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ORIGINAL ARTICLE

Left Bundle Branch Pacing Versus Biventricular Pacing for Acute Cardiac Resynchronization in Patients With Heart Failure

Yixiu Liang, MD*; Jingfeng Wang, MD*; Xue Gong, MD*; Hongyang Lu, PhD; Ziqing Yu, MD; Lei Zhang, MD; Minghui Li, MD; Lei Pan, MD; Xueying Chen, MD; Jie Cui, MD; Weiwei Zhang, MD; Ruogu Li, MD; Xiaohong Zhou, MD; Weijian Huang, MD; Yangang Su, MD; Junbo Ge, MD

BACKGROUND: Left bundle branch pacing (LBBP) has emerged as an alternative to biventricular pacing (BVP) for delivering cardiac resynchronization therapy. We sought to compare the acute improvement of electrical and mechanical synchrony, and hemodynamics between LBBP and BVP in patients with heart failure and left bundle branch block.

METHODS: LBBP and BVP were performed and compared in a crossover fashion in patients with heart failure and left bundle branch block undergoing cardiac resynchronization therapy implantation. Electrical synchrony was assessed by QRS duration and area, mechanical synchrony by the SD of time to peak velocity of 12 left ventricular segments (Ts-SD) and interventricular mechanical delay, and hemodynamics by the maximum rate of left ventricular pressure rise (dP/dt_{max}).

RESULTS: Twenty-one patient with heart failure and left bundle branch block (mean age 67±10 years, 48% male, and 90% nonischemic cause) were included. Both LBBP and BVP provided significant improvements in electrical and mechanical synchrony, and hemodynamics compared to the baseline. Compared with BVP, LBBP achieved a larger reduction in QRS duration (−11 ms [95% CI, −17 to −4 ms]; P=0.003) and QRS area (−85 μVs [95% CI, −113 to −56 μVs]; P<0.001); LBBP achieved a greater decrease in Ts-SD (−14 ms [95% CI, −21 to −7 ms]; P=0.001), with no significant difference in interventricular mechanical delay (−2 ms [95% CI, −13 to 8 ms]; P=0.63). The increase in dP/dt_{max} from LBBP was significantly higher than that from BVP (6% [95% CI, 2%–9%]; P=0.002).

CONCLUSIONS: LBBP delivers greater acute electrical and mechanical resynchronization and hemodynamic improvement than BVP in predominantly nonischemic heart failure patients with left bundle branch block.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: biventricular pacing ■ cardiac resynchronization therapy ■ heart failure ■ hemodynamics ■ left bundle branch pacing

Cardiac resynchronization therapy (CRT) via biventricular pacing (BVP) is an established treatment for patients with heart failure, reduced left ventricular (LV) ejection fraction (LVEF), and wide QRS duration, especially left bundle branch block (LBBB). Recently, left bundle branch pacing (LBBP) has emerged as a promising alternative to BVP, through correction of LBBB with transseptally pacing beyond the block region.[1] Feasibility and short- to mid-term safety of LBBP in patients with heart failure and LBBB have been demonstrated in

Correspondence to: Yangang Su, MD, Department of Cardiology, Zhongshan Hospital of Fudan University, No. 180, Fenglin Rd, Shanghai, China, Email su.yangang@zs-hospital.sh.cn or Junbo Ge, MD, Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China, Email ge.junbo@zs-hospital.sh.cn
*Y. Liang, J. Wang, and X. Gong contributed equally.
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WHAT IS KNOWN?

- Left bundle branch pacing (LBBP) has emerged as an alternative to biventricular pacing for delivering cardiac resynchronization therapy.
- Evidence from observational comparative studies suggested that LBBP was at least equal to biventricular pacing in patients with heart failure with regard to electrocardiographic and echocardiographic assessments including QRS duration and left ventricular ejection fraction at mid-term follow-up.

WHAT THE STUDY ADDS

- For cardiac resynchronization therapy in patients with heart failure and left bundle branch block, LBBP is associated with greater acute electrical and mechanical synchrony and hemodynamic improvement than biventricular pacing.
- Well powered randomized controlled clinical trials of LBBP versus biventricular pacing in patients with heart failure and LBBB in diverse populations are needed to determine whether these acute changes are accompanied by longer-term favorable clinical outcomes.

Nonstandard Abbreviations and Acronyms

BVP	biventricular pacing
CRT	cardiac resynchronization therapy
HBP	His bundle pacing
IVMD	interventricular mechanical delay
LBB	left bundle branch
LBBB	left bundle branch block
LBBP	left bundle branch pacing
LV	left ventricular
LVSP	left ventricular septal pacing
RV	right ventricular

previous studies, with results showing improved electrical synchrony, LV structure and function, and clinical function during follow-up.[2,3]

Contrary to conventional BVP with the combination of electrical conduction through myocardial tissue, which is initiated from the right ventricular (RV) endocardium and the LV epicardium, LBBP directly captures the left bundle branch (LBB) followed by the propagation of wavefront along the native LBB-Purkinje conduction system. Therefore, LBBP has been recognized to be a more physiological pacing strategy to preserve the LV electromechanical synchrony compared with BVP.[4] In line with this hypothesis, several observational comparative studies suggested that LBBP was at least equal to BVP in patients with heart failure regard to electrocardiographic and echocardiographic assessments including QRS duration and LVEF at follow-up,[5–7] although it deserves emphasis that evidence from randomized controlled trials is lacking.

It is well recognized that the clinical benefit of CRT is primarily driven by restoring synchronous electromechanical activations, which eventually translates into enhanced systolic performance and further LV reverse remodeling.[8] This is evidenced by a recent study demonstrating that LV septal pacing (LVSP), which was performed by pacing the LV endocardial side of the interventricular septum without capture of the LBB, provided short-term electrical resynchronization and hemodynamic improvement that was comparable with BVP in CRT patients.[9] Given the different mechanisms of the 2 pacing modalities and the evidence from clinical studies, we hypothesized that LBBP would achieve more favorable acute electromechanical and hemodynamic effects over conventional BVP. Meanwhile, there has been no direct within-patient comparison between LBBP and BVP, which could overcome the limitation of selection bias introduced in observational cohort studies. The aim of the present study was to compare the acute electrical and mechanical resynchronization, and hemodynamic improvement between LBBP and BVP in patients with heart failure with LBBB in a randomized crossover fashion.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We prospectively enrolled consecutive heart failure patients with indications for CRT at 2 centers (Zhongshan Hospital and Shanghai Chest Hospital) from September 2020 to September 2021. The inclusion criteria were as follows: New York Heart Association (NYHA) class II to ambulatory NYHA class IV despite optimal heart failure medication for at least 3 months, LVEF ≤35%, and sinus rhythm in the presence of LBBB. LBBB was defined as QRS duration ≥130 ms, QS or rS in lead V1, broad (frequently notched or slurred) R waves in leads I, aVL, V5, or V6, and absent q waves in leads V5 and V6.[10] Patients were excluded if they had second to third degree atrioventricular block, frequent premature ventricular complexes, moderate-to-severe aortic stenosis, LV thrombus, or significant peripheral vascular disease.

The study was approved by the institutional review boards (registration number SK2020-035 and B2021-270), and all patients provided written informed consent. The study conforms with the principles outlined in the Declaration of Helsinki, and was registered in ClinicalTrials.gov (NCT04505384).

