Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Left Bundle Branch Area Pacing Improves Left Atrial Outcomes in Pacemaker-Dependent Patients: A Prospective Cohort Study Using Speckle Tracking and Three-Dimensional Echocardiography

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Purpose: Evidence that left bundle branch area pacing (LBBAP) is more effective than conventional right ventricular (RV) pacing in enhancing left atrial (LA) outcomes is lacking. The aim of this study was to investigate LA outcomes using 2-dimensional speckle tracking echocardiography (2D-STE) and real-time 3-dimensional echocardiography (RT-3DE) at 6-months of follow-up in patients that received LBBAP, RV septal pacing (RVSP), or RV apical pacing (RVAP).

Methods: A total of 90 patients with normal left ventricular ejection fraction (LVEF) underwent dual-chamber pacemaker implantation for bradycardia at Beijing Anzhen Hospital between January 2021 and July 2021. Patients were divided into three groups based on the pacing site: LBBAP, RVSP, or RVAP.

Results: There were no significant differences in baseline characteristics and echocardiographic findings among patients that received LBBAP, RVSP, or RVAP. At 6-months of follow-up, left atrial volume index (LAVI), LA reservoir strain (LASr), LA contractile strain (LASct), global longitudinal strain (GLS), global circumferential strain (GCS), and synchronization parameters (Tmsv-16SD, Tmsv-12SD, Tmsv-6SD, longitudinal Tε-dif, circumferential Tε-dif) were significantly improved in patients that received LBBAP, while they had significantly worsened with RVSP and RVAP. Compared to baseline, at 6-months of follow-up, patients that received LBBAP had significantly improved LASr (28.17 ±10.12% vs 35.4±17.17%, *P*=0.024), LASct (−12.03±2.15% vs −17.53±7.37%, *P*=0.045), E/e' ratio(12.61±3.8 vs 10.85±3.75,P=0.014) and LVEF (65.74±7.90% vs 68.81±5.92%, *P*=0.023). The 6-minute walking distance significantly increased at 6-months of follow-up compared to baseline in all patients, but the increase was most prominent for LBBAP (403.00±98.46 m vs. 469.34±59.32m, *P*=0.015). LBBAP was associated with a lower risk of new-onset atrial fibrillation.

Conclusion: In pacemaker-dependent patients, LBBAP achieved better LA strain, LV strain, and LV synchronization than RVSP or RVAP at 6-months of follow-up.

Plain Language Summary: This registered prospective study (ChiCTR2100048503) used two-dimensional speckle tracking echocardiography (STE) and real-time 3D echocardiography (RT-3DE) to comprehensively evaluate LA and LV function and mechanical synchrony in LBBAP. This study demonstrates that LBBAP can achieve better LA strain, LV strain and LV synchronization than RVSP or RVAP at 6-months of follow-up.

Keywords: left atrial, left ventricular, mechanical synchrony, left bundle branch area pacing, real-time 3-dimensional echocardiography, speckle tracking echocardiography

Received: 7 September 2024
Accepted: 14 January 2025
Published: 13 September 2025

Introduction

Left bundle branch area pacing (LBBAP), a novel pacing technique for patients with left bundle branch block and heart failure, was introduced by Huang et al[1] in 2017. The LBBAP is paced beyond the conduction block to restore the His–Purkinje conduction system. LBBAP is emerging as a safe and feasible pacing modality that is characterized by a consistent and stable pacing threshold, a narrow-paced QRS duration, and good R-wave sensing.[2–5] While the majority of research has examined the electrocardiographic profiles, pacing parameters, and impact on left ventricular (LV) function and synchronization associated with LBBAP in comparison to alternative pacing modalities,[6] some studies have investigated the incidence of atrial fibrillation (AF) and left atrial (LA) structure and function within the context of LBBAP.

Building on this foundation, the role of LA strain measurements becomes particularly relevant. LA strain measurements using two-dimensional speckle tracking echocardiography (2D-STE) reflect LA function and are a sensitive marker of LV filling pressure and diastolic function. 2D-STE enables the measurement of both LA and LV function, which can be instrumental in detecting early-stage cardiomyopathies.[7–10] Real-time 3D echocardiography (RT-3DE) is a cutting-edge imaging technique that provides a practical and reproducible approach for evaluating LA and LV function, as well as LV mechanical dyssynchrony. Imaging modalities such as 2D-STE and RT-3DE are essential for the precise assessment of LA and LV size, structure and function.

Evidence supporting the superiority of LBBAP over conventional right ventricular (RV) pacing in enhancing LA and LV function and LV mechanical synchrony is limited. Building on the findings from our prior study, which investigated the effects over a 4-week period, we observed that the LBBAP exhibited stable pacing parameters, superior LV electrical and mechanical synchrony, and LBBAP was considered a more physiological pacing approach compared to right ventricular septal pacing (RVSP) or right ventricular apical pacing (RVAP).[6] Building on these findings, the present study used an echocardiographic perspective to investigate the structure and function of the LA, LV diastolic function, and outcomes related to new-onset AF following pacemaker implantation.

Methods

Study Population and Ethical Considerations

Patients who attended Beijing Anzhen Hospital and elected to have a permanent dual-chamber pacemaker implanted in accordance with the current guidelines (Class I)[11] between January 2021 and July 2021 were eligible for this study.

