Original Article

CMJ

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Initial Experience with Left Bundle Branch Area Pacing in Patients with Atrioventricular Block and Impaired LV Function

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Chronic right ventricular (RV) pacing can exacerbate heart failure in patients with a low left ventricular ejection fraction (LVEF). Left bundle branch area pacing (LBBAP) has emerged as a novel physiological pacing technique; however, information remains limited on its use among patients with a low EF. This study investigated the safety and short-term clinical outcomes of LBBAP among patients with impaired left ventricular (LV) function. This retrospective analysis of pacemakers at Chosun University Hospital, South Korea, included all patients with impaired LV function (EF < 50%) who underwent pacemaker implantation for atrioventricular blockage from 2019-2022. Clinical characteristics, 12-lead electrocardiography findings, echocardiography findings, and laboratory parameters were evaluated. Composite outcomes were defined as all-cause mortality, cardiac death, and hospitalization due to heart failure during the 6-month follow-up. Altogether 57 patients (25 men; mean age, 77.4±10.8 y; LVEF, 41.5±3.8%) were divided into LBBAP (n=16), biventricular pacing (BVP; n=16), and conventional RV pacing (RVP; n=25) groups. In the LBBAP group, the mean paced QRS duration (pQRSd) was narrower (119.5±14.7 vs. 140.2±14.3 vs. 163.2±13.9; p < 0.001) and cardiac troponin I level was elevated post-pacing (1.14±1.29 vs. 0.20±0.29 vs. 0.24±0.51, p=0.001). Lead parameters were stable. One patient was hospitalized, and four died (one patient each from heart failure admission, myocardial infarction, unexplained death, and pneumonia in RVP vs. one from intracerebral hemorrhage in BVP) during the follow-up period. In conclusion, LBBAP is feasible in patients with impaired LV function without acute or significant complications and provides a remarkably narrower pQRSd with a stable pacing threshold.

Key Words: *Atrioventricular Block; Pacemaker, Artificial; Heart failure*

Article History:
Received November 27, 2022
Revised December 14, 2022
Accepted December 20, 2022

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INTRODUCTION

Chronic right ventricular pacing (RVP) can cause or worsen heart failure and increase cardiac mortality rates among patients with a low left ventricular ejection fraction (LVEF).[1-4] Therefore, physiological interventions such as biventricular pacing (BVP) are recommended in patients with a reduced EF requiring ventricular pacing.[5,6] Left bundle branch area pacing (LBBAP) has gained steady interest in recent years as a novel physiological pacing technique.[7] LBBAP, which provides a low and constant pacing threshold with lead stability, has a postoperative success rate of 82-92%.[8,9] LBBAP has emerged as a novel physiological pacing technique; however, there are only limited studies on its safety and clinical outcomes among patients with impaired left ventricular (LV) function undergoing permanent pacemaker (PPM) placement in Korea. Here, we aimed to investigate the safety and short-term clinical outcomes of patients who underwent PPM implantation.

https://doi.org/10.4068/cmj.2023.59.1.54

MATERIALS AND METHODS

1. Study population

This was a retrospective analysis of PPM use at Chosun University Hospital in South Korea. Patients aged >18 years who underwent de novo transvenous pacemaker implantation for a persistent atrioventricular block at Chosun University Hospital from January 2019 to June 2022 were recruited. Patients were included if they underwent de novo PPM implantation and had an LVEF ≤50% and ventricular pacing >40%. The patients were divided into three groups according to ventricular lead site (LBBAP vs. BVP vs. conventional RVP). Detailed histories and examinations of all patients were recorded at baseline. Clinical characteristics as well as 12-lead electrocardiography (ECG) and echocardiography parameters were evaluated. All patients enrolled in this study were clinically followed up with as outpatients every 3 months with respect to hospitalization or cardiac death caused by heart failure. The primary endpoints were defined as: 1) overall mortality; 2) cardiac death; and 3) hospitalization for heart failure during the 6-month follow-up period. All deaths were considered of cardiac origin unless a definite non-cardiac cause could be established.