Implantation Procedure

Intracardiac electrograms along with 12-lead surface ECGs were continuously recorded during the procedure using an electrophysiology recording system (CardioLab EP Recording

System 2000, GE Medical Systems, Milwaukee, WI). For all patients, the RV lead (Model 6935/5076, Medtronic, Minneapolis, MN) was first positioned at the RV apex via the standard percutaneous transvenous approach and connected to a temporary pulse generator at VVI 40 beats per minute in case of cardiac arrest. Subsequently, the LV lead (Model 4196, Medtronic, Minneapolis, MN) was placed preferentially in the lateral or posterolateral vein by standard-of-care implantation techniques after retrograde fluoroscopic venography of coronary sinus. An anterolateral site was acceptable when the lateral or posterolateral vein was unavailable. Afterwards, the LBBP lead (Model 3830, Medtronic, Minneapolis, MN) was implanted to deliver LBBP.[11] In brief, the 3830 lead was first advanced through a delivery sheath (Model C315HIS, Medtronic, Minneapolis, MN) to locate the His bundle region as an anatomic marker, then further 1 to 2 cm toward RV apex and perpendicularly screwed toward the left side of the septum. When a terminal R-wave of the paced QRS complex emerged in lead V1, low- and high-output pacing was conducted to confirm LBB capture. The following criteria were used to confirm LBB capture: (1) right bundle branch block morphology in lead V1 with terminal R-wave during unipolar tip pacing; (2) abrupt shortening of the stimulus to peak LV activation time (defined as the interval from the pacing stimulus to the upstroke peak of the R wave in lead V6) with increasing output and then remaining shortest and constant at high and low outputs or demonstration of output-dependent nonselective LBBP and selective LBBP at near-threshold outputs; and/or (3) recording of LBB potentials during escape rhythm or premature beats (Figure 1; Figure S1).[3,11] Finally, the right atrial lead (Model 4574, Medtronic, Minneapolis, MN) was placed in the right atrium.

Pacing Test

Patients were blocked (block size of 4) randomized to receive either BVP or LBBP first, and underwent simultaneous electrocardiographic, echocardiographic, and hemodynamic recordings. Afterward, pacing was switched to the other modality (LBBP or BVP) to complete the crossover. Randomization was based on a computer-generated random number list prepared by an independent statistician with no involvement in the study.

To minimize the rate-dependent variability, all pacing was delivered at a fixed rate of 10 beats per minute above the patient's intrinsic heart rate.[9] For baseline assessment, the atrial lead was connected to the atrial port of a pacing system analyzer (Model 2290, Medtronic, Minneapolis, MN), and pacing was delivered in AAI mode. For BVP, with the atrial lead in position, both the RV and LV leads were connected to the ventricular port of the analyzer, and pacing was set to DDD mode. For LBBP, the atrial and LBB leads were connected to atrial and ventricular ports of the analyzer, respectively, and paced with DDD mode, while the RV and LV leads were disconnected. Throughout the pacing test, the pacing was unipolar and the output was set at 3.5 V with a pulse width of 0.5 ms. To optimize BVP and LBBP, multiple atrioventricular delays were programmed with 20 ms increments from 80 ms to the atrioventricular delay that lost ventricular capture (Figure 2A). The interventricular delay during BVP was set to 0 ms throughout the study.[12] A period of at least 2 minutes was respected before each transition between the pacing modalities for hemodynamic stabilization.

After all pacing tests were completed, the leads were connected to the CRT generator to finish the study (Figure 1; Figure S2).

Electrocardiography

Cardiac electrical synchrony was assessed with QRS duration and QRS area. QRS duration was defined as the interval between the earliest onset of the QRS waveform in any lead till the latest offset in any lead on the surface ECG. With ventricular paced QRS complexes during BVP and LBBP, the onset of the QRS complex instead of the pacing artifact was considered as the beginning of the QRS complex.

For the calculation of QRS area, the raw data of electrocardiographic signals stored in the electrophysiology recording system were exported to generate the vectorcardiograms (VCGs) with 3 orthogonal vectorcardiography leads (X, Y, and Z) using the inversed Dower matrices.[13] QRS area was calculated as the sum of the area under the QRS complex in the calculated X, Y, and Z lead (QRS area=[QRS area$_x^2$+QRS area$_y^2$+QRS area$_z^2$]$^{1/2}$; Figure S3). The calculation was processed using customized programs in MATLAB (version R2020a, MathWorks, Natick, MA).

Echocardiography

Transthoracic echocardiographic examinations were performed during CRT implantation using a commercially available system (CX50, Philips, Amsterdam, Netherlands). Images were acquired in the standard parasternal and apical views with a minimum of 3 consecutive beats recorded from each view. Standard 2-dimensional and Doppler data triggered to the QRS complex was digitally stored in a cineloop format for offline analysis.

For assessment of intraventricular mechanical dyssynchrony, the regional time intervals of LV 12 segments between the onset of the QRS complex and the peak of systolic myocardial velocity during the ejection phase (Ts) were measured from color tissue Doppler images, and the standard deviation of Ts (Ts-SD) of all 12 segments were calculated. Inter-ventricular mechanical dyssynchrony was assessed with the interventricular mechanical delay (IVMD), defined as the difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at the pulmonary and aortic valve levels using pulsed-wave Doppler.

The echocardiographic data were analyzed by an experienced echocardiologist blinded to the clinical data or pacing modality. All the measurements were evaluated following the standard criteria of the American Society of Echocardiography.

Hemodynamics

Following the successful implantation of all leads, a pressure micromanometer (Pressure Wire X, Abbott, St. Paul, MN) was placed in the LV cavity via retrograde transaortic catheterization through the radial artery and connected to a pressure recording system (Quantine, Abbott, St. Paul, MN). A bolus of intravenous unfractionated heparin was administered to reduce risk of thromboembolic complication.

A "multi-beat averaging and multiple repeated alternations" approach was applied during measurement and analysis for more precision in measurements.[14] In detail, hemodynamic data

