)	22(59.5)	14(56.0)	8(66.7)
NYHA IV, *n* (%)	9(24.3)	6(24.0)	3(25.0)
Ischaemic cardiomyopathy, *n* (%)	7(18.9)	5(20.0)	2(16.7)
Hypertension, *n* (%)	10(27.0)	7(28.0)	3(25.0)
Diabetes Mellitus, *n* (%)	6(16.2)	4(16.0)	2(16.7)
Atrial fibrillation, *n* (%)	7(18.9)	5(20.0)	2(16.7)
Baseline QRSd, ms	177.9 ± 18.8	175.6 ± 17.3	182.1 ± 21.3
Left atrium, mm	43.7 ± 5.9	43.5 ± 5.2	44.1 ± 7.7
LVEDD, mm	66.5 ± 8.1	66.5 ± 8.3	66.6 ± 7.8
LVEF, mm	29.3 ± 5.9	29.6 ± 6.0	28.6 ± 6.0
RV, mm	23.7 ± 8.9	25.4 ± 10.9	21.0 ± 3.1
NT-proBNP, pg/mL	1731.5 (601.5, 2697.8)	1750.0 (829.5, 2715.5)	1768 (588.0, 3807.0)
Drug therapy			
Digitalis, *n* (%)	27 (73.0)	19(76.0)	8(66.7)
Diuretics, *n* (%)	37(100.0)	25(100.0)	12(100.0)
ACEI/ARB, *n* (%)	37(100.0)	25(100.0)	12(100.0)
Mineralocorticoid receptor antagonist, *n* (%)	37(100.0)	25(100.0)	12(100.0)
Beta-blocker, *n* (%)	35(94.6)	23(92.0)	12(100.0)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York heart association; RV, right ventricle.

Table 2 Patient characteristics, electrocardiographic, and echocardiographic outcomes of patients with left bundle branch area pacing or left bundle branch area pacing-optimized cardiac resynchronization therapy

					QRS duration				LVEF		NYHA			LBBAP lead	LBBAP
Patient	Age	Sex	Cause	Morphology	Pre	LBBAP	LBBAP+LV	Selective LBBP	Pre	Post	Pre	Post	Device	connection	strategy
1	50	M	ICM	LBBB	160	144	120	No	30.0	32.0	3	3	CRT-D	RV	Primary
2	49	M	NICM	LBBB	196	124	-	Yes	28.0	47.0	3	1	CRT-P	RV	Primary
3	66	M	ICM	LBBB	174	111	-	Yes	30.0	45.0	3	1	CRT-D	LV	primary
4	62	M	NICM	LBBB	200	149	136	No	27.0	50.0	3	1	CRT-D	RV	Primary
5	59	F	NICM	LBBB	186	124	-	No	33.0	46.0	3	1	CRT-D	LV	Primary
6	45	F	NICM	LBBB	196	130	-	No	33.0	53.0	2	1	CRT-P	LV	Primary
7	54	M	ICM	LBBB	176	150	128	No	29.0	37.0	3	1	CRT-D	A[a]	Primary
8	63	F	NICM	LBBB	158	120	-	Yes	25.0	57.0	3	1	CRT-D	LV	Primary
9	33	M	NICM	LBBB	190	125	-	Yes	34.0	54.0	2	1	CRT-P	LV	Primary
10	52	M	NICM	LBBB	176	118	-	No	27.0	53.0	2	1	CRT-D	LV	Primary
11	75	M	NICM	LBBB	170	106	-	No	33.0	45.0	2	1	CRT-D	LV	Primary
12	72	M	NICM	LBBB	176	110	-	No	34.1	50.0	2	1	CRT-D	RV	Primary
13	66	M	NICM	LBBB	160	120	-	No	27.0	37.0	4	2	CRT-D	RV	Primary
14	54	M	NICM	LBBB	148	102	-	Yes	18.8	36.0	4	2	CRT-P	RV	Primary
15	52	F	NICM	LBBB	138	110	-	No	20.4	42.0	4	2	CRT-D	RV	Primary
16	71	F	NICM	LBBB	186	109	-	Yes	28.0	50.0	4	1	CRT-P	RV	Primary
17	63	F	NICM	LBBB	156	110	-	Yes	30.0	50.0	3	2	CRT-P	RV	Primary
18	60	M	ICM	LBBB	200	122	-	Yes	35.0	51.0	3	2	CRT-P	RV	Primary
19	39	F	NICM	LBBB	180	109	-	Yes	32.0	50.0	3	1	CRT-D	LV	Primary
20	57	F	NICM	LBBB	187	129	-	No	23.0	40.0	3	2	CRT-D	RV	Primary
21	58	F	NICM	LBBB	175	121	-	No	32.0	50.0	3	1	CRT-D	LV	Primary
22	47	M	NICM	LBBB	220	120	-	Yes	23.0	41.0	3	2	CRT-D	LV	Rescue
23	71	M	ICM	LBBB	184	148	-	No	27.0	25.0	3	3	CRT-D	LV	Rescue
24	67	M	NICM	LBBB	170	130	-	No	24.0	50.0	3	1	CRT-D	LV	Rescue
25	55	F	NICM	LBBB	162	126	-	No	23.0	25.0	4	3	CRT-P	LV	Rescue
26	70	M	NICM	LBBB	178	128	-	No	32.0	43.0	3	2	CRT-D	LV	Rescue
27	68	F	NICM	LBBB	192	130	-	No	28.0	44.0	4	2	CRT-D	LV	Rescue
28	44	F	ICM	LBBB	164	128	-	No	29.0	38.0	4	2	CRT-D	LV	Rescue
29	59	F	NICM	LBBB	209	145	-	No	35.0	31.0	3	2	CRT-D	LV	Rescue
30	70	M	NICM	LBBB	160	122	-	Yes	35.0	58.0	3	1	CRT-D	LV	Rescue