2. PPM implantation

All patients received commercially available transvenous PPM approved by the Korean Food and Drug Administration. Pacemaker leads (Tendril STS model 2088TC lead; Abbott, USA) were inserted through the axillary vein using standard implantation techniques. Implantation procedures were performed using the pectoral approach. In the conventional RVP group, the RV leads were positioned at the RV apex or RV septum at the operator's discretion. Electrical measurements were performed with an R-wave amplitude >5 mV and a pacing threshold <1.5 V. When satisfactory testing was achieved, ventricular pacing lead positions were confirmed by fluoroscopy in the left anterior oblique and right anterior oblique views (to cover the cardiac septum and not the free wall) and through evaluation of ECG characteristics.

In the LBBAP group, a lead was placed through the electrode-incorporated steerable catheter (Agilis HisPro™; Abbott) while monitoring paced QRS morphology and unipolar impedance. Continuous recording of a 12-lead ECG and intracardiac electrogram was performed using an electrophysiology system (Prucka CardioLab; GE Healthcare, Waukesha, WI, USA). The details have been previously described.[10] Briefly, the sheath was introduced into the RV and on the right side of the interventricular septum. The location for LBBAP was 1-1.5 cm distal to the His signal. At this site, the sheath pacing showed a 'W' pattern with a notch at the nadir of the QRS in the V_1 lead. After the pacing lead was delivered from the tip of the sheath, paced QRS morphology showed unipolar pacing. Thereafter, clockwise rotation of the lead was applied for three to four turns at a time. During the procedure, lead depth inside the septum was measured using sheath angiography. As the pacing lead approached the LV endocardial site, the notch was displaced to the end of the QRS and finally showed a typical 'r' pattern in lead V_1, a peak LV activation time <80 ms in lead V_6, and a V_6-V_1 interval >40 ms.[9,11] Whenever LBB pacing was not achieved, left posterior fascicular pacing was attempted. Reshaping of the sheath allowed for an extended access such that the pacing lead could be positioned inferior to the previously attempted site toward the apex deep inside the septum. LV septal myocardial capture was diagnosed if the LBB capture criteria were not fulfilled but a terminal R/r in lead V_1 was present.

In the BVP group, a Quartet lead (Abbott) was implanted according to standard clinical practice. The LV lead electrode was inserted through the coronary sinus into the lateral or posterolateral vein whenever possible. The final LV pacing vector was determined according to threshold tests and paced QRS duration (pQRSd) at different electrode configurations. Within 24 h, baseline ECG parameters were those acquired closest to PPM implantation; the pQRSd was measured from the beginning of the pacing stimulus to the end of the QRS complex on 12-lead ECG at 25 mm/s.

3. Echocardiography

All patients underwent comprehensive echocardiographic evaluation within 7 days after PPM implantation. The images were obtained with a standard ultrasound machine using a 2.5-MHz phased-array transducer (Vivid 9; GE Vingmed, Horton, Norway). Standard techniques were used to obtain M-mode, two-dimensional, and Doppler measurements following the American Society of Echocardiography guidelines. LVEF was measured using the modified Simpson's biplane method and LV stroke volume was calculated. Mitral inflow was assessed in an apical four-chamber view using pulsed-wave Doppler ultrasonography. Diastolic function was evaluated using color tissue Doppler imaging.[12] These were assessed by including mitral flow velocities, a mitral annular septal E′ velocity of <7 cm/s, an E/E′ ratio of >14, peak velocity of the tricuspid regurgitant jet of >2.8 m/s, and a left atrial maximum volume index of >34 mL/m^2.

4. Programming and follow-up

The pacing threshold was determined before hospital discharge. All patients underwent routine clinical follow-up at standard time intervals (every 3 months), and the occurrence of heart failure symptoms or rehospitalization was tracked. Pacing parameters were measured, including pacing threshold, sensing, and impedance. The percentage of ventricular pacing was determined. Each ECG was recorded at the time of implantation and at each follow-up visit.

5. Statistical analysis

Baseline characteristics are summarized as mean± standard deviation for continuous variables and as fre-

quencies with percentages for categorical variables. Comparisons of continuous data among groups were conducted by analysis of variance with post hoc analysis and the chi-squared test or Fisher's exact test for categorical variables as appropriate. Event rate curves were obtained using Kaplan-Meier analysis and compared using the log-rank test. All statistical tests were two-sided and were performed using IBM SPSS (version 24.0; IBM Corp., Armonk, NY, USA). p values <0.05 were considered statistically significant.