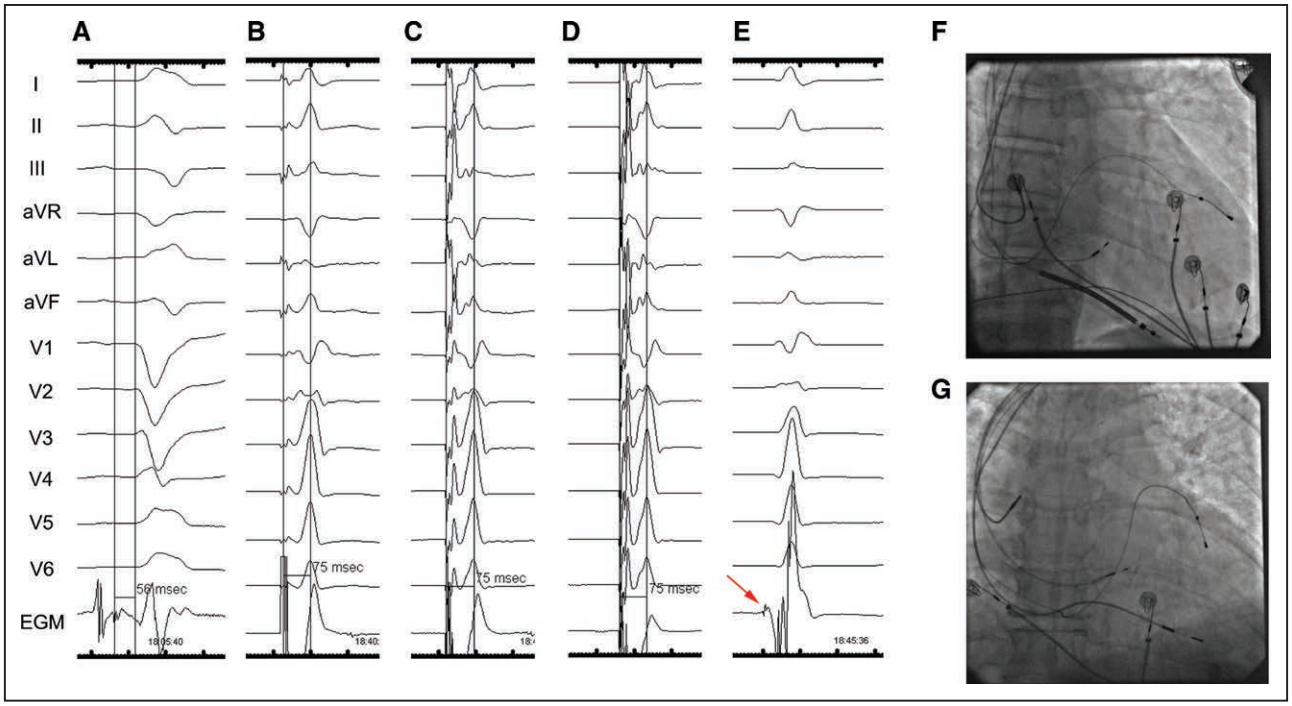

Figure 1. Representative electrocardiograms and fluoroscopy during implantation.
A, Intrinsic QRS with His potential mapped (His-ventricular interval of 56 ms). **B**, Left bundle branch (LBB) pacing (LBBP) at the threshold output of 1.0V@0.48 ms with stimulus to peak left ventricular (LV) activation time of 75 ms, demonstrating selective LBBP. **C**, LBBP at an output of 3.0V@0.48 ms with stimulus to peak LV activation time of 75 ms, demonstrating non-selective LBBP. **D**, LBBP at a high output of 10.0V@0.48 ms with stimulus to peak LV activation time of 75 ms, demonstrating non-selective LBBP. **E**, An LBB potential recorded during an escape beat with a potential-ventricular interval of 18 ms (red arrow). **F**, Fluoroscopy during cardiac resynchronization therapy (CRT)-defibrillator implantation with LBBP lead in place. **G**, Fluoroscopy during CRT-pacemaker implantation with LBBP lead in place. A right ventricular (RV) pacing lead was temporarily placed at the RV apex to implement biventricular pacing (BVP) and would be extracted after hemodynamic data acquisition.

were acquired first in AAI mode for 10 to 15 seconds as baseline, then in DDD mode of either BVP or LBBP modality for another 10 to 15 seconds. This was repeated for a given atrioventricular delay until a total of 8 transitions from AAI to DDD mode was completed. Subsequently, the process of 8 transitions was repeated for different atrioventricular delays as aforementioned. Finally, the data were processed with customized programs in MATLAB. In the blinded analysis, the dP/dt was derived to determine dP/dt_{max} for each beat. Mean dP/dt_{max} of 10 beats before and after each transition was firstly calculated into relative change, which was then averaged over 8 transitions into the increase for the index alternation (Figure S4). Any ectopic beat and the 2 subsequent beats were excluded during the analysis. The atrioventricular delay that provided the largest LV dP/dtmax improvement in each pacing mode was deemed as optimal (Figure 2B) and used for all further analyses.

Statistical Analysis

The process of sample size calculation is presented in the Supplemental Methods. Normally distributed continuous variables were expressed as the mean with SD and compared with 2-tailed independent or paired *t* test, and non-normally distributed variables were expressed as medians and interquartile range and compared with Mann-Whitney *U* test or Wilcoxon paired test, as appropriate. Normality of distribution was assessed with Shapiro-Wilk test. Categorical variables were expressed as numbers and proportions, and compared using Fisher exact test. A *P* below 0.05 was considered statistically significant for all analyses. Statistical analysis was performed in SPSS (version 25, SPSS, Chicago, IL).

RESULTS

Patient Characteristics

A total of 25 patients were enrolled. All patients received successful BVP leads implantation. LBBP was unsuccessful in 1 patient due to failure of LBB capture, and 3 patients developed complete atrioventricular block during the procedure and were unable to undergo hemodynamic assessment. These 4 patients were therefore excluded from the analysis. The baseline characteristics of the included and excluded patients are shown in Table 1 and Table S1.

Procedural Characteristics

The LV lead was placed at the posterolateral or lateral wall in 18 (86%) patients and at the anterolateral wall in 3 (14%) patients. With respect to LBBP, selective to nonselective LBBP was observed in 12 patients (57%), and the remaining patients demonstrated only

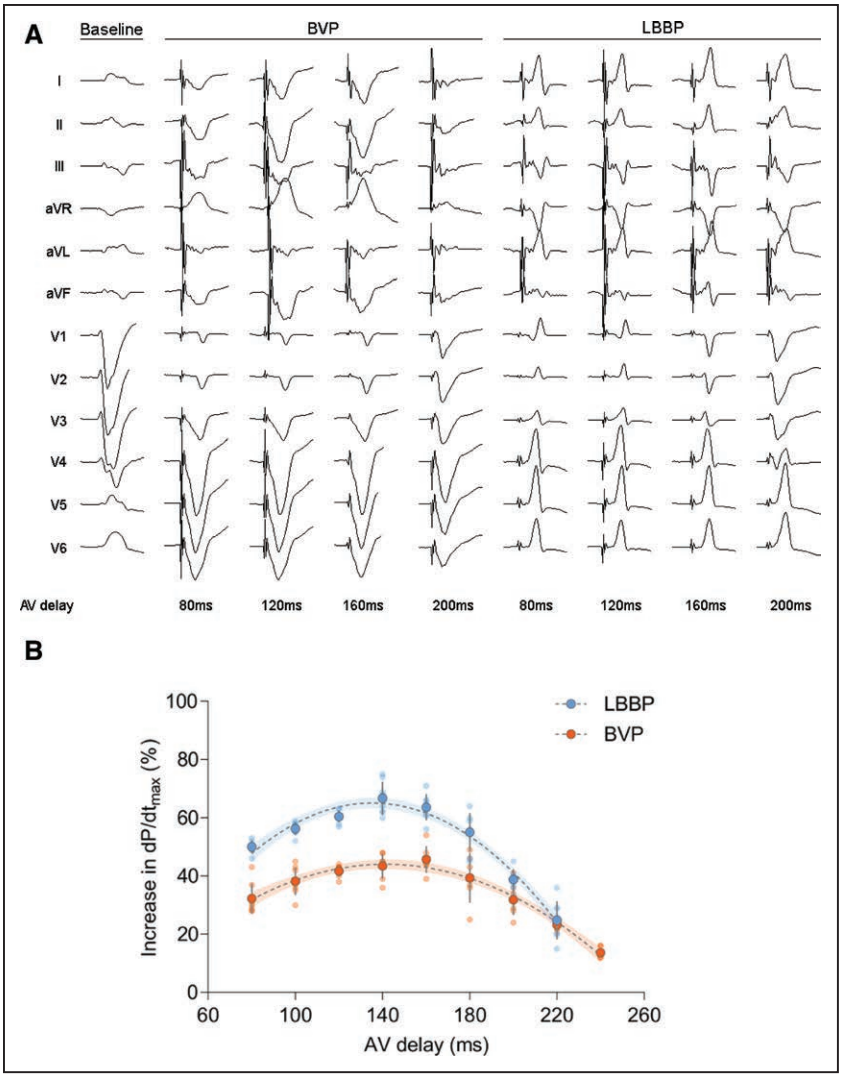

Figure 2. Paced QRS complex and increase in dP/dtmax during atrioventricular (AV) delay programming.
A, An example of baseline, paced QRS complex by biventricular pacing (BVP), and paced QRS complex by left bundle branch pacing (LBBP) during AV delay programming. **B**, The mean and 95% CI are calculated for each atrioventricular (AV) delay for BVP and LBBP. A quadratic curve was fitted from the mean value of each AV delay for estimation of the increase in dP/dt_{max} during AV delay programming for BVP and LBBP, respectively.

nonselective LBBP. LBB potential was recorded at escape beats in 2 patients (10%). The stimulus to peak LV activation time was 85±10 ms. No periprocedural complications were observed.

