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Left Bundle Branch Area Pacing for Cardiac Resynchronization Therapy

Results From the International LBBAP Collaborative Study Group

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ABSTRACT

OBJECTIVES The aim of this study was to assess the feasibility and outcomes of left bundle branch area pacing (LBBAP) in patients eligible for cardiac resynchronization therapy (CRT) in an international, multicenter, collaborative study.

BACKGROUND CRT using biventricular pacing is effective in patients with heart failure and left bundle branch block (LBBB). LBBAP has been reported as an alternative option for CRT.

METHODS LBBAP was attempted in patients with left ventricular ejection fraction (LVEF) <50% and indications for CRT or pacing. Procedural outcomes, left bundle branch capture, New York Heart Association functional class, heart failure hospitalization, echocardiographic data, and lead complications were recorded. Clinical (no heart failure hospitalization and improvement in New York Heart Association functional class) and echocardiographic responses (≥5% improvement in LVEF) were assessed.

RESULTS LBBAP was attempted in 325 patients, and CRT was successfully achieved in 277 (85%) (mean age 71 ± 12 years, 35% women, ischemic cardiomyopathy in 44%). QRS configuration at baseline was LBBB in 39% and non-LBBB in 46%. Procedure and fluoroscopy duration were 105 ± 54 and 19 ± 15 min, respectively. LBBAP threshold and R-wave amplitudes were 0.6 ± 0.3 V at 0.5 ms and 10.6 ± 6 mV at implantation and remained stable during mean follow-up of 6 ± 5 months. LBBAP resulted in significant QRS narrowing from 152 ± 32 to 137 ± 22 ms ($p < 0.01$). LVEF improved from 33 ± 10% to 44 ± 11% ($p < 0.01$). Clinical and echocardiographic responses were observed in 72% and 73% of patients, respectively. Baseline LBBB (odds ratio: 3.96; 95% confidence interval: 1.64 to 9.26; $p < 0.01$) and left ventricular end-diastolic diameter (odds ratio: 0.62; 95% confidence interval: 0.49 to 0.79; $p < 0.01$) were independent predictors of echocardiographic response.

CONCLUSIONS LBBAP is feasible and safe and provides an alternative option for CRT. LBBAP provides remarkably low and stable pacing thresholds and was associated with improved clinical and echocardiographic outcomes.
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ABBREVIATIONS AND ACRONYMS

BVP = biventricular pacing

CRT = cardiac resynchronization therapy

HBP = His bundle pacing

ICM = ischemic cardiomyopathy

LBBAP = left bundle branch area pacing

LBB = left bundle branch

LBBB = left bundle branch block

LV = left ventricular

LVEDD = left ventricular end-diastolic diameter

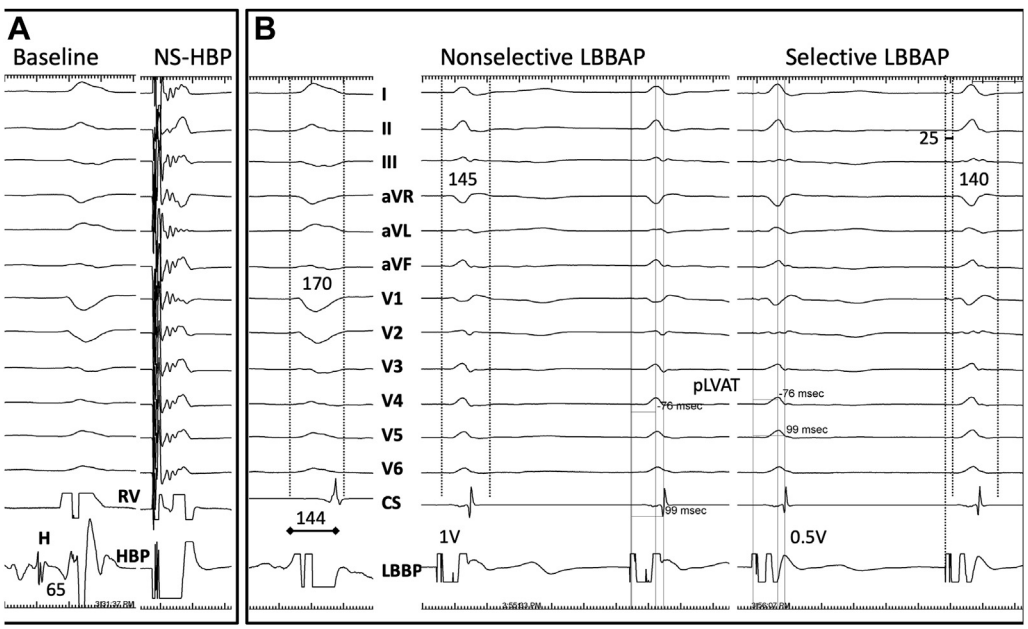
LVEF = left ventricular ejection fraction

NICM = nonischemic cardiomyopathy

NYHA = New York Heart Association

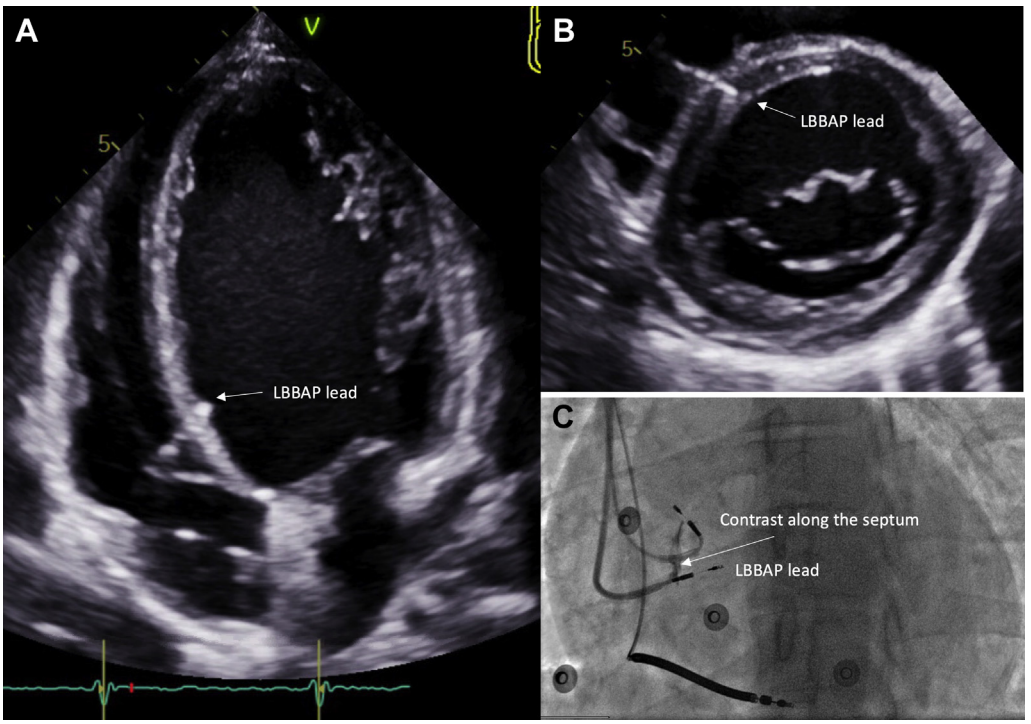
Cardiac resynchronization therapy (CRT) using biventricular pacing (BVP) is a well-established therapy for patients with cardiomyopathy, reduced left ventricular ejection fractions (LVEFs), heart failure, and left bundle branch block (LBBB). Several prospective randomized studies have shown that BVP improves quality of life, increases exercise capacity, reduces heart failure hospitalization, and decreases all-cause mortality (1–5). BVP is also an accepted therapy for patients undergoing atrioventricular node ablation and those requiring >40% right ventricular pacing (6). However, up to one-third of patients treated with BVP may not derive clinical or echocardiographic benefit, and some may worsen (1,3,7). Recently, permanent His bundle pacing (HBP) has emerged as an acceptable alternative to deliver physiological ventricular pacing and is a Class IIa recommendation in patients with atrioventricular block and LVEFs of 35% to 50% (8) and a Class I recommendation for patients with tachycardiomyopathy undergoing atrioventricular node ablation (9). Several observational studies using HBP have demonstrated improved clinical and echocardiographic outcomes in patients with LBBB and left ventricular (LV) dysfunction (10–12). However, HBP may be associated with higher pacing thresholds to correct LBBB and lower success rates in addition to increased incidence of lead revisions (10–12). Intraseptal left bundle branch area pacing (LBBAP) is a novel technique to pace the conduction system beyond the site of block and is associated with low and stable capture thresholds (13–15). Recently LBBAP has been shown to restore LV synchrony in patients with LBBB (16). LBBAP has the potential advantage of backup LV septal capture in addition to left bundle branch (LBB) capture in these patients. The aim of this multicenter study was to assess the feasibility and outcomes of LBBAP in CRT-eligible patients or those who had CRT was unsuccessful.