RESULTS

1. Study population

Fig. 1 shows a patient flow diagram of this study. Among all patients, 57 with atrioventricular block (25 men [43.0%]; overall mean age, 77.4±10.8 y) were included. The patients were divided into three groups: LBBAP (n=16), BVP (n=16), and RVP (n=25).

In the LBBAP group, the lead was successfully implanted in the left conduction system in 14 patients for an acute success rate of 87%. The proximal left bundle was captured in five patients (31.2%), and the left posterior fascicular was captured in nine (56.2%). Two patients underwent LV septum pacing with a pQRSd >130 ms despite several attempts. In all 16 patients, ECG demonstrated a right bundle branch pattern with a pQRSd of 119.5±14.7 ms. The LBBB potential could be recorded in seven patients from the LBB lead (43%). The mean LV activation time for all LBBA pacing patients was 71.5±7.4 ms and V_6-V_1 interpeak interval was 46.3±5.1 ms. R-wave amplitude, pacing impedance, and capture threshold were 9.56±3.67 mV, 613±63 Ω, and 0.75±0.44 V/0.4 ms, respectively. In the BVP group, the LV lead was successfully implanted in the lateral, posterolateral or posterior branch in 16 patients (100%). The baseline clinical characteristics of the participants are shown in Table 1. There were no significant differences in sex or cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, cerebrovascular accident, and coronary artery disease) except for LVEF. The LVEF was lower in the BVP groups (41.2±3.8 vs, 38.5±2.2 vs. 43.3±3.5, p=0.001). The diastolic function variables did not differ between the groups.

2. Device-related parameters

Table 2 lists the device-related characteristics. The average P and R wave amplitudes, pacing thresholds, and impedance values were not different between the groups. The mean pQRSd was narrower in the LBBAP than in the other groups (119.5±14.7 vs. 140.2 ±14.3 vs. 163.2±13.9; $p<0.001$; Fig. 2). No patient experienced perioperative stroke, heart failure, or an unplanned intensive care unit stay. Cardiac troponin I (cTnI) was significantly elevated after procedure in the LBBA pacing group (1.14±1.29 vs. 0.20±0.29 vs. 0.24±0.51; p=0.001). However, there were no changes in symptoms or ECG findings, and cardiac enzyme levels decreased spontaneously. No planned cardiac angiography or percutaneous coronary intervention procedures were performed.

3. Clinical outcomes

The clinical outcomes are presented in Table 3. One patient was hospitalized and four died (one each from heart failure admission, myocardial infarction, unexplained death, and pneumonia in the RVP group vs. one from intracerebral hemorrhage in the BVP group). The coronary sinus and left bundle lead parameters were stable during the follow-up period, and the ventricular pacing rate was $>98\%$. There were no instances of lead dislodgement, loss of capture, infection, embolism, or stroke associated with the implantation.

DISCUSSION

The principal findings are as follows. First, LBBAP is feasible and safe in patients with atrioventricular blocks and impaired LV function. The success rate of LBB capture using Agilis HisPro was high (87% [14/16]) without com-

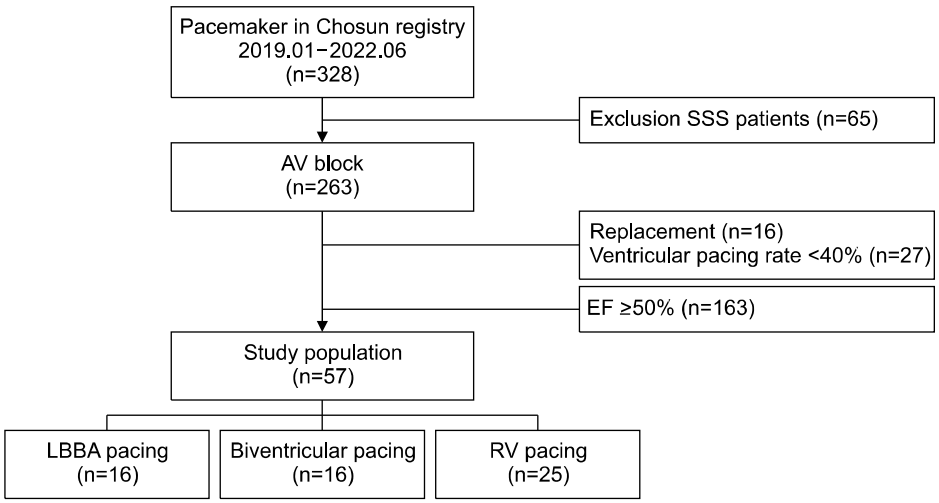

FIG. 1. Flow chart of study protocol.