The time from atrial pacing stimulus to the beginning of the QRS complex during AAI mode was 229±44 ms. The optimal atrioventricular interval to achieve the greatest increase in LV dP/dt_{max} was 161±29 ms for BVP, and 134±24 ms for LBBP, respectively (P<0.001).

Electrocardiography

The reduction of QRS duration and QRS area by BVP and LBBP is demonstrated in Figure 3A. Both BVP and LBBP significantly shortened QRS duration compared with baseline (132±19 ms and 121±16 ms, respectively; both P<0.001). Furthermore, the QRS duration achieved by LBBP was significantly shorter than that achieved by BVP (−11 ms [95% CI, −17 to −4 ms], P=0.003; Figure 3B).

Compared with baseline, QRS area was significantly reduced by BVP (149±73 μVs, P=0.01) and further reduced by LBBP (64±25 μVs, P<0.001). Moreover, LBBP achieved a significantly more pronounced reduction in QRS area compared with BVP (−85 μVs [95% CI, −113 to −56 μVs]; P<0.001; Figure 3C).

Echocardiography

Intraventricular synchrony assessment showed the baseline Ts-SD was 52±16 ms, which was significantly reduced by BVP (39±18 ms, P=0.001) and LBBP (25±12 ms, P<0.001). The reduction of Ts-SD achieved by LBBP was significantly greater than that induced by BVP (−14 ms [95% CI, −21 to −7 ms]; P=0.001; Figure 4A).

Interventricular synchrony assessment showed the baseline IVMD was 42±33 ms. Both BVP and LBBP significantly reduced IVMD compared with baseline (20±17 ms, P=0.01, and 17±11 ms, P=0.01, respectively). In contrary to the Ts-SD result, there was no significant difference in the IVMD between BVP and LBBP (−2 ms [95% CI, −13 to 8 ms]; P=0.63; Figure 4B).

Table 1. Baseline Characteristics of Included Patients (n=21)

Age	**67±10**
Male (n, %)	10 (48)
Body mass index, kg/m^2	24±3
Nonischemic cause (n, %)	19 (90)
New York Heart Association class II/III/IV	6 (29)/12 (57)/3 (14)
Medical history	
Hypertension (n, %)	8 (38)
Diabetes (n, %)	2 (10)
Prior atrial fibrillation (n, %)	1 (5)
Electrocardiography	
PR interval, ms	169±36
QRS duration, ms	180±17
QRS area, μVs	194±59
Echocardiography	
Left ventricular end diastolic diameter, mm	64±7
Left ventricular end diastolic volume, mL	176±48
Left ventricular end systolic diameter, mm	55±9
Left ventricular end systolic volume, mL	149±71
Left ventricular ejection fraction, %	28±6
Medication	
Angiotensin receptor-neprilysin inhibitor (n, %)	21 (100)
Beta-adrenergic blocking agents (n, %)	20 (95)
Aldosterone antagonist (n, %)	19 (90)
Sodium-glucose cotransporter-2 inhibitor (n, %)	13 (62)

Hemodynamics

A representative case of LV dP/dt$_{max}$ changes in BVP and LBBP modalities is shown in Figure 5A, in which LV dP/dt$_{max}$ increased by 27% in BVP modality and by 46% in LBBP modality compared with baseline. Overall, the baseline LV dP/dt$_{max}$ was 729±192 mmHg/s. The increase in dP/dt$_{max}$ was 32±15% for BVP, while LBBP produced an increase in LV dP/dt$_{max}$ of 37±17%. The increase in LV dP/dt$_{max}$ achieved by LBBP was significantly higher than that achieved by BVP (6% [95% CI, 2%–9%], *P*=0.002; Figure 5B).

Subgroup Analysis of Patients With Ischemic Cause

There were 2 patients with ischemic cause, one with prior myocardial infarction and the other with stable coronary artery disease, and both had received coronary stent implantation. The results of the electrocardiographic, echocardiographic and hemodynamic analyses of the 2 patients are presented in Table 2. Both patients showed improved electrical and mechanical synchrony during BVP and LBBP. Particularly, LBBP achieved greater increase in LV dP/dt$_{max}$ over BVP in both patients (55% versus 51%, and 53% versus 48%, respectively).

DISCUSSION

The present study is the first comprehensive evaluation of the acute effects on ventricular resynchronization between LBBP versus BVP in heart failure patients with LBBB. The results demonstrated that both LBBP and BVP significantly improved ventricular electrical and mechanical resynchronization and LV hemodynamics, and LBBP produced significantly larger QRS narrowing, more reduction in QRS area, and greater increase in LV dP/dt$_{max}$ than BVP.

Comparison Between LBBP and BVP

Standardized and optimized approaches of BVP and LBBP were employed in the present study. BVP was achieved by pacing both ventricles simultaneously, as implemented in the landmark randomized controlled trials as well as in most clinical practice. LBBP was accomplished with single ventricular lead, with LBB capture prudently pursued. Confirmation of LBB capture is essential to distinguish LBBP from LVSP, as LBBP ensures rapid LV activation propagation via conduction system rather than myocardial endocardium and hence improves ventricular electrical synchrony.[15,16] By using single ventricular lead in lieu of RV pacing or LV epicardial pacing, we managed to investigate the true effect of LBBP and further to raise the possibility of CRT by means of dual-chamber cardiac pacemaker implantation.

The benefit of fusion pacing for BVP has been well documented,[17] and theoretically LBBP can be fused with intrinsic RV activation to attain normal ventricular synchronization.[18] In the present study, both BVP and LBBP were optimized for fusion pacing by extensive adjustment of atrioventricular delay to ensure a fair comparison of both pacing modalities with maximal performance evidenced by the largest LV dP/dt$_{max}$.

Electrical Resynchronization Effect of LBBP Versus BVP

The principal mechanism for pacing therapy to treat heart failure is the correction of LV dyssynchronous activation and contraction with electrical stimulations. In comparison with the baseline condition, this restoration of electrical synchrony was successfully achieved by both BVP and LBBP, as indicated by a significant reduction of both QRS duration and QRS area. Furthermore, LBBP showed a better effect in improving electrical synchrony with respect to shorter QRS duration and smaller QRS area compared with BVP.

QRS duration has been the fundamental indicator of electrical synchrony assessed for CRT. Consistent with previous observational studies,[6,7] the present study demonstrated significantly shortened QRS duration by LBBP over BVP. Although pacing the LBB only may lead to