In this study, we included patients aged over 18 years who were diagnosed with sick sinus syndrome (dual nodal lesions) and persistent high-grade atrioventricular block, with a ventricular pacing ratio exceeding 70%, and who exhibited normal cardiac function (LVEF>50%) at baseline.

The study excluded patients who were younger than 18 years; patients with moderate-to-severe valvular diseases or who were in NYHA functional class III or IV, indicating a more advanced heart condition; patients who had experienced a myocardial infarction, had undergone coronary revascularization in the past three months, or who had a history of cardiomyopathy; patients with significant respiratory diseases or severe dysfunctions in the liver or kidneys; pregnant women; patients with a poor acoustic window, which could be due to emphysema or other factors that would hinder ultrasound imaging; or those who were unable to commit to follow-up visits at our clinic, as consistent follow-up was crucial for study outcomes.

LBBAP is an emerging pacing modality, while RVSP and RVAP are established and widely utilized strategies in clinical practice. During this study, the attending clinician engaged in comprehensive discussions with patients, covering various aspects including, but not limited to, the pacing approach, risks associated with the procedure, success rates, potential complications, and costs. Ultimately, the choice of pacing strategy was determined through a joint discussion between the clinician and the patient.

This study was approved by the Medical Ethics Committee of Beijing Anzhen Hospital (NO.2021083X) and conducted according to the Declaration of Helsinki and the recommendations of the ethics committee. All patients provided written informed consent before participation. The study was registered with the Chinese Clinical Trial Registry (ChiCTR2100048503).

Data Collection and Follow-up

Patients' baseline demographic and clinical characteristics were recorded. Cardiac function was assessed with the NYHA classification, the 6-minute walk test, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Device data were recorded at implantation, predischarge, and 6-months of follow-up. Baseline and follow-up exams were performed using the same EPIQ 7C ultrasound system (Philips Medical Systems). Parameters were independently assessed by two experienced specialists who were blinded to the study design and patient outcomes.

Pacemaker and Lead Implantation

LBBAP was established utilizing a select secure pacing lead (Model 3830, Medtronic Inc., Minneapolis, MN, USA) in the basal ventricular septum, as previously described.[5] The pacing lead was delivered to the His bundle region through a C315 sheath (Medtronic Inc., Minneapolis). The right anterior oblique (RAO) 30° fluoroscopic view was used to visualize the intervention site. The LBBAP lead was implanted using the New Nine Partition Method,[12] which employs fluoroscopy to identify nine key areas for pacing. Each area is evaluated for optimal outcomes based on its proximity to the His bundle, approach angle, and activation sequence. This technique enhances LBBAP by refining lead placement, shortening procedure duration, and reducing the need for intraoperative adjustments. The 3830 lead and C315 sheath were inserted 1.0 to 3.0 cm into the ventricular apex and rotated clockwise. When pace mapping at the lead tip revealed a W-shaped QRS morphology in V1, the lead was screwed in by applying 8 to 10 clockwise rotations. When the pacemaker's paced QRS morphology showed a "QR/Qr" pattern in V1 and the pacing stimulus to LV activation time (Stim-LVAT) in V5 or V6 was 75 ms and consistent during high and low outputs, the lead was fixed. Threshold testing was carried out during implantation using a Medtronic CareLink™ Programmer. Successful LBBAP was achieved when fluoroscopic imaging confirmed the lead's proximity to the left bundle branch, unipolar pacing exhibited a right bundle branch block pattern with a short QRS duration (130 ms), and the stimulus to peak left ventricular activation time was less than 90 ms.[12,13] Additional evidence for a successful LBBAP and LBB capture included LBB potential, selective LBBAP, and non-selective LBBAP, detected using an electrophysiological recording system.

Conversely, the implantation of RV leads, which serves a different aspect of the pacing strategy, was executed using a routine procedure at the RV apex or septum.

Patients with SND or intact AV conduction were evaluated with an automatic AV search algorithm to avoid unnecessary ventricular pacing. This algorithm collects ECG data and optimizes AV delay for synchronization. In patients with intermittent AV block, AV delay is tailored to intrinsic conduction, while those with complete AV block default to a 180/150 ms AV interval for synchrony.

Electrocardiography

A 12-lead surface ECG was performed at 100mm/s with a GE Cardiolab electrophysiology recording system (GE Healthcare Inc, Marlborough) before and after pacemaker implantation. An intracardiac electrogram (IEGM) was obtained during pacemaker implantation from the tip electrode of the 3830 lead. Intrinsic QRS duration (QRSd), paced QRSd, and stimulus to left ventricular activation time (Stim-LVAT) were measured sequentially. QRSd was calculated as the time from the onset to the end of the intrinsic or paced QRS complex in all 12 leads of the ECG. Stim-LVAT was measured as the interval from stimulus to the peak of the R-wave in V4-V6.

Echocardiography

Transthoracic 2D echocardiography was performed with a standard ultrasound system (EPIQ 7C, Philips Medical Systems) with S5-1 and X5-1 transducers. The patient was in the left lateral decubitus position. LV diastolic function was evaluated by measuring transmitral inflow, including peak early filling (E wave) and late diastolic filling (A wave) velocities, and the E/A ratio. Early diastolic mitral annular velocity (E′) was obtained from tissue-Doppler imaging. Other parameters included conventional M-mode Doppler variables, mitral regurgitation (MR), and LVEF, measured following the most recent recommendations from the American Society of Echocardiography.