A, atrium; CRT-D, cardiac resynchronization therapy defibrillator; CAF, chronic atrial fibrillation; CRT-P, cardiac resynchronization therapy pacemaker; F, female; ICM, ischaemic cardiomyopathy; LBBB, left bundle branch block; LV, left ventricle; M, male; NICM, non-ischaemic cardiomyopathy; RV, right ventricle; NSR, normal sinus rhythm.
[a]A patient diagnosed as chronic atrial fibrillation.

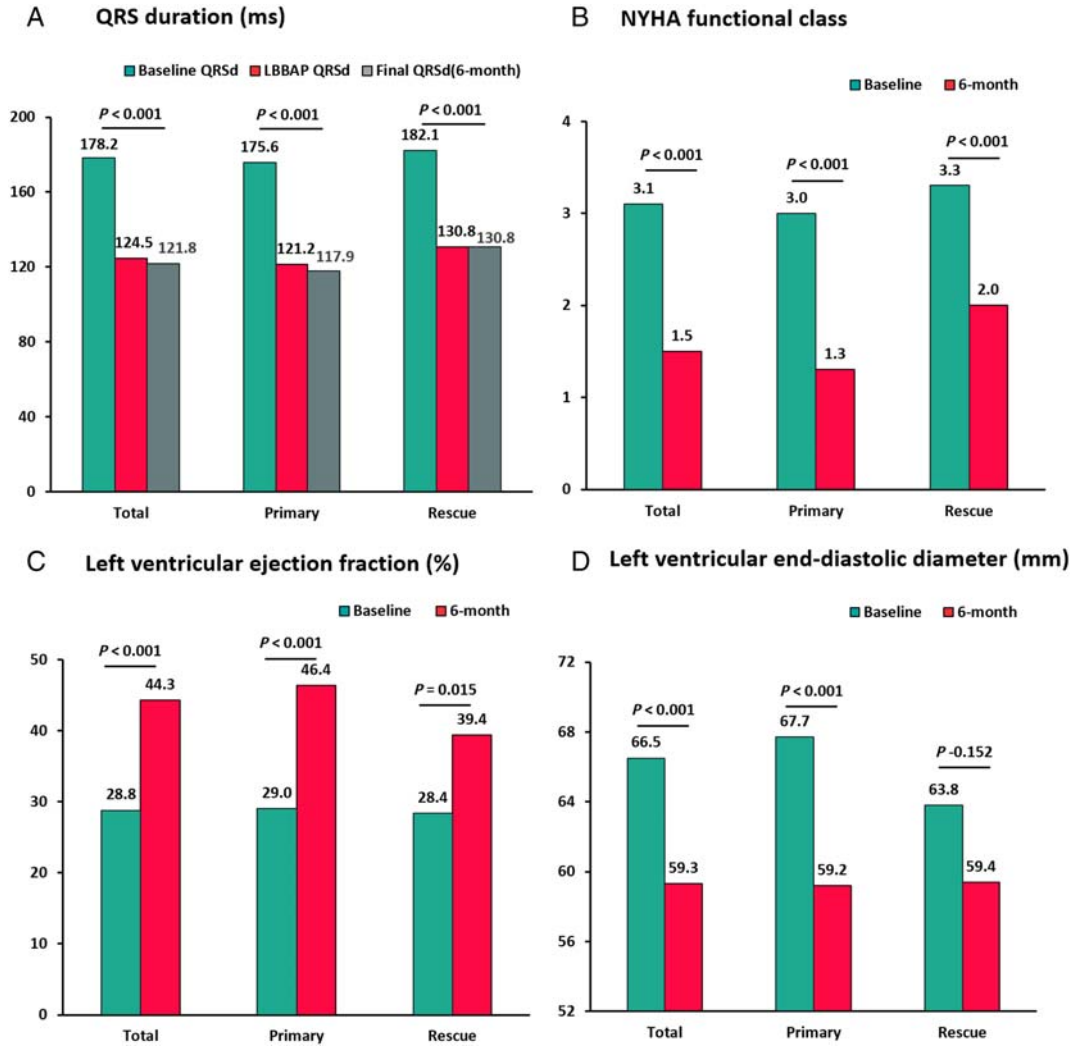
successful LBBAP as the primary pacing strategy (*Figure 2A—2F* shows the ECG from a patient with full correction of the LBBB and the location of the LBBAP lead), and partial shortening of the QRSd was observed in three patients (patient no.1, no. 4, and no.7). The additional CS-LV lead pacing achieved further narrowing of the QRSd in the three patients (Figure S1A—C). In nine patients who received LBBAP as a rescue procedure, seven patients had full LBBB correction with a QRSd $\leq$ 130 ms, and partial QRS narrowing was achieved in the other two patients (patient no.23 and No. 29; Figure S2). In total, complete correction of the LBBB was achieved in 83.3% of patients (25 of 30) with successful LBBAP and in 67.6% of patients (25/37) for whom the procedure was attempted.

The LBBAP procedure failed in seven patients because of an inability to achieve conduction system capture with a wide QRSd similar to the intrinsic QRSd (n = 4) or an inability to penetrate into the LV septum at the target site (n = 2). In the remaining patient, who had ischaemic cardiomyopathy, the LBBAP lead was abandoned because malignant ventricular tachycardia was repeatedly induced by pacing the LBB area during the pacing test (Figure S3), even though the LBBAP