FIGURE 1 LBBAP in a Patient With LBBB



Twelve-lead electrocardiogram and intracardiac electrograms are shown at a sweep speed of 100 mm/s. **(A)** Left bundle branch block (LBBB) is corrected by nonselective His bundle pacing (NS-HBP) at high output. **(B)** At baseline, the surface QRS onset to left ventricular activation (Q-LV) in the coronary sinus (CS) lead was 144 ms. During decremental, asynchronous left bundle branch area pacing (LBBAP) from 1 to 0.5 V, transition from nonselective LBBAP (left ventricular [LV] septal + left bundle branch [LBB] capture, **blue circle**) to selective LBBAP (LBB-only capture, **red circle**) is seen. Note that the stimulus to LV activation time in the CS lead and peak LV activation time (pLVAT) in leads V_4 to V_6 remain unchanged at 99 and 76 ms, respectively. QRS duration decreased from 170 ms at baseline to 145 ms with nonselective LBBAP and 140 ms during selective LBBAP with stimulus to QRS onset of 25 ms. RV = right ventricle.

FIGURE 2 **Echocardiographic and Fluoroscopic Visualization of LBBAP Lead**



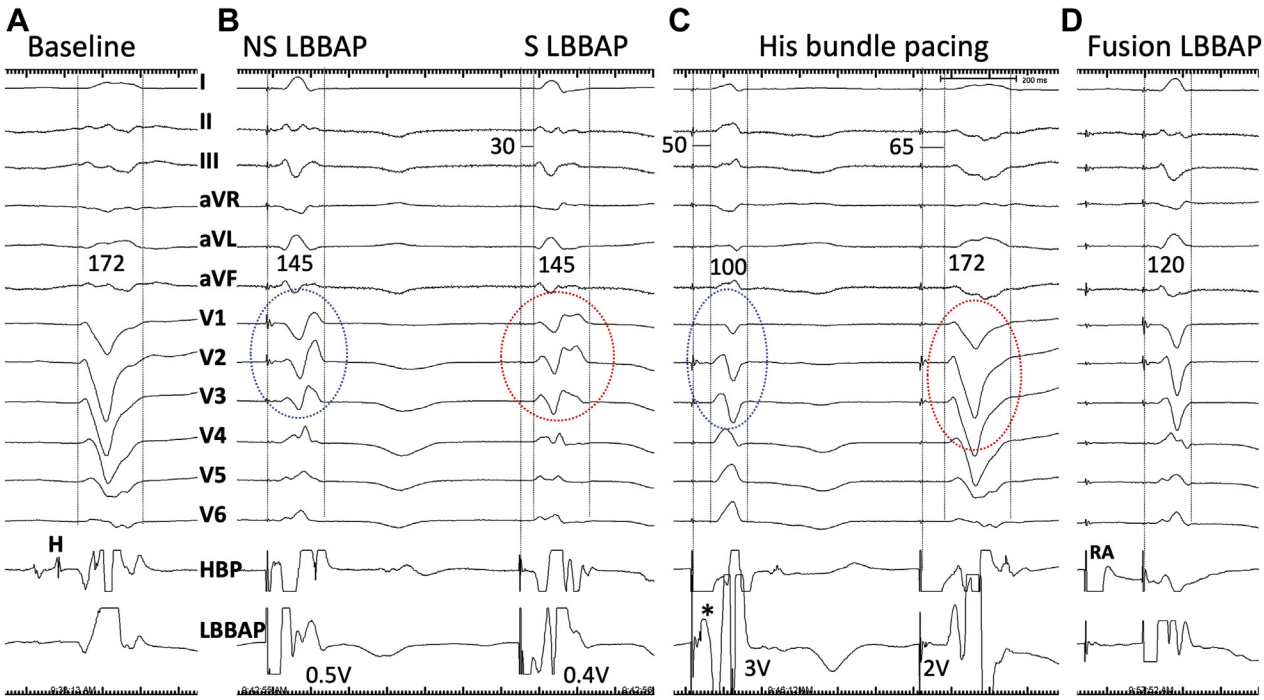
(A) Apical 4-chamber echocardiographic view shows the location of the left bundle branch area pacing (LBBAP) lead in the proximal interventricular septum. **(B)** Short-axis view demonstrating the lead tip in the basal septum. **(C)** Fluoroscopic view in left anterior oblique projection at 30° shows contrast delineating the right ventricular septum and the depth of the LBBAP lead.

METHODS

STUDY POPULATION. This was a retrospective, multicenter, observational cohort study designed to evaluate the real-world experience of LBBAP. The study population included all patients who had LBBAP was attempted to achieve CRT at 8 centers (4 in the United States, 1 in Spain, 1 in India, 1 in Brazil, and 1 in Poland). All patients had New York Heart Association (NYHA) functional class II to IV heart failure symptoms, baseline LVEFs ≤50%, and indications for ventricular pacing and/or CRT. Patients provided informed consent and demonstrated an understanding of LBBAP as a nonstandard approach to achieve cardiac resynchronization. Baseline patient demographics together with relevant clinical information (QRS configuration and QRS duration, presence of coronary artery disease, hypertension, diabetes, etc.) were recorded. LBBB was defined as QRS duration >140 ms in men (>130 ms in women) and the presence of at least 2 mid-QRS notches or slurs in leads I, aVL, V_1, V_2, V_5, and V_6. Data collection was approved by the Institutional Review Board at each site.