Speckle Tracking Strain Echocardiography

Apical four-chamber, three-chamber, and two-chamber views of 2D images underwent 2D-STE analysis with appropriate software (QLAB V.13.0: Philips Medical Systems). Data were collected from four consecutive cardiac cycles. ECG was used to determine heart rate during those cycles. LA strain parameters included LA strain during the reservoir phase (LASr), LA strain during the conduit phase (LAScd), and LA strain during the contractile phase (LASct). LV strain parameters included global longitudinal strain (GLS), global circumferential strain (GCS), the time to peak systolic longitudinal and circumferential strain, and the maximum difference in time to peak systolic strain among the 18 LV segments (longitudinal T-dif and circumferential T-dif).

Real-Time Three-Dimensional Echocardiographic

RT-3DE datasets were analyzed using automated software (HeartModel; Philips Medical System). The sector width and depth were adjusted to include the entire LA myocardium and endocardial surface in the pyramidal volume scan. LA parameters included LA volume index (LAVi), LA maximum volume (LAVmax), and LA minimum volume (LAVmin). LV parameters included LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), stroke volume (SV), LVEF, cardiac index (CI), and end-diastolic mass (ED Mass). LV mechanical synchrony was evaluated using time volume curves generated by semi-automated contour tracing software (3DQ Advanced, Philips Medical System). The LV systolic dyssynchrony index (SDI) was calculated as the standard deviation (SD) of the time to minimum systolic volume (TMSV) of 16, 12, and 6 LV segments (SD-Tmsv-16, SD-Tmsv-12, SD-Tmsv-6) corrected for the RR interval. The analyses used mean data from four cardiac cycles.

Statistical Analysis

Statistical analysis was performed using SPSS statistics version 22.0 (Chicago, IL, USA). The Shapiro–Wilk test was used for normality testing. Continuous variables with normal distribution are expressed as mean±standard deviation (SD) and were compared using one-way analysis of variance. Continuous variables with non-normal distribution were compared with the Kruskal–Wallis test. Fisher's least significant difference (LSD) test was used for multiple comparisons. Bonferroni correction was used to adjust P values of multiple comparisons. Categorical variables are expressed as percentages (n [%]) and were compared using $\chi 2$. Changes in variables in patients that received LBBAP, RVSP, or RVAP from baseline to 6-months of follow-up were identified using the paired *t*-test. Tests were two-sided, and the significance level was 0.05.

Results

Patient Characteristics

During the study period, a total of 197 consecutive patients underwent elective implantation of permanent dual-chamber pacemakers. Following application of the inclusion and exclusion criteria, 97 patients were enrolled in the study population. Subsequently, seven patients were excluded from the analysis owing to inadequate quality of 2D-STE. Among the patients that received LBBAP, one (3.23% of the sample) had an unsatisfactory outcome and subsequently underwent RVSP as an alternative treatment. Consequently, the final analysis included 30 patients each for LBBAP, RVSP, and RVAP. Table 1 summarizes the demographic and clinical characteristics of the patients included in the final analysis. Patients had a mean±SD age of 63.9±13.63 years, and there were 49 males (54.4%). There were no significant differences in baseline demographics, medical history, comorbidities, electrocardiography or medication use between patients that received LBBAP, RVSP, or RVAP.

NT-pro BNP

There were no significant differences in baseline NT-pro BNP levels in patients that received LBBAP, RVSP, or RVAP (67.00 [36.00–229.00] vs 78.50 [45.75–171.50] vs 56.00 [20.50–187.50] pg/mL, *P*=0.421). At 6-months of follow-up, NT-pro BNP level was significantly lower in patients that received LBBAP compared to patients that received RVSP or RVAP (67.05 [22.74–111.36] vs 136 [32.76–239.25] vs 287.29 [152.64–421.95] pg/mL, *P*=0.003).