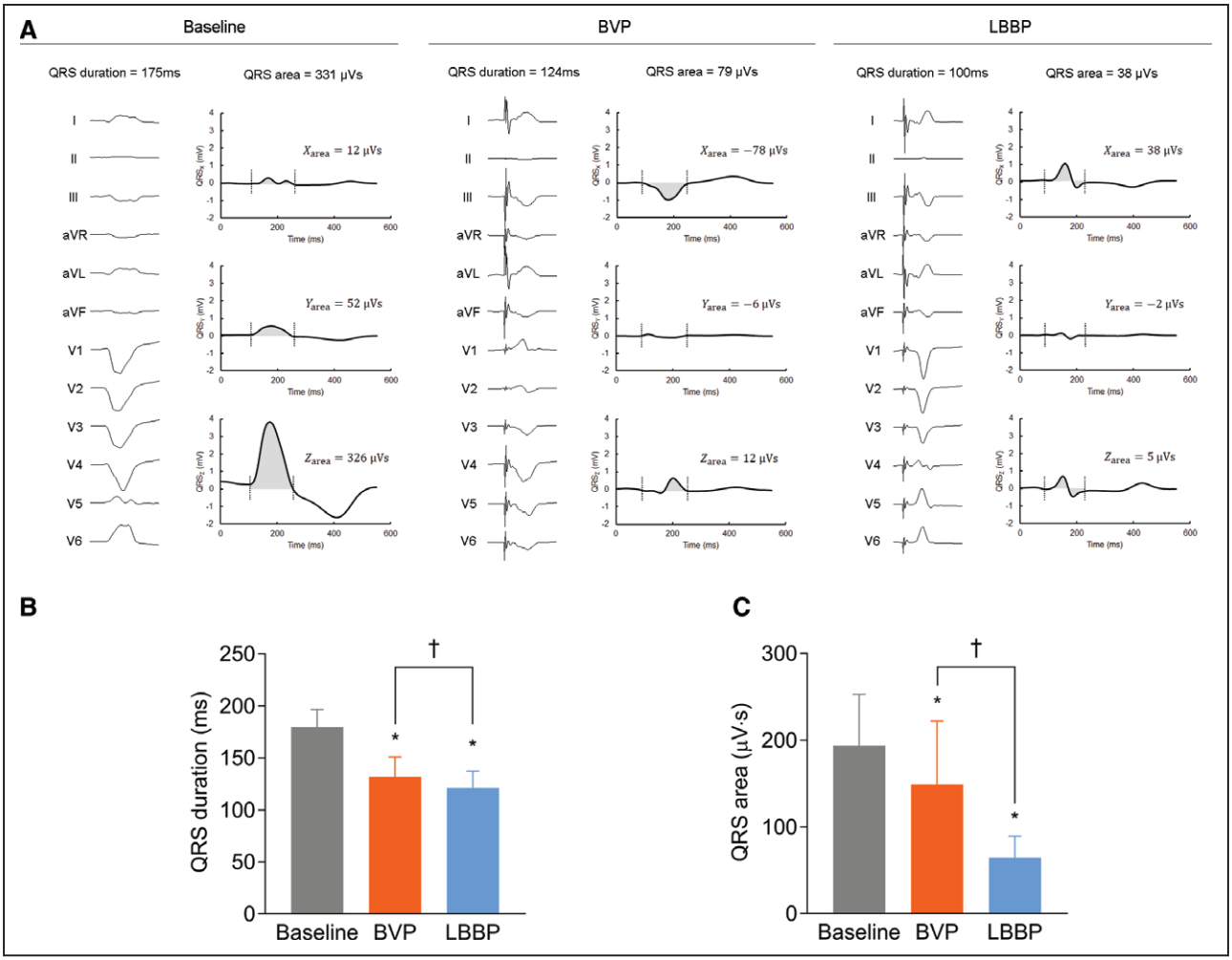

Figure 3. Assessment of electrical synchrony.
A, An example of ECGs and vectorcardiograms (VCGs) during baseline, biventricular pacing (BVP), and left bundle branch pacing (LBBP) with corresponding QRS duration and QRS area. **B**, Comparison of QRS duration among baseline, BVP, and LBBP**. C**, Comparison of QRS area among baseline, BVP, and LBBP. *P<0.05 versus baseline; †P<0.05 LBBP versus BVP.

QRS duration prolongation due to pacing-induced RV activation delay, fusion of LBBP with intrinsic RV activation generated an optimized QRS duration, which was narrower than that optimized in BVP, suggesting a better ventricular electrical resynchronization. Moreover, the present study demonstrated a more pronounced reduction in QRS area by LBBP over BVP. In comparison with QRS duration, which merely depicts ventricular depolarization time, QRS area provides more information about ventricular synchrony by representing the temporal and spatial integration of ventricular depolarization, and consequently has a stronger association with echocardiographic and clinical response in conventional CRT patients.[19] The significant reduction in both QRS duration and QRS area reinforced the evidence of the superiority of LBBP over BVP to restore the electrical synchrony.

It is conceivable that the difference of electrical synchrony restoration between LBBP and BVP is primarily driven by the difference of ventricular activation pattern. LV pacing during BVP results in myocardial cell-to-cell electrical wavefront propagation and leaves potential for further improvement of resynchronization.[20] In contrast, LBBP produces the electrical wavefront propagation along the LBB-Purkinje conduction system and preserves physiological LV depolarization on a similar level as His bundle pacing (HBP).[16]

Mechanical Effect of LBBP Versus BVP

Results suggest that BVP and LBBP improved both intra- and interventricular mechanical synchrony. While LBBP delivered greater improvement in intra-ventricular synchrony over BVP, there was no significant difference in inter-ventricular synchrony.

The mechanism underlying the superiority of LBBP over BVP to improve intraventricular synchrony is straightforward with a more physiological propagation pattern and timing of pacing-induced LV mechanical contraction. The electrical activation during LBBP results in prompt and synchronous contraction of LV, while BVP produced