PROCEDURAL DETAILS. At centers with extensive experience, HBP was attempted first, and if satisfactory electric outcomes (acceptable His capture or bundle branch block correction thresholds) were not achieved, LBBAP was attempted (**Figure 1**). At other centers, LBBAP was chosen as the first-line therapy without attempting HBP. LBBAP was also attempted when coronary sinus lead placement was unsuccessful. LBBAP was performed using the SelectSecure pacing lead (model 3830, 69 cm, Medtronic, Minneapolis, Minnesota) as previously described (17). The lead was delivered through a fixed curve sheath (C315His, Medtronic) or a deflectable sheath (C304His, Medtronic). Briefly, the His bundle region was mapped with the lead and marked as a reference image, and the sheath and lead were advanced about 1 to 2 cm apical (right anterior oblique projection) in the right ventricular septum. The lead was then rapidly rotated until it penetrated deep into the

FIGURE 3 Demonstration of LBB Potential in a Patient With LBBB



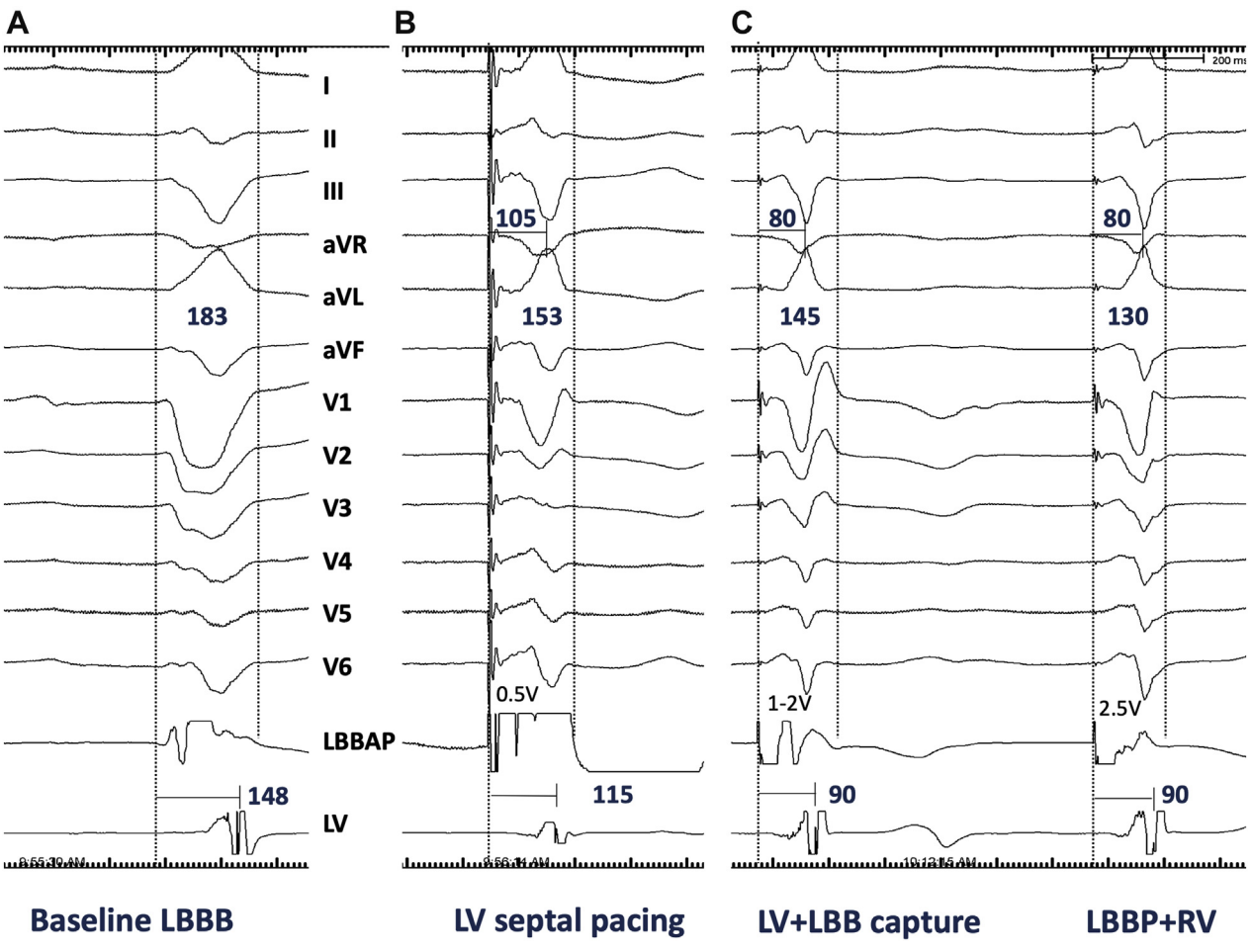
(A) Baseline LBBB with QRS duration (QRSd) of 170 ms and HV interval of 45 ms is shown. Note the absence of potentials in the LBBAP lead due to proximal conduction block. **(B)** During threshold testing from LBBAP lead, nonselective (NS) **(blue circle)** to selective (S) LBB capture **(red circle)** is seen. **(C)** Selective HBP with **(blue circle)** and without **(red circle)** LBBB correction is shown. During corrective HBP, LBB potentials with injury current **(asterisk)** is clearly seen. **(D)** Sequential DDD pacing with right atrial (RA) to LBBAP at 150-ms delay shows normalization of QRS configuration due to fusion with native conduction via right bundle branch. QRSd and stimulus to QRS onset intervals during pacing are shown. Abbreviations as in Figure 1.

interventricular septum. Unipolar-tip paced QRS configuration and pacing impedance were monitored along with measurement of peak LV activation times in leads V_4 to V_6 (Figure 1B). The depth of the lead in the interventricular septum was assessed by contrast injection via the sheath in the left anterior oblique projection (Figure 2). Presence of Purkinje potentials recorded from the LBBAP lead and the potential to QRS onset intervals (LBB-V) were documented. Pacing thresholds were assessed by evaluating the transition from nonselective to selective LBB capture (Figure 3) or nonselective LBB capture to LV septal myocardial capture. These phenomena were usually observed at near threshold pacing outputs. If primary LBBAP was unsuccessful, an LV lead was implanted via the traditional coronary venous approach in patients who had conduction system pacing was chosen as the initial approach.

DETERMINATION OF LBB CAPTURE. During unipolar-tip pacing, right bundle branch configuration was observed in addition to 1 or more of the following findings: 1) LBB potentials (LBB-V intervals of 15 to 35 ms); 2) transition from nonselective to selective LBB capture; 3) transition from nonselective LBB capture to left septal capture at near threshold outputs (Figure 4); 4) short and constant peak LV activation time (stimulus to peak of the R wave in leads V_4 to V_6 [peak LV activation time]) of <90 ms at high- and low-output pacing; and 5) programmed (extrastimulus testing) deep septal stimulation to differentiate LV septal versus nonselective LBB capture (Supplemental Figure S1) (14,17,18). If LBB capture could not be confirmed, only LV septal capture was considered to be present.