Table 1 Demographic and Clinical Characteristics of the Patient Population

Variables	LBBAP (n=30)	RVSP (n=30)	RVAP (n=30)	F/X^2	*P*
Age (years)	62.45±13.29	66.15±12.27	63.41±15.27	0.543	0.583
Male, n (%)	18.00 (60.00%)	15.00 (50.00%)	16.00 (53.30%)	0.376	0.829
BMI (kg/m^2)	25.74±5.22	25.85±2.68	24.64±3.36	0.815	0.446
Systolic blood pressure (mm Hg)	135.26±14.94	135.96±16.37	136.24±16.01	0.031	0.969
Diastolic blood pressure (mm Hg)	74.45±8.28	75.31±11.19	74.03±9.11	0.127	0.881
Resting heart rate (beats/min)	55.77±11.45	60.58±19.89	58.28±10.42	0.807	0.450
Comorbidities n (%)					
Hypertension	17.00 (56.67%)	17.00 (56.67%)	15.00 (50.00%)	1.134	0.567
Coronary heart disease	3.00 (10.00%)	4.00 (13.33%)	3.00 (10.00%)	2.113	0.576
Diabetes mellitus	10.00 (33.33%)	9.00 (30.00%)	7.00 (23.33%)	2.377	0.468
Stroke	1.00 (3.33%)	3.00 (10.00%)	2.00 (6.68%)	1.506	0.471
Chronic kidney disease	1.00 (3.33%)	1.00 (3.33%)	0.00 (0.00%)	1.066	0.587
Hyperlipidemia	6.00 (20.00%)	8.00 (26.67%)	9.00 (30.00%)	1.351	0.509
Clinical diagnosis n(%)					
Sick sinus syndrome	6.00 (20.00%)	5.00 (16.67%)	6.00 (20.00%)	1.153	0.667
Atrioventricular block	24.00 (80.00%)	25.00 (83.33%)	24.00 (80.00%)	2.056	0.559
LBBB	3.00 (10.00%)	3.00 (10.00%)	2.00 (6.68%)	2.234	0.534
RBBB	5.00 (16.67%)	4.00 (13.33%)	5.00 (16.67%)	2.014	0.425
Medications n (%)					
Aspirin	7.00 (23.33%)	8.00 (26.67%)	4.00 (13.33%)	2.302	0.316
Anticoagulant drugs	5.00 (16.67%)	6.00 (20.00%)	4.00 (13.33%)	2.123	0.435
Ace-inhibitor/ARB	9.00 (30.00%)	15.00 (50.00%)	10.00 (33.33%)	5.326	0.070
Beta blocker	1.00 (3.33%)	1.00 (3.33%)	1.00 (3.33%)	0.016	0.992
Calcium-antagonists	10.00 (33.33%)	12.00 (40.00%)	11.00 (36.66%)	1.229	0.678
Insulin treatment	7.00 (23.33%)	7.00 (23.33%)	4.00 (13.33%)	1.231	0.459
Statin use	8.00 (26.67%)	11.00 (36.67%)	7.00 (23.33%)	2.596	0.273
Smoking history	10.00 (33.33%)	6.00 (20.00%)	10.00 (33.33%)	0.940	0.625
Alcohol consumption	3.00 (10.00%)	2.00 (6.68%)	5.00 (16.68%)	1.348	0.498
ECG (ms)					
Pre-pacing PR interval	206.65±70.82	200.77±66.87	195.17±55.20	0.236	0.791
Pre-pacing QRS duration	111.26±24.07	102.88±18.78	101.55±16.09	2.057	0.134
Post-pacing QRS duration	115.56±21.43*	130.51±26.34‡	158.25±25.35†	4.987	0.027
NT-proBNP					
BNP at implant (pg/mL)	67.00 (36.00–229.00)	78.50 (45.75–171.50)	56.00 (20.50–187.50)	0.875	0.421
BNP at 6 months (pg/mL)	67.05 (22.74–111.36)*	136 (32.76–239.25)‡	287.29 (152.64–421.95)†	6.655	0.003
Change	0.05 (15.27–77.22)	57.5 (41.7–69.6)	231.3 (19.8–298.4)	12.679	0.001
P	0.727	0.026	0.001		
TNI					
TNI at implant (ng/mL)	0.25±0.04	0.19±0.05	0.27±0.04	0.510	0.602
TNI at 6 months (ng/mL)	0.23±0.03	0.21±0.04	0.22±0.03	1.675	0.446
Changes	−0.02±0.01	0.03±0.02	−0.05±0.03	3.456	0.567
P	0.756	0.835	0.937		
NYHA class I, n (%)	23.00 (76.67)	23.00 (76.67)	22.00 (73.33)	3.358	0.187
6 min walk test					
6MWD at implant (m)	403.00±98.46	401.00±96.57	405.00±95.70	1.898	0.345
6MWD at 6 months (m)	469.34±59.32	437.35±63.53	433.16±70.11	2.049	0.118
Change	66.34±44.2	37.36±55.67	28.16±34.5	3.654	0.023
P	0.015	0.025	0.654		
New onset AF	3 (10)	5 (16.7)	7 (23.3)	1.333	0.069

Note: Categorical variables are presented as numbers (percentage). †P<0.05 RVAP vs LBBAP, *P<0.05 LBBAP vs RVSP, ‡P<0.05 RVSP vs RVAP. Post-pacing QRS duration was measured from stimulus to the end of the last QRS complex deflection in the 12 lead electrocardiogram. Pre-pacing QRS duration was measured from the first to last sharp vector of the QRS complex crossing the isoelectric line 12 lead electrocardiogram.

Abbreviations: LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; NT-pro BNP, N-terminal pro-brain natriuretic peptides; RBBB, right bundle branch block; RVSP, right ventricular septal pacing; RVAP, right ventricular apical pacing; 6MWD, Six-Minute Walk Distance.

There was no significant difference in NT-pro BNP levels at 6-months of follow-up compared to baseline in patients that received LBBAP (P>0.05), while NT-pro BNP levels were significantly increased at 6-months of follow-up compared to baseline in patients that received RVSP or RVAP (all P<0.05) (Table 1).

6-min Walking Distance

The 6-min walking distance (6MWD) was significantly longer at 6-months of follow-up compared to baseline in all patients, but the most improvement was observed in patients that received LBBAP (469.34±59.32 m vs 403.00±98.46 m, P=0.015) (Table 1).