procedure resulted in partial correction of LBBB. Two of the three patients that failed in the rescue procedure finally received epicardial LV lead implantation, while the other patient received a single-chamber implantable cardioverter defibrillator implant because surgery was unacceptable for the patient. Four patients with failure of the primary LBBAP procedure finally received BVP. CRT-D was implanted in 22 patients, and a CRT-P was implanted in the remaining eight patients. Except for pacing-induced ventricular tachycardia during LBBAP, there were no septal perforations or lead dislodgements intraoperatively or by the 6-month follow-up.

Clinical outcomes of LBBAP at the 6-month follow-up

As shown in *Figure 3*, the mean QRSd was significantly shortened for all patients after LBBAP compared with that at baseline (178.2 vs. 121.8 ms, $P < 0.001$). During the 6-month

Figure 3 QRS duration and cardiac function at baseline and at the 6-month follow up in LBBAP patients. Intrinsic QRS duration at baseline, narrowed QRS duration by LBBAP at implant, and final paced QRS duration at 6-month follow-up (A). NYHA functional class and left ventricular ejection fraction improvement from baseline to the 6-month follow-up (B to C). Left ventricular end-diastolic diameter changes from baseline to the 6-month follow-up (D). NYHA, New York Heart Association.



follow-up period, the NYHA functional class improved from 3.1 at baseline to 1.5 ($P < 0.001$), with significantly improved cardiac function (LVEF from 28.8% to 44.3%; LVEDD from 66.5 to 59.2 mm, all $P < 0.001$). Four patients did not respond to LBBAP even though two of them showed significant QRSd narrowing (*Table 2*).