FOLLOW-UP. Patients were followed in the device clinic at 2 weeks, 3 months, and 1 year and by remote monitoring every 3 months. R-wave amplitudes, capture thresholds, lead impedance, and percentage of ventricular pacing were recorded at each visit. All capture thresholds were defined using a pulse width of 0.5 ms. QRS duration during pacing was measured from stimulus to the end of the QRS complex. In patients with LBBB and normal PR intervals, further QRS narrowing was achieved by fusing with native

FIGURE 4 Nonselective to LV Septal Capture During LBBAP



(A) Baseline LBBB with QRSd of 183 ms and Q-LV of 148 ms is shown. **(B)** Unipolar LBBAP at threshold shows LV septal capture only with QRSd of 153 ms, pLVAT of 105 ms, and stimulus to LV activation time of 115 ms. **(C)** Bipolar pacing at 1 to 2 V resulted in nonselective LBB capture with QRSd of 145 ms and at 2.5 V resulted in anodal right ventricular septal capture in addition to nonselective LBBAP, resulting in further narrowing of QRSd to 130 ms. Note the pLVAT and stimulus to LV activation time are further reduced to 80 and 90 ms. pLVAT was measured in lead aVL as a surrogate because of slurred R waves in leads V_4 to V_6. Abbreviations as in Figures 1 and 3.

conduction (Figure 3D). Lead-related complications were routinely tracked. Echocardiographic indexes, including LVEF, LV end-diastolic diameter (LVEDD), and LV volumes, were recorded pre-implantation and at 3- to 6-month follow-up. Change in NYHA functional class, any heart failure-related hospitalizations, and death of any cause were recorded.

Echocardiographic response was defined as a ≥5% increase in LVEF. Superresponse was defined as an absolute improvement in LVEF of ≥20% or improvement in LVEF to >50% (in patients with LVEFs ≤35%) between baseline and follow-up echocardiography (19). Clinical response to CRT was defined as an improvement in NYHA functional class by at least 1 class and no heart failure hospitalization (18). Heart failure hospitalization was defined as a hospital admission or an urgent care visit for intensive treatment for heart failure with intravenous diuretic agents or intravenous inotropic medications.

STATISTICAL ANALYSIS. Values are expressed as frequencies and percentages for categorical variables and as mean ± SD or median (interquartile range) for continuous variables. Descriptive statistics were reported for the full sample and stratified by various subgroups, such as type of cardiomyopathy, baseline conduction disease, and whether conduction system pacing was first-line or a bailout procedure. Comparison between groups was accomplished using

TABLE 1 Baseline Characteristics

	All Patients (N = 325)	Successful LBBP (n = 277)	Unsuccessful (n = 48)	p Value
Age	71 ± 12	70 ± 13	75 ± 8	0.03
Female	113 (35)	101 (36)	12 (25)	0.07
Medical history				
HTN	224 (69)	188 (68)	36 (75)	0.11
DM	113 (35)	100 (36)	13 (27)	0.08
CAD	161 (50)	126 (46)	35 (73)	0.01
AF	184 (57)	166 (60)	18 (38)	0.01
Ischemic cardiomyopathy	144 (44)	114 (41)	30 (63)	0.01
Baseline NYHA functional class III or IV	209 (64)	184 (68)	25 (52)	0.24
Baseline NYHA functional class	2.7 ± 0.7	2.7 ± 0.7	2.5 ± 0.7	0.92
Echocardiographic parameters				
LVEF	32 ± 12	33 ± 10	27 ± 10	0.06
LVEDD (mm)	57 ± 10	56 ± 9	61 ± 9	0.03
LVESV (ml)	115 ± 70	114 ± 68	124 ± 81	0.45
LVEDV (ml)	170 ± 86	169 ± 84	175 ± 90	0.18
LA volume index (ml/m^2)	58 ± 22	58 ± 23	59 ± 16	0.92
IVSD (mm)	11.6 ± 3	11.4 ± 2	14 ± 3	0.04
Electrocardiographic parameters				
Baseline QRS duration (ms)	154 ± 32	152 ± 32	169 ± 35	0.02
Baseline QRS duration >150 ms	198 (61)	168 (62)	30 (63)	0.86
LBBB	126 (39)	116 (42)	10 (21)	0.02
RBBB	54 (17)	48 (17)	6 (13)	0.81
IVCD	49 (15)	32 (12)	17 (35)	0.02
RV paced	48 (14.5)	36 (13)	12 (25)	0.06
Narrow	48 (14.5)	45 (16)	3 (6)	0.62

Values are mean ± SD or n (%).

AF = atrial fibrillation; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; IVCD = intraventricular conduction delay; IVSD = interventricular septal diameter; LA = left atrial; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular.

the chi-square or Fisher exact test and the 2-sample Student's *t*-test or Wilcoxon rank sum test. Comparisons of continuous variables within groups were carried out using the paired Student's *t*-test or Wilcoxon signed rank test. Univariate logistic regression analyses were used to estimate the odds ratios for achieving echocardiographic response as defined earlier for various baseline characteristics. Multivariate regression analysis was then performed on variables with odds ratios with p values <0.10. A backward stepwise regression method was then used to determine the final multivariate regression model. Statistical analysis was performed using SPSS version 25 (SPSS, Chicago, Illinois). A p value of <0.05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. LBBAP was attempted in 325 patients at the 8 implanting centers. Baseline characteristics of the entire study population are shown in Table 1. The mean age of the patients was 71 ± 12 years (35% women). All patients had cardiomyopathy at baseline, with a mean LVEF of 32 ± 12% (68% with LVEFs ≤35%); 64% of patients were in NYHA functional class III or IV. Ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) were present in 44% and 56% of the patients, respectively; 39% had underlying LBBB, 46.5% had non-LBBB (14.5% had ventricular paced rhythm, 17% had right bundle branch block, 15% had intraventricular conduction defects), and the remaining 14.5% of patients had narrow QRS complexes. Baseline QRS duration was 154 ± 32 ms. Patients were followed for an average duration of 6 ± 5 months (median 5 months; range 1 to 23 months).

PROCEDURAL OUTCOMES. The approach to CRT was quite variable among the centers and also varied among the operators within centers. His bundle electrogram mapping and pacing were attempted prior to performing LBBAP in 133 patients (Figures 1 and 3). LBBAP was attempted as the primary approach to CRT in 157 patients. In 35 patients, LBBAP was used as a rescue attempt after failed coronary sinus lead placement.

Permanent LBBAP was achieved in 277 of 325 patients (85%) and was unsuccessful in 48 patients because of inability to penetrate the septum (21 patients) and inadequate electric resynchronization (27 patients). BVP with coronary sinus lead placement was performed in all but 4 patients who had LBBAP was unsuccessful. Patients in the unsuccessful group were older, had ICM, had larger LVEDDs, had thicker interventricular septa, had wider baseline QRS duration, and had intraventricular conduction defects (Table 1). The presence of LBBB (defined by Strauss criteria) predicted success with LBBAP (92%). LBBAP was successful in 32 of 35 patients (91%) who had coronary sinus lead placement was initially unsuccessful.

Procedural outcomes are noted in Table 2. In patients receiving CRT devices (58%), the LBBAP lead was connected to the LV port (LV-to-right ventricular offset was maximized to achieve functional right ventricular noncapture). In 5 patients with chronic atrial fibrillation and need for ICDs, the LBBAP lead was connected to the atrial port (the device was programmed to DDIR mode to prevent right ventricular pacing). In patients receiving dual-chamber pacemakers (n = 87 [31%]), the LBBAP lead was connected to the right ventricular port. In patients with LBBB and normal PR intervals (<200 ms), the atrioventricular delay was optimized to achieve fusion

correction of right bundle branch block pattern induced by LBBAP (Figure 3D).