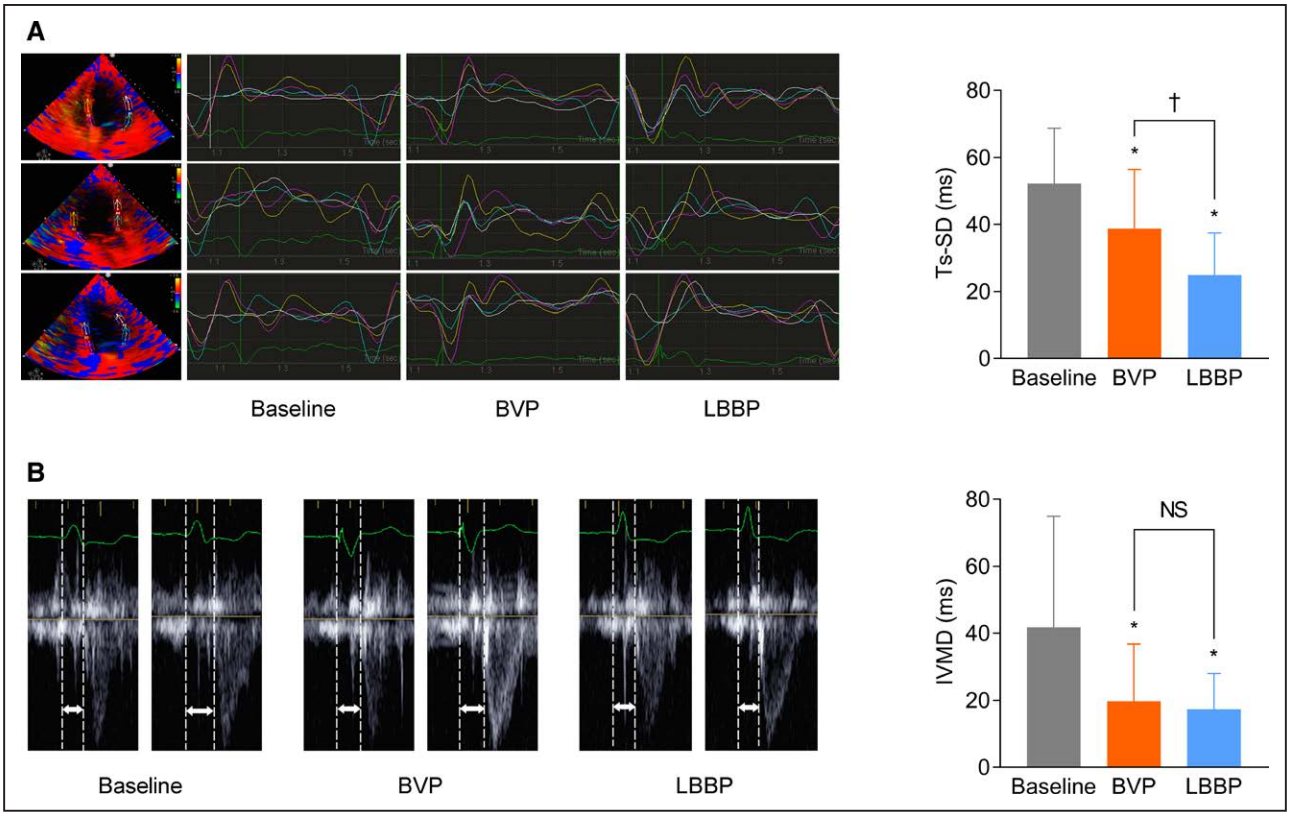

Figure 4. Echocardiographic assessment of intra-ventricular and interventricular mechanical synchrony.
A, (left) An example of Ts-SD as calculated with longitudinal velocity from apical 4-chamber, 2-chamber, and long-axis views of tissue Doppler images with time to peak velocity from basal and midventricular sites, of baseline, biventricular pacing (BVP) and left bundle branch pacing (LBBP). (right) Comparison of Ts-SD among baseline, BVP, and LBBP. **B**, (left) An example of interventricular mechanical delay (IVMD) as calculated as the difference between RV ejection (left) and LV ejection (right; white arrow), of baseline, BVP and LBBP. (right) Comparison of IVMD among baseline, BVP, and LBBP. *P<0.05 versus baseline; †P<0.05 LBBP versus BVP.

less physiological contraction pattern as suggested by the results. Nevertheless, the reason for the similarity in IVMD between LBBP and BVP is unclear. One possible explanation is that LBBP improved the IVMD by the quick occurrence and shortening of the LV activation time, while the effect of BVP comprised of 2 components of simultaneously shortened LV and RV activation. The mechanism underlying this finding requires further investigation.

Compared with inter-ventricular dyssynchrony, intraventricular delay plays a more important role in predicting response and outcomes after CRT.[21] Therefore, the present study suggested that LBBP may have greater benefit to CRT with more improved intraventricular synchrony than BVP.

Hemodynamic Effects of LBBP Versus BVP

The increase in LV dP/dt_{max} during BVP over baseline was ≈ 30% in the present study and higher than previously reported,[22] which could be attributed to the appropriate selection of patients, the optimal location of LV leads, and the adjustment of atrioventricular delays. Despite this remarkable effect of BVP, LBBP demonstrated a significantly more favorable hemodynamic effect. Since the mechanism of beneficial hemodynamic effect from CRT is comprised of atrioventricular timing optimization and ventricular resynchronization,[23] and the benefit of atrioventricular delay optimization has been controlled between the 2 pacing modalities, we propose the superior hemodynamic improvement be predominantly driven by the greater effect in electrical and mechanical resynchronization by LBBP over BVP.

The increase in LV dP/dt_{max} over baseline during acute assessment has been proved capable of predicting reverse remodeling after conventional CRT with a cutoff value of 10%.[24] Correspondingly, despite a significant difference in LV dP/dt_{max} increase from the 2 pacing modalities as demonstrated in the present study, the relative increase in dP/dt_{max} achieved by LBBP over BVP was approximately 4%. It needs to be investigated whether this modest hemodynamic improvement of LBBP over BVP would translate into significantly greater effect in reverse remodeling or further clinical function. It is noteworthy that the role of the power of LV dP/dt_{max} in LBBP to predict CRT response is still unclear, and previous observational studies comparing the 2 pacing modalities bear inherent limitation of selection bias.

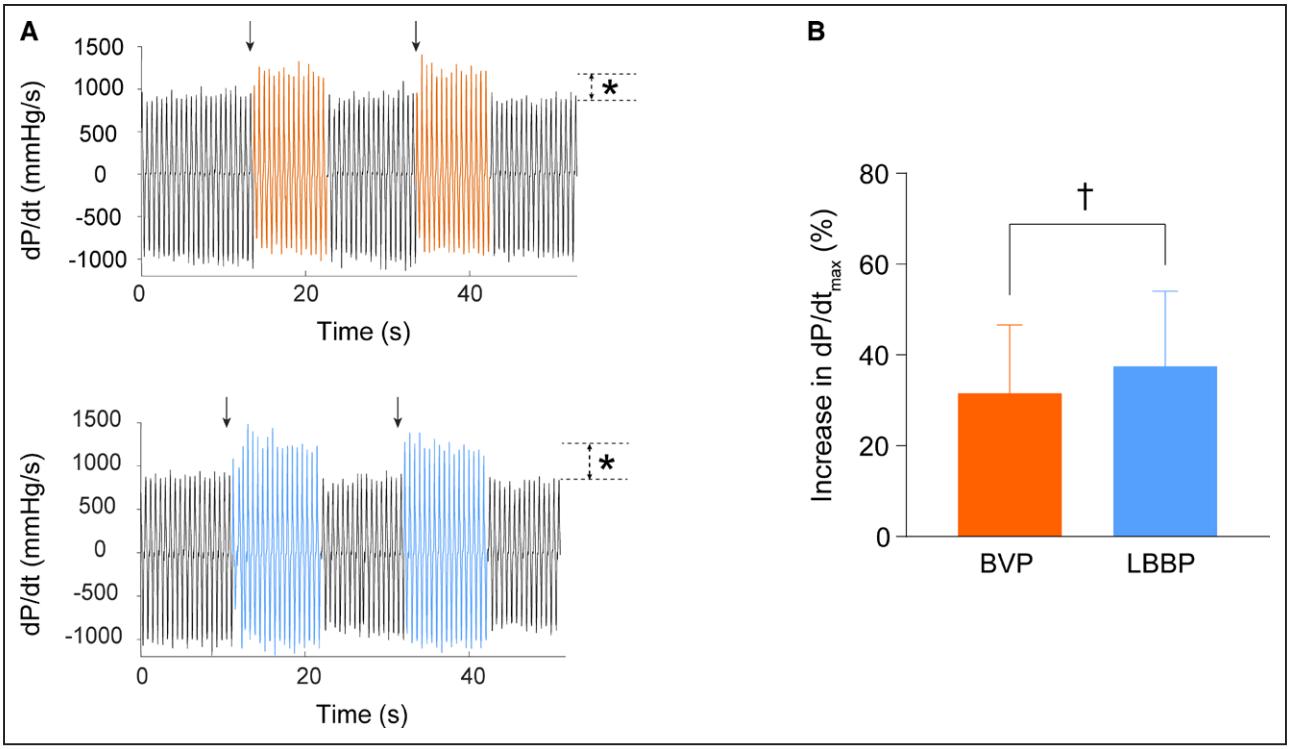

Figure 5. Assessment of hemodynamics.
A, An example of increase in dP/dt_{max} over baseline during biventricular pacing (BVP; top) and left bundle branch pacing (LBBP; bottom), with the first 2 of the total 8 transitions demonstrated. **B**, Comparison of increase in dP/dt_{max} between BVP and LBBP. * the increase of dP/dt_{max} was 27% during BVP, and 46% during LBBP. †$P<0.05$ LBBP versus BVP.

Hence, the present study highlights the need for high-quality randomized controlled trials to evaluate and compare the effect of LBBP and BVP on clinical outcomes.

Clinical Implications

The present study has laid the groundwork for further exploration of clinical evidence to support the application of LBBP for CRT in patients with heart failure and LBBB. In the framework of pacing therapy for heart failure, BVP performs as the cornerstone with solid evidence, while novel approaches including HBP, LBBP, and LVSP have been emerging. These pacing modalities are able to overcome major shortcomings of BVP, such as the difficulties of lead placement in a coronary venous tributary, the high risks of phrenic nerve stimulation, and the epicardial-to-endocardial activation sequence associated with increased risks of arrhythmic events.