LV Diastolic Function

E/A and E/e′ are recognized as parameters for assessing LV diastolic function. E/A was slightly decreased at 6-months of follow-up compared to baseline in patients that received LBBAP (1.1±0.47 vs 1.16±0.59, P=0.417), but significantly lower in patients that received RVSP (0.92±0.41 vs 1.1±0.47, P=0.011) or RVAP (0.87±0.43 vs 1.16±0.53, P=0.005).

At 6-months of follow-up, mean E/e′ ratio was significantly lower in patients that received LBBAP compared to RVSP or RVAP (10.85±3.75 vs 14.18±3.41 vs 16.96±3.79, P=0.023). Mean E/e′ ratio was significantly lower at 6-months of follow-up compared to baseline in patients that received LBBAP (10.85±3.75 vs 12.61±3.8, P=0.014), but significantly increased in patients that received RVAP (16.96±3.79 vs 14.40±7.11, P=0.001) (Table 2).

Table 2 Conventional Echocardiographic, Global and Regional Strain, and Dyssynchrony Parameters

Variables	LBBAP (n=30)	RVSP (n=30)	RVAP (n=30)	F/χ2	*P*
LAD (mm)					
Baseline	35.33±4.02	36.38±3.55	35.7±4.11	1.313	0.275
6 months	35.04±3.85	36.29±4.39	36.19±3.55	0.830	0.440
LA strain component					
Reservoir					
Baseline	28.17±10.12	32.86±16.19	29.94±14.58	0.805	0.450
6 months	35.40±17.17*	34.36±14.69‡	27.86±10.63†	4.526	0.024
Change	7.23±10.11	1.5±15.57	2.08±12.27	1.502	0.230
P	0.024	0.497	0.341		
Conduit					
Baseline	−19.13±8.61	−19.97±11.45	−17.90±8.08	0.326	0.723
6 months	−18.90±10.34	−17.82±11.83	−16.33±7.11	0.439	0.646
Change	0.23±8.92	2.17±11.15	1.57±12.52	2.76	0.07
P	0.822	0.026	0.024		
Contractile					
Baseline	−12.03±2.15	−10.62±1.97	−9.04±1.39	0.691	0.504
6 months	−17.53±7.37*	−16.52±6.49‡	−11.45±5.86†	6.026	0.004
Change	5.5±3.14	5.9±4.15	2.41±3.98	2.178	0.054
P	0.045	0.041	0.156		
LVEDD (mm)					
Baseline	48.94±5.60	47.73±4.16	48.28±4.75	0.430	0.652
6 months	45.08±5.94	47.25±5.02	48.85±5.64	1.068	0.349
Change	3.86±3.85	0.48±3.63	0.57±3.01	0.758	0.472
P	0.011	0.739	0.498		
LVESD (mm)					
Baseline	30.65±5.47	30.50±3.13	29.17±5.21	0.836	0.437
6 months	28.62±4.35	28.13±5.14	28.08±3.77	0.999	0.737
Change	2.03±4.22	2.37±3.05	1.09±3.19	0.127	0.881
P	0.669	0.645	0.855		

(*Continued*)

Table 2 (Continued).

Variables	LBBAP (n=30)	RVSP (n=30)	RVAP (n=30)	F/χ2	*P*
LVEF (%)					
Baseline	65.740±7.90	65.42±5.97	65.80±5.09	0.027	0.973
6 months	68.81±5.92	64.90±5.46	63.56±5.78	0.460	0.633
Change	3.07±1.44	0.52±5.21	2.24±5.96	0.669	0.515
P	0.023	0.709	0.046		
E					
Baseline	1.11±0.31	1.21±0.21	1.11±0.29	0.029	0.913
6 months	1.01±0.26	0.99±0.19	0.84±0.23	0.513	0.687
A					
Baseline	0.95±0.46	1.1±0.45	0.96±0.45	0.718	0.576
6 months	0.92±0.33	1.07±0.43	0.97±0.45	0.557	0.665
E/A					
Baseline	1.16±0.59	1.10±0.47	1.16±0.53	0.102	0.903
6 months	1.1±0.47	0.92±0.41	0.87±0.43	0.450	0.640
Change	0.06±0.59	0.18±0.37	0.29±0.64†	0.311	0.073
P	0.417	0.011	0.005		
e′ (cm/s)					
Baseline	7.33±2.84	7.33±2.68	6.48±1.72	1.123	0.330
6 months	6.53±1.72	6.21±1.93	5.71±1.73	1.321	0.273
E/e′					
Baseline	12.61±3.80	13.70±5.94	14.40±7.11	0.749	0.476
6 months	10.85±3.75*	14.18±3.41‡	16.96±3.79†	2.160	0.023
Change	1.76±3.37*	0.48±3.25‡	2.56±4.47†	5.578	0.038
P	0.014	0.159	0.001		
MR degree					
MR VCM (cm)					
Baseline	0.25±0.12	0.16±0.12	0.22±0.17	0.897	0.568
6 months	0.25±0.13	0.22±0.12	0.27±0.13	0.987	0.141
MR jet area/LAA (%)					
Baseline	10.55±9.68	9.78±7.27	10.45±8.57	0.887	0.678
6 months	11.57±5.22	12.36±5.68	13.45±6.99	0.773	0.383
LV global longitudinal SD (ms)					
Baseline	32.50 (17.00–46.10)	31.60 (11.20–55.95)	52.10 (20.80–71.60)	0.802	0.452
6 months	18.10 (9.90–49.60)	31.50 (9.30–66.05)	41.30 (18.90–63.30)	0.184	0.832
GLS (%)					
Baseline	−20.47±3.23	−19.75±4.47	−21.10±4.78	0.682	0.509
6 months	−19.34±2.17*	−17.12±3.69‡	−16.85±2.30†	6.061	0.004
Change	1.13±3.94	2.63±3.29	4.25±5.29	5.551	0.003
P	0.093	0.031	0.011		
Longitudinal Tε-dif (ms)					
Baseline	112.00 (44.00–189.00)	143.00 (98.00–173.00)	114.00 (37.50–189.00)	0.172	0.842
6 months	31.31 (14.97–47.65)*	104.04 (70.50–137.57)‡	135.52 (101.68–169.36)†	13.853	<0.0001
Change	80.69±25.9	39±24.3	21.53±68.2	3.489	0.036
P	0.037	0.038	0.049		
GCS (%)					
Baseline	−29.82±8.76	−33.42±7.46	−30.15±17.18	0.709	0.495
6 months	−32.83±5.87*	−29.13±6.83‡	−26.26±5.11†	7.735	0.001
Change	3.01±1.11	4.29±2.13	3.89±2.35	5.223	0.033
P	0.494	0.241	0.336		
Circumferential Tε-dif (ms)					
Baseline	225 (148–271)	168.5 (124.5–249.25)	176 (120–299)	1.137	0.326
6 months	56.73 (40.60–72.86)*	202.12 (144.83–259.40)‡	246.33 (98.91–393.76)†	4.172	0.019
Change	−168.27±101.6	33.62±108.7	316.33±325.7	3.942	0.008
P	0.002	0.221	0.001		