The average procedure duration and fluoroscopy time were 105 ± 54 and 19 ± 15 min, respectively. The fluoroscopy time for LBBAP lead placement (when available; n = 153) was 15 ± 13 min (range 1.2 to 62 min).

LBB CAPTURE. Evidence for LBB capture was observed in 255 of 277 patients (92%). Electrocardiographic changes to suggest delayed right ventricular depolarization (rSR′ or qR pattern in lead V_1 or deep S in lead V_6) during LBBAP was observed in all but 10 patients. LBB potentials were observed in 98 of 277 patients (35%). In patients with LBBB, potentials were observed during corrective HBP (Figure 3, Supplemental Figure S2C) or during premature ventricular complexes in 12 patients. During threshold testing, transition from nonselective to selective LBB capture at near threshold output was observed in 93 patients (Figures 1B and 3B), and transition from nonselective to LV septal capture (Figure 4) was observed in 55 patients. Programmed stimulation was used to prove conduction system capture in 49 patients. Mean stimulus to peak LV activation time during LBBAP was 83 ± 16 ms. Peak LV activation time >90 ms was observed in 62 patients, the majority of whom had underlying intraventricular conduction defects (Figure 5) or right ventricular pacing at baseline.

PACING OUTCOMES. Average LBBAP capture threshold and R-wave amplitudes at implantation were 0.6 ± 0.3 V at 0.5 ms and 10.6 ± 6 mV, respectively, and remained unchanged (0.7 ± 0.3 V at 0.5 ms and 12.5 ± 5.7 mV) during a mean follow-up duration of 6 ± 5 months. Pacing impedance decreased significantly from 674 ± 193 Ω at implantation to 530 ± 123 Ω during follow-up. Lead dislodgements into the right ventricular cavity were observed in 5 patients: in 3 patients lead dislodgements occurred within 24 h, and in 2 patients they were observed at 2-week follow-up. In 2 other patients, loss of LV septal/LBB capture (no right bundle branch block pattern) was noted within 24 h, while midseptal/right ventricular capture was still maintained. Pneumothorax was seen in 3 patients, pocket hematoma requiring evacuation in 2 patients, and device infection requiring system explantation in 2 patients. acute perforation of the lead into the LV cavity during implantation as determined by high capture threshold, low impedance, and small R waves was recognized in 10 patients. In these patients, the lead was removed and repositioned at a different location. No patient developed late perforation of the lead into the LV cavity or stroke during follow-up.

TABLE 2 Procedural Outcomes

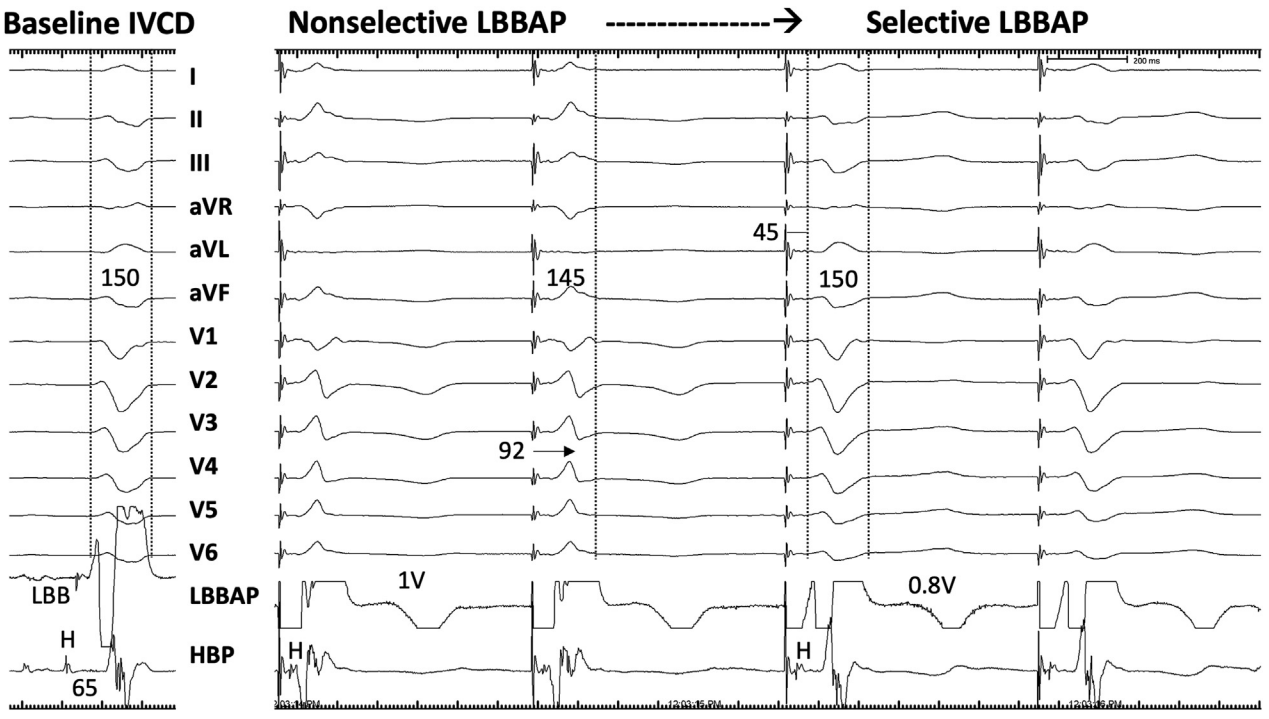
		Value	
Procedural outcomes			
Total number of successful cases		277 (85)	
Procedure duration (min)		105 ± 54	
Fluoroscopy duration (min)		19 ± 15	
LBBP lead fluoroscopy time (n = 153) (min)		16 ± 13	
Type of device			
CRT		162 (58)	
CRT pacemaker		56 (20)	
CRT defibrillator		106 (38)	
Dual-chamber defibrillator		5 (2)	
Dual-chamber pacemaker (DDD)		87 (31)	
Single-chamber pacemaker (VVI)		23 (8)	
Pacing characteristics	Baseline	Follow-up	p value
R-wave amplitude (mV)	10.6 ± 6	12.5 ± 5.7	0.06
Impedance (Ω)	674 ± 193	530 ± 123	<0.001
LBBP threshold (V at 0.5 ms)	0.6 ± 0.3	0.7 ± 0.3	0.17
Stimulus to peak LV activation time (ms)	83 ± 16		
Complications			
Pneumothorax		3 (1)	
Pericardial effusion		0	
Device infection		2 (0.7)	
Stroke		0	
LV perforation		0	
Lead dislodgement		7 (2.5)	
Loss of left septal capture		2 (0.7)	

Values are n (%) or mean ± SD.
CRT = cardiac resynchronization therapy; LBBP = left bundle branch pacing; LV = left ventricular.

ELECTROCARDIOGRAPHIC AND ECHOCARDIOGRAPHIC PARAMETERS. Overall, QRS duration decreased from 152 ± 32 ms at baseline to 137 ± 22 ms ($p < 0.01$) during LBBAP (Table 3). Patients with baseline LBBB had more dramatic QRS narrowing (from 162 ± 24 ms to 133 ± 22 ms; $p < 0.01$). The reduction in QRS duration in patients with non-LBBB (baseline right bundle branch block, intraventricular conduction defects, or right ventricular pacing) was less than that observed in patients with LBBB ($p < 0.01$) (Supplemental Table S1). Although QRS duration decreased in patients with ICM and NICM compared with baseline, this reduction was greater in patients with NICM ($p < 0.01$) (Supplemental Table S1).