Electrocardiogram, pacing characteristics, and procedure parameters between left bundle branch area pacing and biventricular pacing

Fifty-four patients were selected among 130 patients with BVP by using 2 to 1 propensity score matching to be compared with 27 patients with LBBAP (three patients with LBBAP + CS-LV pacing were excluded) (*Table S1*). There were no significant differences in the baseline clinical characteristics between the LBBAP and BVP patients except for plasma NT-proBNP level.

As shown in *Table 3*, the mean paced QRSd was significantly narrower in the LBBAP than in the BVP patients, although the 12-lead ECG QRSd was shortened significantly from baseline in both groups. Compared with the BVP group, the LBBAP group demonstrated significantly lower capture thresholds and pacing impedance at implantation, and the X-ray exposure time of the LBBAP procedure was significantly shorter than that of the BVP procedure. At the 6-month follow-up, the paced QRSd continued to be narrower in the LBBAP group than in the BVP group (121.8 ± 10.8 vs. 158.2 ± 21.5 ms, $P < 0.001$), and the

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Table 3 Electrocardiogram, pacing characteristics, and procedure parameters at implant and 6-month follow up

Variables	BVP ($N = 54$)	LBBAP ($N = 27$)	*P* value
CRT-D, *n* (%)	39(72.2)	19(70.4)	0.862
At implant			
(LV or 3830 lead) threshold, at 0.4 ms, V	1.22 ± 0.62	0.81 ± 0.30	0.002
Paced QRSd, ms	158.7 ± 22.3	124.5 ± 12.0	< 0.001
X-ray exposure duration (total), min	39.6 ± 9.2	16.9 ± 6.4	< 0.001
Impedance	817.5 ± 222.1	644.9 ± 158.4	< 0.001
6-month follow-up			
VP%	96.4 ± 3.2	97.2 ± 1.1	0.161
Paced QRSd, ms	158.2 ± 21.5	121.8 ± 10.8	< 0.001
LV or 3830 lead threshold, at 0.4 ms, V	1.43 ± 0.74	0.75 ± 0.31	< 0.001
LV or 3830 lead impedance, Ω	712.4 ± 189.2	563.9 ± 122.3	< 0.001

VP%: percentage of ventricular pacing; other abbreviations see *Table 1* and *Table 2*.

differences in LBBAP capture thresholds and pacing impedance persisted between the two groups.

Echocardiographic and clinical response between biventricular pacing and left bundle branch area pacing

The intra-observer variability of the LVEF and LVEDD were analysed, and high reproducibility is displayed in *Figure S4*. As shown in *Table 4*, greater improvement in echo-LVEF and LVEDD was observed in the LBBAP than in the BVP group at 6-month follow-up. The rate of echocardiographic response and super response were significantly higher in the LBBAP than in the BVP group. Patients who received LBBAP also have significantly improved NYHA functional class, plasma NT-proBNP levels, and higher clinical response than those received BVP procedure group (96.3% vs. 75.9%, $P = 0.028$). During 6-month follow up, no events of HF rehospitalization or all-cause death were observed in both groups.

Figure 4 summarizes the changes in QRSd, NT-proBNP level, LVEDD, and LVEF from baseline to the 6-month follow-up between two groups. LBBAP resulted in significantly more QRS narrowing (58.0 [40.0, 65.3] vs. 12.5 [0.0, 40.0] ms, $P < 0.001$), greater improvement in the LVEF (17.1 [10.8, 20.4] % vs. 7.0 [1.0, 11.0] %, $P < 0.001$), and slightly more reduction in the LVEDD (8.0 [−1.0, 12.3] vs. 0.5 [0.0, 8.0], $P = 0.048$) compared with BVP. The reduction in NT-proBNP did not differ significantly between LBBAP and BVP. In all patients before propensity score matching, the multivariate analysis confirmed LBBAP as an independent predictor for super response and clinical response, but it was not independently associated with the echocardiographic response to resynchronization therapy (Supplementary Table S2).