Notes: †P<0.05 RVAP vs LBBAP, *P<0.05 LBBAP vs RVSP, ‡P<0.05 RVSP vs RVAP.
Abbreviations: GCS, global circumferential strain; GLS, global Longitudinal strain; LAA, left atrium area; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LS, longitudinal strain; MR, mitral regurgitation; SD, standard deviation; Tε-dif, absolute max difference of time to peak strain; TR, tricuspid regurgitation.

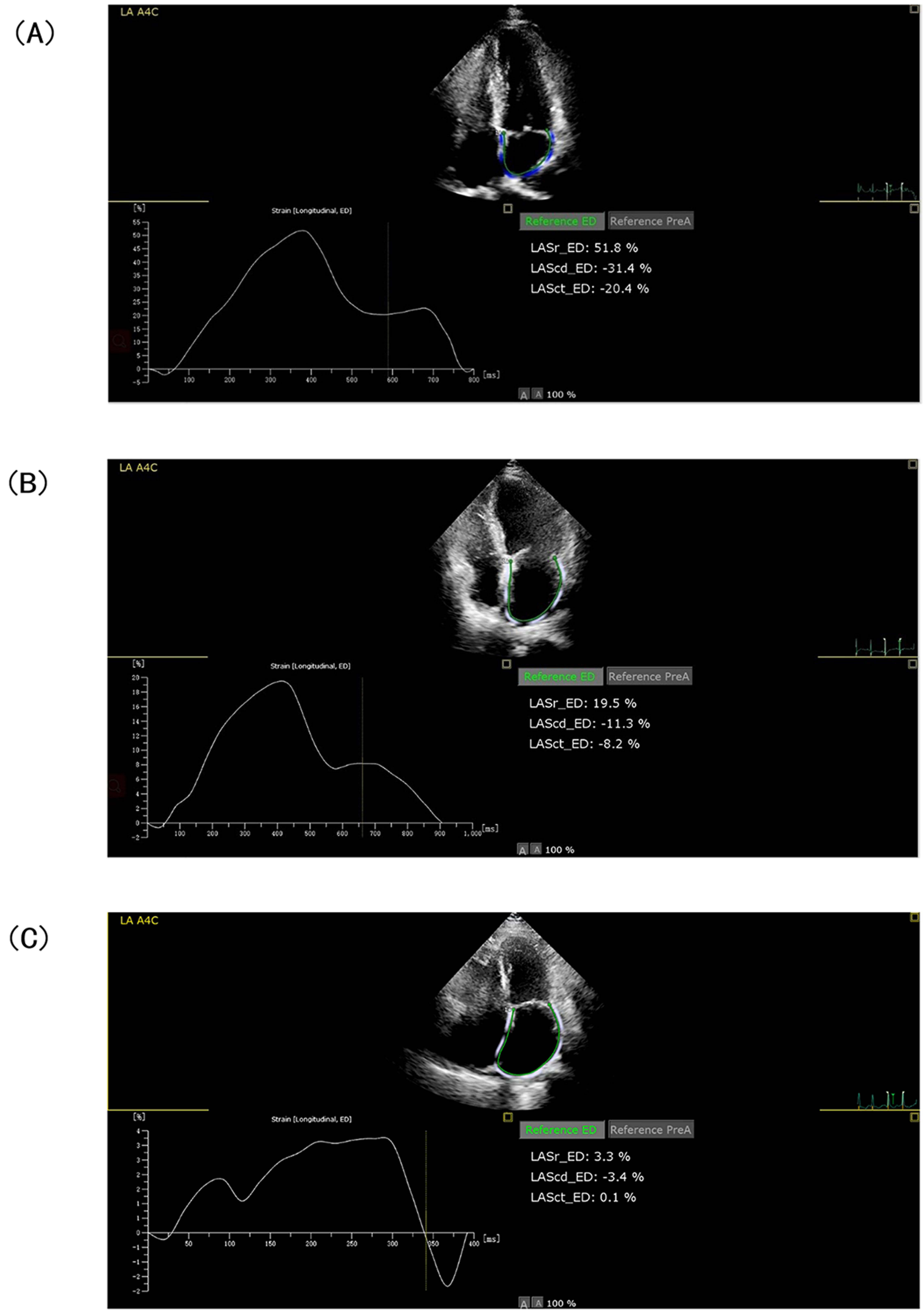

Figure 1 At 6-months of follow up, LA strain (including LA reservoir strain, LA conduit strain and LA contractile strain) in patients that received LBBAP (**A**) was improved compared to patients that received RVSP (**B**) or RVAP (**C**). LA strain parameters were lowest in patients that received RVAP.

LA Function

There were no significant differences in LASr, LAScd or LASct at baseline in patients that received LBBAP, RVSP, or RVAP. At 6-months of follow-up, LASr (35.40±17.17% vs 34.36±14.69% vs 27.86±10.63%, P=0.024) and LASct (−17.53±7.37% vs −16.52±6.49% vs −11.45±5.86%, P=0.004) were significantly improved in patients that received LBBAP compared to patients that received RVSP or RVAP, but there were no significant differences in LAScd (P>0.05).

At 6-months of follow-up, LBBAP and RVSP had effectively enhanced LA strain compared to baseline, reflected by LASr and LASct, whereas RVAP was associated with a detrimental effect on these parameters (Table 2 and Figure 1).

There were no significant differences in LAVI at baseline. At 6-months of follow-up, LAVI was significantly decreased in patients that received LBBAP compared to patients that received RVSP or RVAP (37.55±10.32 vs 44.6 ±8.26 vs 45.88±13.32, $P<0.001$). Patients who received LBBAP could maintain LAVI at 6-months of follow-up (37.55 ±10.32 vs 34.04±10.72, $P=0.324$), while patients who received RVSP and RVAP showed various degrees of impairment (all $P<0.05$). Moreover, at 6-months of follow-up, there were no significant differences in LAV max, LAV min or LAEF in patients that received LBBAP, RVSP, or RVAP (Table 3).