Follow-up echocardiographic data were available for 202 of 277 patients (73%) (Table 3). Echocardiographic response (≥5% improvement in LVEF) was noted in 148 patients (73%) (68% of those with ICM and 77% of those with NICM) (Supplemental Table S1). Response rates were greater among patients with LBBB compared with those with non-LBBB (87% vs. 67%; $p < 0.01$). Overall, LVEF improved significantly from 33 ± 10% at baseline to 44 ± 11% at follow-up ($p < 0.01$). Improvement in LV function was

FIGURE 5 LBBAP in a Patient With an Intraventricular Conduction Defect



Electrograms from the LBBAP lead show an LBB potential in this patient with an LBBB-type intraventricular conduction defect (IVCD) and HV interval of 65 ms. LBBAP at 1 V demonstrated nonselective LBB capture with pLVAT of 92 ms and QRSd of 145 ms. Pacing at 0.8 V resulted in loss of left septal capture and demonstrated selective capture of the LBB with QRS configuration identical to native complex. LV ejection fraction improved from 36% at baseline to 44% during follow-up. Abbreviations as in Figures 1 and 3.

noted in patients with ICM and those with NICM and similarly in patients with LBBB and those with non-LBBB.

Among patients with LVEFs ≤35% (n = 131), LVEF increased from 27 ± 7% to 40 ± 121% ($p < 0.01$); 41 patients (31%) met the criteria for superresponse (18% of those with vs. 41% of those with NICM [$p < 0.01$], 38% of those with vs. 24% of those with non-LBBB [$p = 0.09$] (Supplemental Table S1). There were significant reductions in LVEDD (from 56 ± 9 mm to 54 ± 9 mm; $p < 0.01$), LV end-diastolic volume (from 169 ± 84 ml to 142 ± 69 ml; $p < 0.01$), and LV end-systolic volume (from 114 ± 68 to 83 ± 52 ml; $p < 0.01$).

PREDICTORS OF ECHOCARDIOGRAPHIC RESPONSE. Univariate analysis of the cohort with successful LBBAP and follow-up echocardiography (n = 202) showed that baseline LBBB, a wide baseline QRS complex, a greater reduction in QRS duration during pacing, and a shorter stimulus to peak LV activation time were predictive of echocardiographic response. Non-LBBB, narrow QRS configuration, and greater LVEDD at baseline were associated with a lower likelihood of echocardiographic response (Figure 6). There was a trend toward a tendency of response in women and patients with NICM. In a multivariate analysis, LVEDD and baseline LBBB remained predictors of echocardiographic response (odds ratios: 0.62 [95% confidence interval: 0.49 to 0.71] and 3.90 [95% confidence interval: 1.64 to 9.26], respectively; $p < 0.01$).

Univariate analysis identified reduction of paced QRS duration, LVEF, LVEDD, and NICM as predictors of echocardiographic superresponse to LBBAP. Multivariate analysis revealed that baseline LVEDD and reduced QRS duration with LBBAP pacing predicted echocardiographic superresponse (odds ratios: 0.66 [95% confidence interval: 0.50 to 0.86] and 1.29 [95% confidence interval: 1.14 to 1.49], respectively; $p < 0.01$) (Supplemental Table S2).

CLINICAL OUTCOMES. Clinical response (improvement by 1 NYHA functional class and no heart failure hospitalization) to LBBAP was noted in 157 of 207

TABLE 3 Clinical Parameters Before and After Pacing in Patients Who Underwent LBBAP

	All (N = 277)			ICM (n = 114)			NICM (n = 163)			LBBB (n = 116)			Non-LBBB (n = 116)		
	Baseline	LBBAP	p Value	Baseline	LBBAP	p Value	Baseline	LBBAP	p Value	Baseline	LBBAP	p Value	Baseline	LBBAP	p Value
Electrocardiographic response															
QRS duration (mm)	152 ± 32	137 ± 22	<0.01	150 ± 34	143 ± 23	0.07	154 ± 31	133 ± 21*	<0.01	162 ± 24	133 ± 22†	<0.01	160 ± 28	143 ± 23	<0.01
Clinical response															
NYHA functional class	2.7 ± 0.7	1.8 ± 0.6	<0.01	2.7 ± 0.7	1.8 ± 0.7	<0.01	2.7 ± 0.7	1.7 ± 0.7	<0.01	2.8 ± 0.6	1.7 ± 0.7	<0.01	2.7 ± 0.7	1.8 ± 0.7	<0.01
Echocardiographic response															
LVEF	33 ± 10	44 ± 11	<0.01	33 ± 9	42 ± 11	<0.01	33 ± 10	45 ± 11	<0.01	30 ± 8	44 ± 11	<0.01	33 ± 10	43 ± 12	<0.01
LVEF (≤35% baseline)	27 ± 7	40 ± 11	<0.01	28 ± 6	38 ± 11	<0.01	27 ± 7	41 ± 12	<0.01	28 ± 6	42 ± 10	<0.01	27 ± 7	38 ± 12	<0.01
LVEF (36%-50% baseline)	42 ± 5	50 ± 8	<0.01	42 ± 5	49 ± 8	<0.01	42 ± 7	51 ± 7	<0.01	41 ± 5	52 ± 7	<0.01	43 ± 6	50 ± 8	<0.01
LVEDD	56 ± 9	54 ± 9	<0.01	57 ± 9	55 ± 9	0.13	56 ± 10	53 ± 9	0.02	57 ± 9	54 ± 9	0.01	57 ± 10	55 ± 9	0.12
LVESV	114 ± 68	83 ± 52	<0.01	119 ± 66	84 ± 55	<0.01	111 ± 70	82 ± 51	<0.01	123 ± 63	85 ± 56	<0.01	114 ± 76	83 ± 49	<0.01
LVEDV	169 ± 84	142 ± 69	<0.01	175 ± 84	140 ± 74	<0.01	165 ± 85	143 ± 66	0.03	181 ± 79	149 ± 78	<0.01	168 ± 92	139 ± 60	0.02

Values are mean ± SD. Values of $p < 0.05$ were considered to indicate statistical significance. Non-LBBB includes right bundle branch block, intraventricular conduction delay, and right ventricular pacing. *$p < 0.01$ compared with ICM. †$p < 0.01$ compared with non-LBBB.

ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; other abbreviations as in Table 1.

patients (72%) (80% of those with LBBB vs. 67% of those with non-LBBB [p = 0.03], 76% of those with ICM vs. 70% of those with NICM [p = 0.31]) (Supplemental Table S1). Overall, NYHA functional class improved from 2.7 ± 0.7 at baseline to 1.8 ± 0.7 on follow-up ($p < 0.01$). During follow-up, 15 patients were admitted with heart failure hospitalization (5.4%), and 11 patients (4%) died (cardiovascular causes in 6, noncardiovascular causes in 3, and indeterminate causes in 2).