Table 1. Baseline patient characteristics

	LBBAP (n=16)	BVP (n=16)	RVP (n=25)	p value
Age (years)	77.8±7.4	72.8±11.6	80.1±10.0	0.075
Male (n.%)	4 (25.0%)	8 (50.0%)	13 (52.0%)	0.199
Cardiovascular risk factor				
Hypertension	11 (68.8%)	8 (50.0%)	17 (68.0%)	0.437
Diabetes Mellites	5 (37.5%)	5 (31.2%)	8 (32.0%)	0.916
Hyperlipidemia	5 (31.2%)	5 (31.2%)	9 (36.0%)	0.931
Coronary artery disease	1 (6.2%)	1 (6.2%)	5 (20.0%)	0.292
Cerebrovascular disorder	2 (12.5%)	4 (25.0%)	6 (24.0%)	0.611
Echocardiography				
Ejection Fraction	41.2±3.8	38.5±2.2	43.3±3.5	0.001
E/E' >15	4 (25.0%)	5 (33.3%)	14 (58.3%)	0.082
E (septal)' <7	15 (93.8%)	12 (50.0%)	19 (79.2%)	0.429
TR velocity >2.8 m/s	5 (31.2%)	2 (12.5%)	6 (25.0%)	0.438
LAVI >34 m^2	11 (68.8%)	9 (56.3%)	9 (36.0%)	0.108
Atrioventricula Block				0.274
2:1 AV block	3 (18.8)	0 (0%)	1 (4%)	
High degree AV block	1 (6.3%)	1 (6.3%)	1 (4%)	
Complete AV block	12 (74.9%)	15 (93.7%)	23 (92%)	
QRS duration (ms)	117±29	138±40	120±29	0.142
Cardiac enzyme				
Pro BNP	6,069±11,448	8,317+12,345	6,524+8,530	0.813
CK-MB	5.67±3.44	3.80±2.43	4.01±2.35	0.103
Troponin I	1.14±1.29	0.20±0.29	0.24±0.51	0.001
Discharge Medication				
Beta blocker	16 (100%)	16 (100%)	22 (88%)	0.132
RAAS inhibitor	15 (93.8%)	16 (100%)	22 (88%)	0.337
Diuretics	12 (75.0%)	15 (93.8%)	18 (72%)	s0.225

BVP: Biventricular pacing, LAVI: left atrial volume index, LBBAP: Left bundle branch area pacing, RVP: Conventional right ventricular pacing.

Table 2. Device related parameters

	LBBAP (n=16)	BVP (n=16)	RVP (n=25)	p value
Manufacturer				
Abbott	16 (100%)	16 (100%)	25 (100%)	1.000
Atrial leads (at implantation)				
Implant P wave (mV)	2.92±1.67	2.80±1.47	3.29±1.30	0.548
Pacing threshold (V/0.4 ms)	0.83±0.38	0.67±0.49	0.68±0.47	0.599
Impedance (Ω)	460±64	556±143	479±101	0.050
Ventricular leads (implantation)				
Implant R wave (mV)	9.56±3.67	11.3±1.88	10.9±2.23	0.297
Pacing threshold (V/0.4 ms)	0.75±0.44	0.63±0.61	0.52±0.51	0.399
Impedance (Ω)	613±63	640±161	578±94	0.222
Atrial leads (6 months follow up)				
Implant P wave (mV)	2.40±0.69	2.38±1.32	2.88±1.22	0.345
Pacing threshold (V/0.4 ms)	0.77±0.24	0.75±0.25	0.68±0.17	0.508
Impedance (Ω)	443±53	504±142	457±98	0.390
Ventricular leads (6 months follow up)				
Implant R wave (mV)	10.3±2.59	10.6±2.2	10.4±2.7	0.966
Pacing threshold (V/0.4 ms)	0.78±0.23	0.78±0.22	0.75±0.21	0.903
Impedance (Ω)	548±89	556±127	528±106	0.709
Ventricular pacing percentage (%)	98.5±1.0	98.9±0.2	97.9±4.9	0.651

BVP: Biventricular pacing, LBBAP: Left bundle branch area pacing, RVP: Conventional right ventricular pacing.