Among these novel approaches, HBP is the most physiological pacing modality that restores normal ventricular activation and has been demonstrated to achieve greater hemodynamic response over BVP in patients with heart failure and LBBB.[25] However, its application has been limited by the high pacing threshold required to correct LBBB, late threshold rise, and concerns that block may develop in the more distal conduction system. In contrast, LVSP requires no capture of the conduction system at the expense of slower conduction through the myocardial tissue resulting in suboptimal electrical synchrony as well as hemodynamic performance. This notion is supported by evidence that LVSP produced larger QRS area compared with LBBP in pacemaker patients[15] and achieved only comparable acute hemodynamic improvement compared with BVP in patients with heart failure.[9]

Table 2. Analysis of Patients With Ischemic Cardiomyopathy

	Baseline				BVP					LBBP				
Patient no.	QRS duration, ms	QRS area, μVs	Ts-SD, ms	IVMD, ms	QRS duration, ms	QRS area, μVs	Ts-SD, ms	IVMD, ms	Increase in dP/dt_{max} (%)	QRS duration, ms	QRS area, μVs	Ts-SD, ms	IVMD, ms	Increase in dP/dt_{max} (%)
1	161	211	67	36	100	70	67	31	51	93	47	37	36	55
2	171	172	63	18	131	188	62	0	48	128	45	31	31	53

BVP indicates biventricular pacing; dP/dt_{max} indicates maximum rate of left ventricular pressure rise; IVMD, interventricular mechanical delay; LBBP, left bundle branch pacing; and Ts-SD, SD of time to peak velocity of 12 left ventricular segments.

Combining the findings of superior electrical and mechanical resynchronization and hemodynamic improvement by LBBP over BVP in the present study and those in previous studies on its procedure safety, stability of pacing parameters and low cost,[3] LBBP seems a most promising approach to deliver CRT in patients with heart failure with LBBB and thus deserves further systematic evaluation.

Study Limitations

Several limitations of the present study have to be acknowledged. First, the study population is only confined to patients with LBBB; therefore, the conclusion could not be extended to the larger population with non-LBBB and prolonged QRS duration for whom CRT with BVP has also been proved to be effective. Second, most patients in the present study had non-ischemic cardiomyopathy, although subgroup analysis of the 2 patients with ischemic cardiomyopathy were consistent with the major findings. Third, the present study excluded 4 patients who could not complete hemodynamic assessment. However, no significant difference in characteristics was observed between included and excluded patients (Table S1) and thus the bias is supposed to be limited. Fourth, the study was designed to compare LBBP with BVP, thus HBP or LVSP were not included for comparison and analysis. Considering the favorable performance of HBP and LVSP reported in previous studies,[9,25] a systematic comparison between these pacing modalities is required. Fifth, traditional echocardiographic parameters such as Ts-SD and IVMD that were employed for the assessment of mechanical synchrony have been criticized for the limited predictive capability of response after CRT.[26] Last, the present study compared the acute hemodynamic effect of LBPP and BVP; however, there lacks solid evidence for the association between the increase in LV dP/dt_{max} and the long-term outcomes after CRT.[22] The effect of LBBP versus BVP on clinical outcomes in patients with heart failure needs to be evaluated in randomized control trials.

CONCLUSIONS

While both LBBP and BVP effectively restore ventricular synchrony and improve LV hemodynamics, LBBP delivers greater improvements than BVP in predominantly nonischemic heart failure patients with LBBB. These results suggest LBBP may serve as a promising approach to deliver CRT and improve clinical outcomes.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology, Zhongshan Hospital of Fudan University, Shanghai Institute of Cardiovascular Diseases, National Clinical Research Center for Interventional Medicine (Y.L., J.W., Z.Y., L.Z., M.L., L.P., X.C., J.C., Y.S., J.G.). Department of Cardiology, Deltahealth Hospital (X.G.). Cardiac Rhythm Management, Medtronic Technology Center, Medtronic (Shanghai) Ltd (H.L.). Department of Cardiology, Shanghai Chest Hospital of Shanghai Jiao Tong University, China (W.Z., R.L.). Cardiac Rhythm Management, Medtronic plc., Mounds View, MN (X.Z.). Department of Cardiology, First Affiliated Hospital of Wenzhou Medical University, China (W.H.).

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Disclosures

Drs Lu and Zhou are employees of Medtronic. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Table S1
Figures S1–S4
References[9,27–34]

REFERENCES

1. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:3039–3049. doi: 10.1016/j.jacc.2019.10.039
2. Zhang W, Huang J, Qi Y, Wang F, Guo L, Shi X, Wu W, Zhou X, Li R. Cardiac resynchronization therapy by left bundle branch area pacing in patients with heart failure and left bundle branch block. *Heart Rhythm*. 2019;16:1783–1790. doi: 10.1016/j.hrthm.2019.09.006
3. Huang W, Wu S, Vijayaraman P, Su L, Chen X, Cai B, Zou J, Lan R, Fu G, Mao G, et al. Cardiac resynchronization therapy in patients with nonischemic cardiomyopathy using left bundle branch pacing. *JACC Clin Electrophysiol*. 2020;6:849–858. doi: 10.1016/j.jacep.2020.04.011
4. Herweg B, Welter-Frost A, Vijayaraman P. The evolution of cardiac resynchronization therapy and an introduction to conduction system pacing: a conceptual review. *Europace*. 2021;23:496–510. doi: 10.1093/europace/euaa264
5. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, Shi R, Huang Z, Whinnett ZI, Huang W. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. *Can J Cardiol*. 2021;37:319–328. doi: 10.1016/j.cjca.2020.04.037
6. Li X, Qiu C, Xie R, Ma W, Wang Z, Li H, Wang H, Hua W, Zhang S, Yao Y, et al. Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing. *ESC Heart Fail*. 2020;7:1711–1722. doi: 10.1002/ehf2.12731
7. Wang Y, Gu K, Qian Z, Hou X, Chen X, Qiu Y, Jiang Z, Zhang X, Wu H, Chen M, et al. The efficacy of left bundle branch area pacing compared with biventricular pacing in patients with heart failure: a matched case-control study. *J Cardiovasc Electrophysiol*. 2020;31:2068–2077. doi: 10.1111/jce.14628
8. Mullens W, Verga T, Grimm RA, Starling RC, Wilkoff BL, Tang WHW. Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure. *J Am Coll Cardiol*. 2009;53:600–607. doi: 10.1016/j.jacc.2008.08.079
9. Salden FCWM, Luermans JGLM, Westra SW, Weijs B, Engels EB, Heckman LIB, Lamerichs LJM, Janssen MHG, Clerx KJH, Cornelussen R, et al. Short-Term Hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol*. 2020;75:347–359. doi: 10.1016/j.jacc.2019.11.040
10. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, et al; MADIT-CRT Investigators.