DISCUSSION

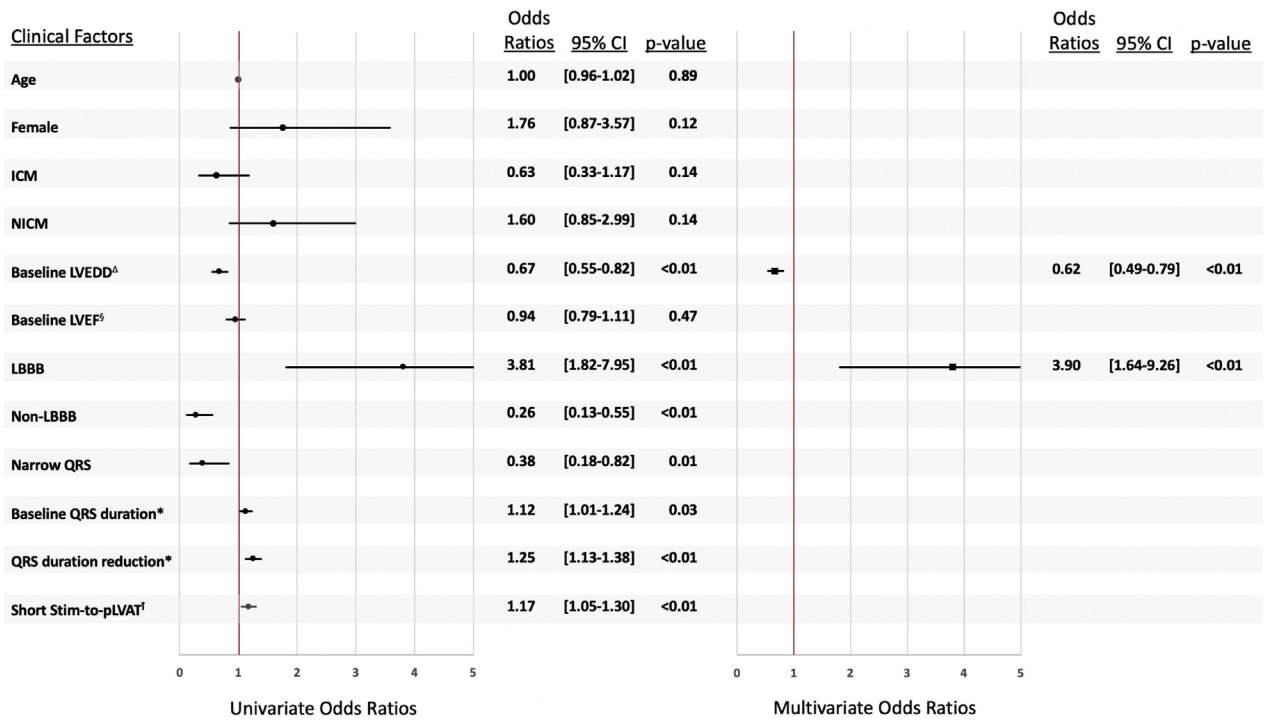
The main findings of this retrospective, observational study are as follows: 1) CRT using LBBAP as an alternative approach is feasible in the majority of patients and is associated with few complications; 2) LBBAP resulted in changes in the cardiac variables of QRS duration, LVEF, LV dimensions and volumes, and NYHA functional class (**Central Illustration**); 3) LBBB at baseline and QRS duration reduction with pacing were independent predictors of echocardiographic response and superresponse, respectively; and 4) greater LVEDD was an independent predictor of a lower likelihood of echocardiographic response and superresponse.

Permanent HBP has been shown to achieve maximal electric resynchronization in patients with proximal LBBB and LV dysfunction and was associated with improved clinical outcomes in several small observational studies (10-12). In a small randomized, crossover study, Lustgarten et al. (10) showed equivalent clinical and echocardiographic improvements with HBP compared with BVP. Arnold et al. (20) compared HBP with conventional BVP in acute experiments performed in the same patients with LBBB and observed that HBP resulted in more effective ventricular resynchronization and hemodynamic performance. However, higher pacing thresholds and inability to correct distal LBBB or intraventricular conduction defects has been a major limitation of this approach, as demonstrated in a small randomized trial comparing HBP with BVP (21).

Huang et al. (13) recently developed a novel but simple and effective method to pace the proximal LBB. Since this initial description of LBBAP, several groups have reported on the feasibility and safety of LBBAP using the currently available SelectSecure pacing lead in short-term studies (13-16). Salden et al. (22) recently compared the acute electrophysiological and hemodynamic effects of transient LV septal pacing with BVP and HBP in 27 patients with LBBB. LV septal pacing was associated with larger reductions in QRS area compared with BVP and similar reductions to HBP. They found that LV septal pacing resulted in acute hemodynamic improvements comparable with BVP and HBP. The ability to capture the left conduction system in addition to LV septal pacing with LBBAP offers additional promise to improve electromechanical LV synchronization.

FEASIBILITY. Our study represents the first international, multicenter, real-world experience in a large series of patients undergoing CRT using LBBAP. The success rate of LBBAP was 85%, limited

FIGURE 6 Forest Plot of Predictors of Echocardiographic Response



See text for description. CI = confidence interval; ICM = ischemic cardiomyopathy; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NICM = nonischemic cardiomyopathy; other abbreviations as in Figure 1.

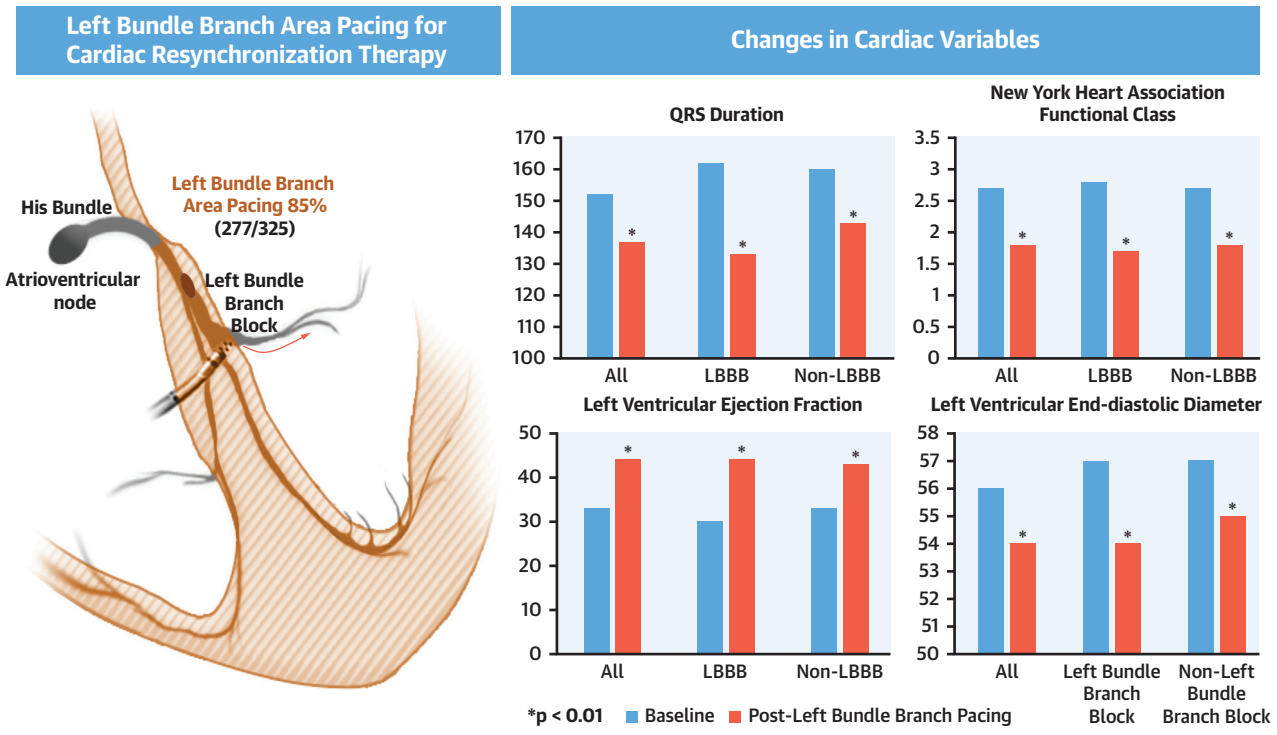
mainly by an inability to penetrate the septum, especially in patients with severely enlarged ventricles, and an inability to improve electric resynchronization in patients with intraventricular conduction defects (Supplemental Figure S3). LBBAP was successful in 92% of patients with LBBB compared with 71% of patients with intraventricular conduction defects. It is important to recognize that in several patients with electrogram-confirmed intraventricular conduction defects (presence of LBB potentials in the setting of intraventricular conduction defects), electric resynchronization was attributed predominantly to left septal endomyocardial capture with possible delayed engagement of arborizing Purkinje fibers (**Figure 5**). The overall success rates are comparable with those in a recent study by Huang et al. (23), who reported a success rate of 97% in a prospective, observational, multicenter study of 63 patients with NICM and LBBB. Compared with the success rates of HBP in this population, LBBAP appears to offer greater promise. Furthermore, the pacing thresholds achieved with LBBAP are lower than those reported in HBP studies to achieve bundle branch block correction (0.6 ± 0.3 V at 0.5 ms in our study vs. 1.89 ± 1.12 V at 0.5 ms and 3.8 ± 2.2 V at 0.7 ms) (10,12).