Table 3 RT-3DE Parameters

	LBBAP (n=30)	RVSP (n=30)	RVAP (n=30)	F/χ2	*P*
LAVI					
Baseline	34.04±10.72	37.6±8.96	35.88±11.73	0.352	0.705
6 months	37.55±10.32*	44.6±8.26‡	45.88±13.32†	10.184	<0.0001
Change	3.51±3.64	7±2.37	10±3.17	3.980	0.023
P	0.324	0.031	0.017		
LAVmax					
Baseline	63.43±25.76	63.42±19.76	63.88±28.07	0.684	0.508
6 months	62.73±27.95	63.28±35.37	65.46±22.57	0.819	0.445
Change	−0.7±6.23	−0.14±6.37	1.58±3.79	0.770	0.467
P	0.591	0.793	0.037		
LAVmin					
Baseline	35.7±3.39	32±3.67	34.67±4.08	0.266	0.767
6 months	35.58±4.15	33.20±2.97	34.26±2.03	1.293	0.280
Change	−0.12±4.58	1.2±2.99	0.41±2.36	0.065	0.937
P	0.950	0.765	0.943		
LAEF					
Baseline	56.4±11.65	54.7±13.87	54.81±14.58	0.409	0.666
6 months	54.04±15.78	58.4±12.54	54.96±16.47	0.591	0.557
Change	−2.42±3.19	3.7±2.14	0.15±3.03	2.111	0.129
P	0.092	0.082	0.455		
LVEDV (mL)					
Baseline	125.70±33.93	122.37±38.88	121.88±46.74	0.076	0.927
6 months	123.38±34.77	123.12±37.21	127.27±28.81	1.933	0.152
LVESV (mL)					
Baseline	46.13±19.27	42.50±18.70	43.33±24.55	0.229	0.796
6 months	46.39±19.99	47.92±19.78	46.92±14.78	2.689	0.075
3DLVEF (%)					
Baseline	64.43±6.13	63.93±14.11	66.33±7.79	0.416	0.661
6 months	64.04±5.85	62.00±8.96	60.26±7.29	1.667	0.196
Change	−0.4±1.79	1.93±1.55	6.07±1.67	4.491	0.016
P	0.491	0.045	0.005		
SV(mL)					
Baseline	79.23±17.82	81.33±23.86	81.67±32.97	0.076	0.927
6 months	73.5±18.72	74.40±22.34	66.85±14.67	1.242	0.295
CI (L/min m2)					
Baseline	2.53±0.88	2.70±0.77	2.54±0.93	0.297	0.744
6 months	2.73±0.86	2.61±0.68	2.49±0.55	0.719	0.491
LVED Mass (g)					
Baseline	144.00±32.61	141.29±29.05	140.98±33.38	0.093	0.911
6 months	146.16±41.03	141.77±34.12	128.31±29.62	1.798	0.173

(*Continued*)

Table 3 (Continued).