Discussion

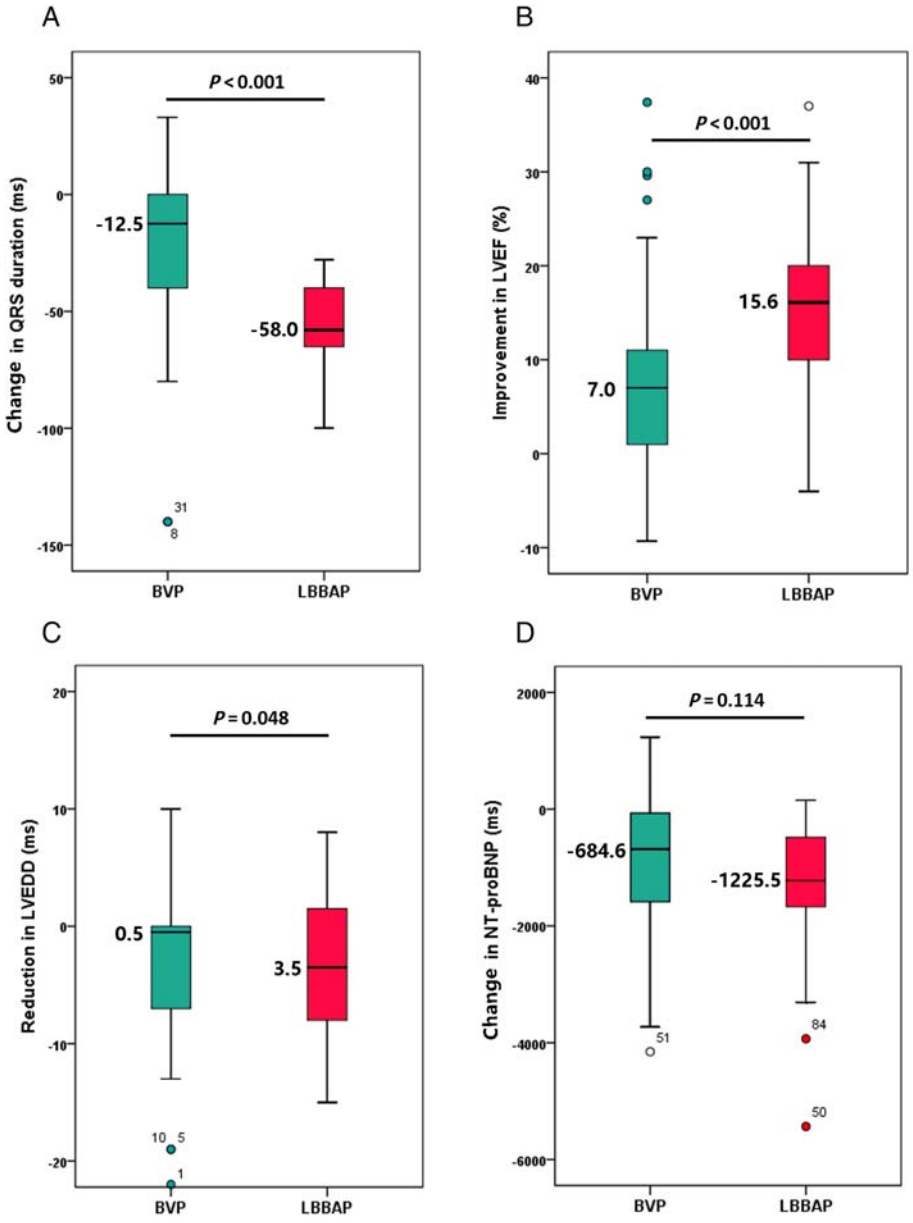
The major findings of this study are as follows: (i) Permanent LBBAP was capable of delivering CRT with a narrowing of the QRSd in most patients with LBBB and HF; (ii) in some patients with partial narrowing of the QRSd by LBBAP, sequential pacing combining LBBAP with CS-LV lead or epicardial LV lead pacing could achieve further narrowing of the QRSd and synchrony of left ventricle; (iii) LBBAP-delivered CRT resulted in a significant improvement in the LVEF and NYHA functional class and a reduction in the LVEDD on short-term