Effectiveness of cardiac resynchronization therapy by qrs morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. 2011;123:1061–1072. doi: 10.1161/CIRCULATIONAHA.110.960898
11. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm*. 2019;16:1791–1796. doi: 10.1016/j.hrthm.2019.06.016
12. Sohaib SM, Kyriacou A, Jones S, Manisty CH, Mayet J, Kanagaratnam P, Peters NS, Hughes AD, Whinnett ZI, Francis DP. Evidence that conflict regarding size of haemodynamic response to interventricular delay optimization of cardiac resynchronization therapy may arise from differences in how atrioventricular delay is kept constant. *Europace*. 2015;17:1823–1833. doi: 10.1093/europace/euu374
13. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J*. 1990;11:1083–1092. doi: 10.1093/oxfordjournals.eurheartj.a059647
14. Shun-Shin MJ, Miyazawa AA, Keene D, Sterliński M, Sokal A, Van Heuverswyn F, Rinaldi CA, Cornelussen R, Stegemann B, Francis DP, et al. How to deliver personalized cardiac resynchronization therapy through the precise measurement of the acute hemodynamic response: Insights from the iSpot trial. *J Cardiovasc Electrophysiol*. 2019;30:1610–1619. doi: 10.1111/jce.14001
15. Heckman LIB, Luermans JGLM, Curila K, Van Stipdonk AMW, Westra S, Smisek R, Prinzen FW, Vernooy K. Comparing Ventricular Synchrony in Left Bundle Branch and Left Ventricular Septal Pacing in Pacemaker Patients. *J Clin Med*. 2021;10:822. doi: 10.3390/jcm10040822
16. Curila K, Jurak P, Jastrzebski M, Prinzen F, Waldauf P, Halamek J, Vernooy K, Smisek R, Karch J, Plesinger F, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Heart Rhythm*. 2021;18:1281–1289. doi: 10.1016/j.hrthm.2021.04.025
17. Starling RC, Krum H, Bril S, Tsintzos SI, Rogers T, Hudnall JH, Martin DO. Impact of a Novel adaptive optimization algorithm on 30-day readmissions: evidence from the adaptive CRT trial. *JACC Heart Fail*. 2015;3:565–572. doi: 10.1016/j.jchf.2015.03.001
18. Huang W, Zhou X, Ellenbogen KA. Pursue physiological pacing therapy: A better understanding of left bundle branch pacing and left ventricular septal myocardial pacing. *Heart Rhythm*. 2021;18:1290–1291. doi: 10.1016/j.hrthm.2021.05.013
19. Ghossein MA, van Stipdonk AMW, Plesinger F, Kloosterman M, Wouters PC, Salden OAE, Meine M, Maass AH, Prinzen FW, Vernooy K. Reduction in the QRS area after cardiac resynchronization therapy is associated with survival and echocardiographic response. *J Cardiovasc Electrophysiol*. 2021;32:813–822. doi: 10.1111/jce.14910
20. Ploux S, Eschalier R, Whinnett ZI, Lumens J, Derval N, Sacher F, Hocini M, Jaïs P, Dubois R, Ritter P, et al. Electrical dyssynchrony induced by biventricular pacing: implications for patient selection and therapy improvement. *Heart Rhythm*. 2015;12:782–791. doi: 10.1016/j.hrthm.2014.12.031
21. Gorcsan J 3rd, Oyenuga O, Habib PJ, Tanaka H, Adelstein EC, Hara H, McNamara DM, Saba S. Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. *Circulation*. 2010;122:1910–1918. doi: 10.1161/CIRCULATIONAHA.110.954768
22. Zweerink A, Salden OAE, van Everdingen WM, de Roest GJ, van de Ven PM, Cramer MJ, Doevendans PA, van Rossum AC, Vernooy K, Prinzen FW, et al. Hemodynamic optimization in cardiac resynchronization therapy: should we aim for dp/dt or stroke work?. *JACC Clin Electrophysiol*. 2019;5:1013–1025. doi: 10.1016/j.jacep.2019.05.020
23. Jones S, Lumens J, Sohaib SMA, Finegold JA, Kanagaratnam P, Tanner M, Duncan E, Moore P, Leyva F, Frenneaux M, et al; BRAVO Investigators. Cardiac resynchronization therapy: mechanisms of action and scope for further improvement in cardiac function. *Europace*. 2017;19:1178–1186. doi: 10.1093/europace/euw136
24. Duckett SG, Ginks M, Shetty AK, Bostock J, Gill JS, Hamid S, Kapetanakis S, Cunliffe E, Razavi R, Carr-White G, et al. Invasive acute hemodynamic response to guide left ventricular lead implantation predicts chronic remodeling in patients undergoing cardiac resynchronization therapy. *J Am Coll Cardiol*. 2011;58:1128–1136. doi: 10.1016/j.jacc.2011.04.042
25. Arnold AD, Shun-Shin MJ, Keene D, Howard JP, Sohaib SMA, Wright IJ, Cole GD, Qureshi NA, Lefroy DC, Koa-Wing M, et al. His resynchronization versus biventricular pacing in patients with heart failure and left bundle branch block. *J Am Coll Cardiol*. 2018;72:3112–3122. doi: 10.1016/j.jacc.2018.09.073
26. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, et al. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation*. 2008;117:2608–2616. doi: 10.1161/CIRCULATIONAHA.107.743120
27. Bogaard MD, Houthuizen P, Bracke FA, Doevendans PA, Prinzen FW, Meine M, van Gelder BM. Baseline left ventricular dP/dtmax rather than the acute improvement in dP/dtmax predicts clinical outcome in patients with cardiac resynchronization therapy. *Eur J Heart Fail*. 2011;13:1126–1132. doi: 10.1093/eurjhf/hfr094
28. Zanon F, Baracca E, Pastore G, Marcantoni L, Fraccaro C, Lanza D, Picariello C, Aggio S, Roncon L, Dell'Avvocata F, et al. Multipoint pacing by a left ventricular quadripolar lead improves the acute hemodynamic response to CRT compared with conventional biventricular pacing at any site. *Heart Rhythm*. 2015;12:975–981. doi: 10.1016/j.hrthm.2015.01.034
29. Sohal M, Hamid S, Perego G, Della Bella P, Adhya S, Paisey J, Betts T, Kamdar R, Lambiase P, Leyva F, et al. A multicenter prospective randomized controlled trial of cardiac resynchronization therapy guided by invasive dP/dt. *Heart Rhythm O2* 2021;2:19–27. doi: 10.1016/j.hroo.2021.01.005
30. Derval N, Steendijk P, Gula LJ, Deplagne A, Laborderie J, Sacher F, Knecht S, Wright M, Nault I, Ploux S, et al. Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. *J Am Coll Cardiol*. 2010;55:566–575. doi: 10.1016/j.jacc.2009.08.045
31. Duckett SG, Ginks M, Shetty AK, Bostock J, Gill JS, Hamid S, Kapetanakis S, Cunliffe E, Razavi R, Carr-White G, et al. Invasive acute hemodynamic response to guide left ventricular lead implantation predicts chronic remodeling in patients undergoing cardiac resynchronization therapy. *J Am Coll Cardiol*. 2011;58:1128–1136. doi: 10.1016/j.jacc.2011.04.042
32. Schau T, Koglek W, Brandl J, Seifert M, Meyhöfer J, Neuss M, Grimm G, Bitschnau R, Butter C. Baseline vectorcardiography as a predictor of invasively determined acute hemodynamic response to cardiac resynchronization therapy. *Clin Res Cardiol*. 2013;102:129–138. doi: 10.1007/s00392-012-0506-5
33. Umar F, Taylor RJ, Stegemann B, Marshall H, Flannigan S, Lencioni M, De Bono J, Griffith M, Leyva F. Haemodynamic effects of cardiac resynchronization therapy using single-vein, three-pole, multipoint left ventricular pacing in patients with ischaemic cardiomyopathy and a left ventricular free wall scar: the MAESTRO study. *Europace*. 2016;18:1227–1234. doi: 10.1093/europace/euv396
34. Okafor O, Umar F, Zegard A, van Dam P, Walton J, Stegemann B, Marshall H, Leyva F. Effect of QRS area reduction and myocardial scar on the hemodynamic response to cardiac resynchronization therapy. *Heart Rhythm*. 2020;17:2046–2055. doi: 10.1016/j.hrthm.2020.07.025