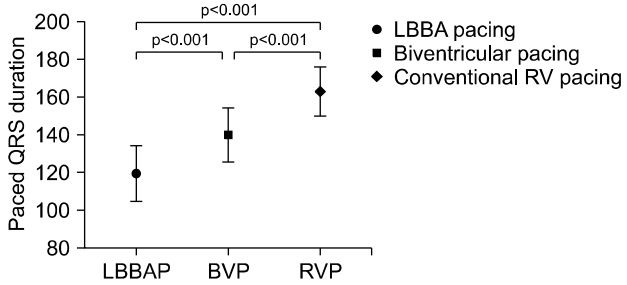

FIG. 2. Paced QRS duration (pQRSd) between three groups. pQRSd was narrower in the left bundle branch area pacing (LBBAP) than the biventricular pacing (BVP) or conventional right ventricular pacing (RVP).

promising pacing threshold (0.75±0.44 V at 0.4 ms) among patients with impaired LV function. Second, LBBAP was superior to BVP as well as RVP and associated with a shorter pQRSd (119.5±14.7 vs. 140.2±14.3 vs. 163.2±13.9; $p < 0.001$).

Since the inception of pacing therapy in 1958, the RV remains the established site for PPM insertion.[1] Although RVP can contract both ventricles relatively effectively, it could induce ventricular dyssynchrony and detrimental hemodynamic effects. In turn, this might lead to progressive adverse remodeling at the cellular and heart chamber levels, resulting in the deterioration of ventricular function.[13] Chronic RVP can cause or worsen heart failure and increase cardiac mortality.[1-4] The adverse clinical outcomes of prolonged RV apical pacing in some patients are increasingly recognized, and they might ultimately result in fatal pacing-induced cardiomyopathy, which occurred in 10.1% of patients during 3 years of follow-up in our previous study.[14]

Previous studies reported that a lower EF is a statistically significant factor for the development of pacing-induced cardiomyopathy.[3,4] Thus, BVP is recommended in patients with a reduced EF and a high degree of atrioventricular blockage requiring ventricular pacing.[5,6] Several studies demonstrated that BVP was superior to RVP among patients with moderate to severe systolic dysfunction who required ventricular pacing to improve the quality of life, New York Heart Association class, and echocardiographic response.[5] Recently, conduction system pacing, including His bundle pacing and LBBAP, was introduced. However, His bundle pacing has been precluded by several limitations, including a relatively low success rate, a delayed rise in capture thresholds leading to a higher revision rate, under-sensing of ventricular signals, and oversensing of atrial or His signals. LBBAP has become an alternative technique for physiological pacing with a higher success rate of 92.4-82.2% and a low and constant pacing threshold with lead stability.[8,9] In our study, the success rate of LBB capture using the Agilis HisPro was 87% (14/16) without compromising pacing threshold (0.75±0.44 V at 0.4 ms). The proximal left bundle was captured in five patients (31.2%), the left posterior fascicle in nine (56.2%), and the left septum in two (12.5%). The reasons for LBB capture failure included inability of the lead to penetrate deep into the septum, inadequate sheath support, and improper sheath-septal orientation. The Abbott Agilis HisPro was developed primarily for His bundle pacing. This makes it difficult to obtain LBB capture in patients with a large atrium (such as those with atrial fibrillation or structural heart disease) because it would not have enough access to cross the tricuspid valve and arrive at the RV septum. Thus, reshaping the secondary curve proximal to the second deflection and septal curve would extend the access beyond the tricuspid valve and enable the reaching of the RV septum perpendicularly.[10] In nine patients with left posterior fascicular pacing, several attempts to deploy the lead at the true left bundle branch trunk failed because the sheath and the lead would have an oblique rather than perpendicular orientation to the RV septum. A more perpendicular septal orientation could be achieved by further unreflecting and retracting the catheter, which positioned the sheath inferior to the previously attempted site toward the apex and left posterior fascicle. Finally, LV septum pacing after left bundle branch pacing failed more than five times in two patients.