Table 4 Echocardiographic and clinical response in 6-month follow-up

Variables	BVP ($N = 54$)	LBBAP ($N = 27$)	*P* value
Echocardiography parameters			
LVEDD, mm	66.2 ± 8.5	59.3 ± 8.5	0.001
LVEF, %	35.0 ± 10.5	44.3 ± 8.7	< 0.001
Echocardiographic response, *n* (%)	36 (66.7)	24 (88.9)	0.035
Super-response, *n* (%)	9 (16.7)	12(44.4)	0.007
NYHA class	2.3 ± 0.7	1.5 ± 0.5	< 0.001
NYHA I, *n* (%)	5 (9.3)	14(51.9)	
NYHA II, *n* (%)	30(55.6)	11(40.7)	
NYHA III, *n* (%)	17 (31.5)	2 (7.4)	
NYHA IV, *n* (%)	2 (3.7)	0 (0.0)	
NT-proBNP, pg/mL	1245.0(633.0, 2401.0)	373.0(228.3. 661.8)	< 0.001
Clinical response,,*n* (%)	41(75.9)	26(96.3)	0.016

Abbreviations see *Tables 1 and 2*.

Figure 4 Comparison of changes in QRS duration and cardiac functional parameters from baseline to 6 months after the procedure between BVP and LBBAP. (A) Reduction in QRS duration; (B) improvement in LVEF; (C and D) reduction in LVEDD and median improvement in NT-proBNP level. LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.



observation; (iv) our preliminary comparison between BVP and LBBAP showed that LBBAP resulted in greater narrowing of the QRSd and greater improvement in echocardiographic and clinical response with low and stable pacing thresholds during 6-month follow-up; and (v) we described eight feasible lead-to-device connection configurations that can be used for LBBAP.

In addition to BVP, permanent His-CRT has been reported to be technically feasible and might be a viable option for CRT.[4,18,19] However, the prospective randomized controlled pilot trial, His-SYNC trial,[3,19] demonstrated that, compared with BVP, His-CRT achieved a comparable correction rate of LBBB and improvement in electrocardiographic or echocardiographic parameters.[19] Furthermore, the high crossover of patients in the His-CRT group with those of the BVP group indicated difficulties and limitations in correction of the LBBB by His-CRT. Because the anatomical characteristics of the LBB provide a wide area under the endocardium of the left side of the ventricular septum, transseptal LBBAP from the right side could achieve conduction system capture beyond the site of LBB block and correct the LBBB. The feasibility of LBBAP in delivering CRT was first reported by Huang *et al*. as a rescue

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pacing modality after failure of CS-LV lead implantation and correction of LBBB with HBP.[11] Chen *et al*.[14] described two cases of LBBB and reduced LVEF in their observational study of LBBP, in which the LVEF was improved from 22% at baseline to 38% at the 3-month follow-up in one patient, while a second patient demonstrated LVEF improvement from 35% to 37%. Recently, Vijayaraman *et al*. also described a high success rate (88%) in the correction of LBBB by LBBAP in a subgroup of 24 patients with baseline LBBB.[10] Chen *et al*.[12] reported the successful correction of LBBB by LBB capture in two cases of dilated cardiomyopathy. The improved cardiac function during short-term follow-up in our study further demonstrated the feasibility of LBBAP resynchronization therapy for patients with indications for CRT. Several factors might have influenced the success rate of LBBB correction with permanent LBBAP in the different studies. First, different definitions of successful LBBAP were observed in different centres.[9–11,14] Most studies did not include the definition of QRSd for the success of LBBAP.[10,13,14] However, QRSd narrowing is an important indicator of the correction of electrical conduction disturbance and is currently the most important measure of the CRT effect on electromechanical resynchronization.[20] In our study, LBBAP achieved a QRSd $\leq$ 130 ms in only 25 of 30 patients who had met the current criteria of successful LBBAP, while partial narrowing of the QRSd was observed in five patients. Our previous study included criteria with a QRSd $\leq$ 130 ms into the definition of successful LBBAP in patients with atrioventricular block and normal heart structure.[9] However, in patients with cardiomyopathy, QRSd narrowing might be associated with a similar clinical response to LBBAP as that to BVP. Future studies are needed to evaluate the effect of QRSd narrowing with LBBAP on clinical outcomes. Second, some LBBB may not be corrected by using His−Purkinje system pacing. In our study, the most common reason for failure of LBBAP was an inability to capture the conduction system. A recent study reported that ECG LBBB patterns may have no discrete block in the His−Purkinje system,[7] which provides evidence for the failure of conduction system pacing in correction of LBBB. In addition, the use of the C315 sheath as the sole delivery tool sometimes makes targeting different locations of the LBB area relatively difficult in patients with relatively large LVs or right atria. Finally, the experience of the operator might be an important factor influencing the success rate of LBBAP, especially in patients with CRT indications.