Fluoroscopy and procedural duration were significantly longer than previously reported for LBBAP and HBP studies (11-14,16). This likely reflects a learning curve at many of the participating centers in addition to the technical challenges posed by the limitations of the implantation tools in patients with advanced heart disease and severe ventricular dilatation.

OUTCOMES. This study demonstrates that LBBAP is associated with reduced paced QRS duration, translating into improved clinical and echocardiographic outcome. Patients with LBBB and/or NICM had significantly greater reductions in QRS duration and improved LVEF compared with patients with non-LBBB and/or ICM. Prior studies of BVP have demonstrated that reduced QRS duration is associated with improved clinical outcomes (24,25).

Echocardiographic response rates were greater in patients with LBBB compared with those with non-LBBB (87% vs. 67%; $p < 0.01$), while superresponse rates were higher in patients with NICM compared with those with ICM (41% vs. 18%; $p < 0.01$).

CENTRAL ILLUSTRATION **Left Bundle Branch Area Pacing for Cardiac Resynchronization Therapy**



Vijayaraman, P. et al. J Am Coll Cardiol EP. 2020;■(■):■–■.

Left bundle branch area pacing (LBBAP) was successful in 85% of patients attempted. LBBAP resulted in significant reductions in QRS duration, New York Heart Association functional class, and left ventricular (LV) end-diastolic diameter along with significant improvement in LV ejection fraction in patients with left bundle branch block (LBBB) and non-LBBB. *p < 0.01. AV = atrioventricular; CRT = cardiac resynchronization therapy; HB = His bundle; LBBAP = left bundle branch area pacing; LBB = left bundle branch; LBBB = left bundle branch block; LBBP = left bundle branch pacing; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association.

Overall, significant improvements in electrocardiographic, echocardiographic, and clinical outcomes were achieved with LBBAP. In multivariate analysis, baseline LBBB (odds ratio: 3.96; 95% confidence interval: 1.64 to 9.26; $p < 0.01$) and reduction in paced QRS duration (odds ratio: 1.29; 95% confidence interval: 1.114 to 1.494; $p < 0.01$) were independent predictors of echocardiographic response and super-response, respectively, while larger LVEDD was predictive of lower likelihood of echocardiographic response. It appears as if the underlying disease substrate and the severity of electric dyssynchrony tend to predict outcomes in patients undergoing CRT. A recent mechanistic study by Upadhyay et al. (26) showed that about two-thirds of patients with LBBB had correctable conduction block in the His bundle or proximal left bundle. These patients are highly likely to benefit from permanent LBBAP at relatively low and stable pacing outputs. The benefit of LBBAP in patients with intraventricular conduction defects was less predictable in our study, with one-third of patients not achieving satisfactory electric resynchronization, translating into less impressive clinical and echocardiographic outcomes. Approximately 15% of patients had narrow QRS complexes in the study group. Requirements for ventricular pacing due to atrioventricular block or atrioventricular node ablation in the setting of LV dysfunction were the reasons for LBBAP. The major advantage is the low risk for LV dyssynchrony induced by LBBAP (16). Longer term, randomized controlled clinical trials comparing these different approaches to resynchronization therapy in different subgroups will be necessary to determine the individual applicability and feasibility of these effective therapeutic options.

STUDY LIMITATIONS. This was a nonrandomized, retrospective, observational study designed as an initial step to assess the feasibility and safety of permanent LBBAP in patients requiring CRT. This

study involved nonconsecutive patients with possible selection bias, and the results may not be applicable to all patients eligible for CRT. Because of the lack of a control group and heterogeneity of the study population, the results should be interpreted with caution. In addition, the high success rates of LBBAP achieved by operators experienced in HBP and LBBAP need to be replicated in prospective studies. Consensus criteria for LBB capture are lacking and need to be better characterized. Another major limitation of the study is the lack of a direct comparison with BVP or HBP. Carefully designed, large, randomized, controlled clinical trials comparing BVP are necessary to confirm the benefits of LBBAP in this population. The long-term electric performance of the deep-septal lead and potential risks associated with lead extraction from this site are unknown and need to be carefully studied.

CONCLUSIONS

LBBAP is feasible, safe, and potentially an alternative option for CRT. LBBAP provides remarkably low and stable pacing thresholds in short-term follow-up. Baseline LBBB and LVEDD were predictive of improved echocardiographic outcomes.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Vijayaraman has received honoraria, consulting fees, and research support from Medtronic; and has received consulting fees from Boston Scientific, Abbott, Biotronik, and Eaglepoint. Dr. Sharma has received honoraria from Medtronic; and has received consulting fees from Abbott, Biotronik, and Boston Scientific. Dr. Subsposh has received honoraria from Medtronic. Dr. Herweg has received honoraria and consulting fees from Abbott and Biotronik. Dr. Jastrzebski has received consulting fees and honoraria from Medtronic and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: BVP is an effective therapy for CRT. Permanent LBBAP is a novel approach to conduction system pacing. LBBAP is feasible and safe and improves clinical and echocardiographic outcomes in patients requiring CRT.

TRANSLATIONAL OUTLOOK: LBBAP may provide a reasonable alternative to traditional BVP. Large randomized controlled clinical trials with long-term follow-up are necessary to confirm the clinical benefits of permanent LBBAP compared with BVP in patients requiring CRT.

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KEY WORDS **biventricular pacing, bundle branch block, cardiac resynchronization therapy, His bundle pacing, left bundle branch area pacing**

APPENDIX **For supplemental figures, please see the online version of this paper.**