TABLE 3. Composite clinical outcomes during 6 months

	LBBAP (n=16)	BVP (n=16)	RVP (n=25)	p value
Overall mortality	0 (0%)	1 (6.3%)	3 (12.0%)	0.262
Cardiac death, n (%)	0 (0%)	0 (0%)	1 (4.0%)	0.513
Non-cardiac death, n (%)	0 (0%)	1 (6.3%)	2 (8.0%)	0.523
Hospitalization HF, n (%)	0 (0%)	0 (0%)	1 (4.0%)	0.494

BVP: Biventricular pacing, LBBAP: Left bundle branch area pacing, RVP: Conventional right ventricular pacing.

Our data showed that the pQRSd was narrower in LBBAP than in BVP and RVP. The pQRSd is a well-known risk factor for pacemaker-induced HF and has a poor prognosis.[15-18] In our previous study, a pQRSd of 168 ms had 75.0% sensitivity and 64.2% specificity for predicting the occurrence of PPM-induced HF.[14] Our data showed that the pQRSd of the LBBAP and BVP was < 168 ms. Moreover, even in unsuccessful LBB capture, LBBAP resulted in a relatively narrow pQRSd with RBBB morphology compared to BVP (Fig. 2).

The cTnI levels were significantly elevated after the procedure in the LBBA pacing group (Fig. 3). LBBA pacing using stylet-driven pacing leads may cause myocardial injury by inducing direct trauma to the myocardium and creating regional ischemia secondary to coronary obstruction or embolization. However, there were no changes in symptoms or ECG findings, and the cardiac enzyme levels spontaneously decreased. No planned cardiac angiography or percutaneous coronary intervention was performed. An increase in cTnI values might be considered a procedural myocardial injury and not a myocardial infarction because of the lack of ECG or echocardiographic changes.[19]

The present study was limited by its retrospective na-

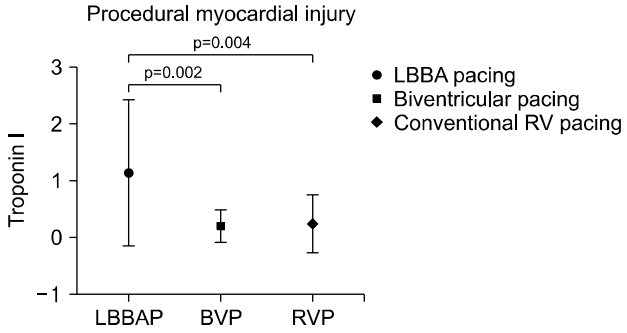

FIG. 3. Cardiac enzyme following the procedure. Cardiac troponin I was elevated in the left bundle branch area pacing (LBBAP) than the biventricular pacing (BVP) or conventional right ventricular pacing (RVP).

ture and single-center setting. First, this study included only a small sample from a single center. Second, this study had a short follow-up period. The small study size and low incidence made it difficult to ascertain the actual impact of LBBAP on periprocedural risk and overall safety outcomes. Therefore, the present trial was underpowered to reveal potentially small differences in the primary endpoints. Future large-scale prospective randomized trials are warranted. Third, the 2D echocardiography and proBNP were not checked routinely if symptoms did not occur newly during the follow up period. The paced QRS duration varies depending on the pacing site and these differences do not directly signify clinical outcomes. Fourth, the EF was significantly lower in the BVP group than in other groups. This seems to present a selection bias because BVP was performed only in patients with an EF $< 40\%$ because of the Korean insurance system. However, although the EF was low, the mean pQRSd and clinical outcomes were comparable to those of RVP and LBBAP.

In conclusion, LBBAP is feasible in patients with impaired LV function without acute or significant complications and provides a remarkably narrower pQRSd with a stable pacing threshold.

ACKNOWLEDGEMENTS

This study was supported by research funds from the Chosun University 2022.

CONFLICT OF INTEREST STATEMENT

None declared.

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