Our findings of the greater echocardiographic and clinical responses with LBBAP compared with those of BVP may not indicate the superiority of LBBAP delivery of CRT. First, the non-randomized study design and small sample size could not provide solid information. Second, the significant lower level of NT-proBNP at baseline might indicate a better baseline cardiac functional status in the LBBAP group compared with the BVP group, which might in turn partly impact on the greater improvement of LVEF at 6-month follow-up. But the differences in clinical response between two groups might rarely be attributed to HF medication effect because the dosages of beta blockers and ACEI/ARB or ARNI had not been changed during 6-month follow-up. Third, the multivariable analysis did not validate LBBAP as an independent predictor for echocardiographic response as compared with BVP-CRT. However, the relatively high rate of super response in patients with LBBAP provided evidence that LBBAP might be an alternative pacing approach to BVP or HBP. In addition, the short procedure time and X-ray exposure duration might be another possible advantage of LBBAP as compared with BVP in patients without acceptable epicardial target veins. Moreover, LBBAP achieved only partial narrowing of QRSd in five patients even though the paced morphology of QRS and the stimulus-peak LVAT at different outputs met the criteria of successful LBBAP. The baseline surface ECG of these five patients showed atypical LBBB morphology. Enlightened by HOT-CRT,[21] our results demonstrated that the sequential pacing combined LBBAP with a CS-LV lead or an epicardial LV lead could achieve more narrowing of QRSd and synchrony of LV in these patients. Our results indicated that patients with typical LBBB might be the desired candidates of LBBAP-CRT.

Study limitations

The main limitations of this study were the small sample size and the non-randomized design. However, our study first summarized a multicentre experience in the utilization of LBBAP for CRT. The propensity score matching method was used to reduce the bias between the LBBAP and BVP groups. Another limitation was the 6-month follow-up duration. A randomized controlled study with longer term observation is needed to gather solid evidence and obtain clinical outcomes of LBBAP.

Conclusion

CRT delivered with LBBAP could achieve narrowing of the QRSd and increased echocardiographic response in patients with HF and LBBB. LBBAP might be a valuable resynchronization therapy alternative to BVP-CRT as a rescue pacing modality or as the primary pacing strategy for patients with CRT indications. Future randomized controlled prospective studies are needed for the utilization of LBBAP for CRT.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline demographic, and echocardiographic characteristics of patients by treatment received
Table S2. Multiple analysis for pacing strategies and 6-month response

Figure S1a LBB pacing, LBBP + LV pacing and narrowing of QRSd in case #1.
Figure S1b LBB pacing, LBBP + LV pacing and narrowing of QRSd in case #4.
Figure S1c LBB pacing, LBBP + LV pacing and narrowing of QRSd in case #7.
Figure S2 LBBAP with partial QRS narrowing of QRSd in case #23 and case #29. LBBAP, left bundle branch area pacing.
Figure S3 LBBAP induced ventricular tachycardia during the LBBAP procedure. LBBAP, left bundle branch area pacing.
Figure S4 Bland–Altman plot analysis of LVEF and LVEDD. The reproducibility of both LVEF and LVEDD were excellent (Intraclass correlation coefficients [ICC] = 0.98 and 0.99, respectively). LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

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