	LBBAP (n=30)	RVSP (n=30)	RVAP (n=30)	F/χ2	*P*
TMSV 16-SD (R-R%)					
Baseline	2.17±0.23	2.22±0.97	2.16±0.99	7.567	0.572
6 months	2.76±0.53*	5.38±0.85‡	6.24±1.11†	4.314	0.017
Change	0.59±0.38	3.16±0.35	4.08±0.79	1.746	0.182
P	0.578	0.035	0.016		
TMSV 12-SD (R-R%)					
Baseline	2.24±0.33	2.25±0.29	2.23±0.32	8.146	0.667
6 months	2.42±0.38*	4.23±0.78‡	6.04±1.13†	4.728	0.011
Change	0.18±0.35	2.18±0.55	3.81±0.98	5.490	0.016
P	0.141	0.016	0.001		
TMSV 6-SD (R-R%)					
Baseline	2.11±0.23	2.22±0.21	2.23±0.22	7.435	0.778
6 months	2.37±0.42*	3.75±0.67‡	5.47±0.94†	3.203	0.037
Change	0.26±0.33	1.53±0.44	3.24±0.77	4.897	0.014
P	0.051	0.018	0.004		

Notes: †P<0.05 RVAP vs LBBAP, *P<0.05 LBBAP vs RVSP, ‡P<0.05 RVSP vs RVAP.
Abbreviations: CI, cardiac index; 3DEF, three-dimensional echocardiographic ejection fraction; LAEF, left atrial ejection fraction; LAFI, left atrial functional index; LAVi, left atrial volume indexed to body surface area; LVED Mass, Left ventricular end-diastolic mass; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; SV, stroke volume; TMSV 16-SD (R-R%), standard deviation of time from the QRS starting point to the minimum systolic volume of 16 LV segments; TMSV 12-SD (R-R%), standard deviation of time from the QRS starting point to the minimum systolic volume of 12 LV segments; TMSV 6-SD (R-R%), standard deviation of time from the QRS starting point to the minimum systolic volume of 6 LV segments.

LV Mechanical Synchrony

2D-STE and RT-3DE were used to evaluate mechanical synchrony of the LV.

For 2D-STE, the LV was divided into 18 segments. There were no significant differences in GLS and GCS at baseline in patients that received LBBAP, RVSP, or RVAP. At 6-months of follow-up, GLS and GCS were significantly improved in patients that received LBBAP compared to patients that received RVSP or RVAP. There were no significant changes in GLS (−19.34±2.17% vs −20.47±3.23%, *P*=0.093) or GCS (−32.83±5.87% vs −29.82±8.76%, *P*=0.494) at 6-months of follow-up compared to baseline in patients that received LBBAP. In contrast, there was a notable decline in GLS at 6-months of follow-up compared to baseline in patients that received RVSP or RVAP (all *P*<0.05) (Table 2 and Figure 2).

There were no significant differences in time to peak systolic strain among the 18 segments (longitudinal Tε-dif and circumferential Tε-dif) at baseline in patients that received LBBAP, RVSP, or RVAP. At 6-months of follow-up, longitudinal Tε-dif (31.31 [14.97–47.65] vs 104.04 [70.50–137.57] vs 135.52 [101.68–169.36] ms, *P*<0.0001) and circumferential Tε-dif (56.73 [40.6–72.86] vs 202.12 [144.83–259.40] vs 246.33 [98.91–393.76] ms, *P*=0.019) were significantly shorter in patients that received LBBAP compared to patients that received RVSP or RVAP (Table 2). Bull's eye plots demonstrated that the time to peak systolic strain in the 18 segments varied between 295 and 397 ms in patients that received LBBAP, 282 to 452 ms in patients that received RVSP, and 84 to 508 ms in patients that received RVAP (Figure 3).

For RT-3DE, there were no significant differences in SDI at baseline in patients that received LBBAP, RVSP, or RVAP. At 6-months of follow-up, SDI (TMSV 16-SD [R-R%] [2.76±0.53 vs 5.38±0.85 vs 6.24±1.11, *P*=0.017]; TMSV 12-SD [R-R%] [2.42±0.38 vs 4.23±0.78 vs 6.04±1.13, *P*=0.011]; TMSV 6-SD [R-R%] [2.37±0.42 vs 3.75±0.67 vs 5.47 ±0.94, *P*=0.037]) was significantly lower in patients that received LBBAP compared to patients that received RVSP or RVAP. There were no significant changes in TMSV 16-SD (*P*=0.578), TMSV 12-SD (*P*=0.141), or TMSV 6-SD (*P*=0.051) at 6-months of follow-up compared to baseline in patients that received LBBAP. In contrast, there was significant worsening in patients that received RVSP or RVAP (all *P*<0.05) (Table 3 and Figure 4).

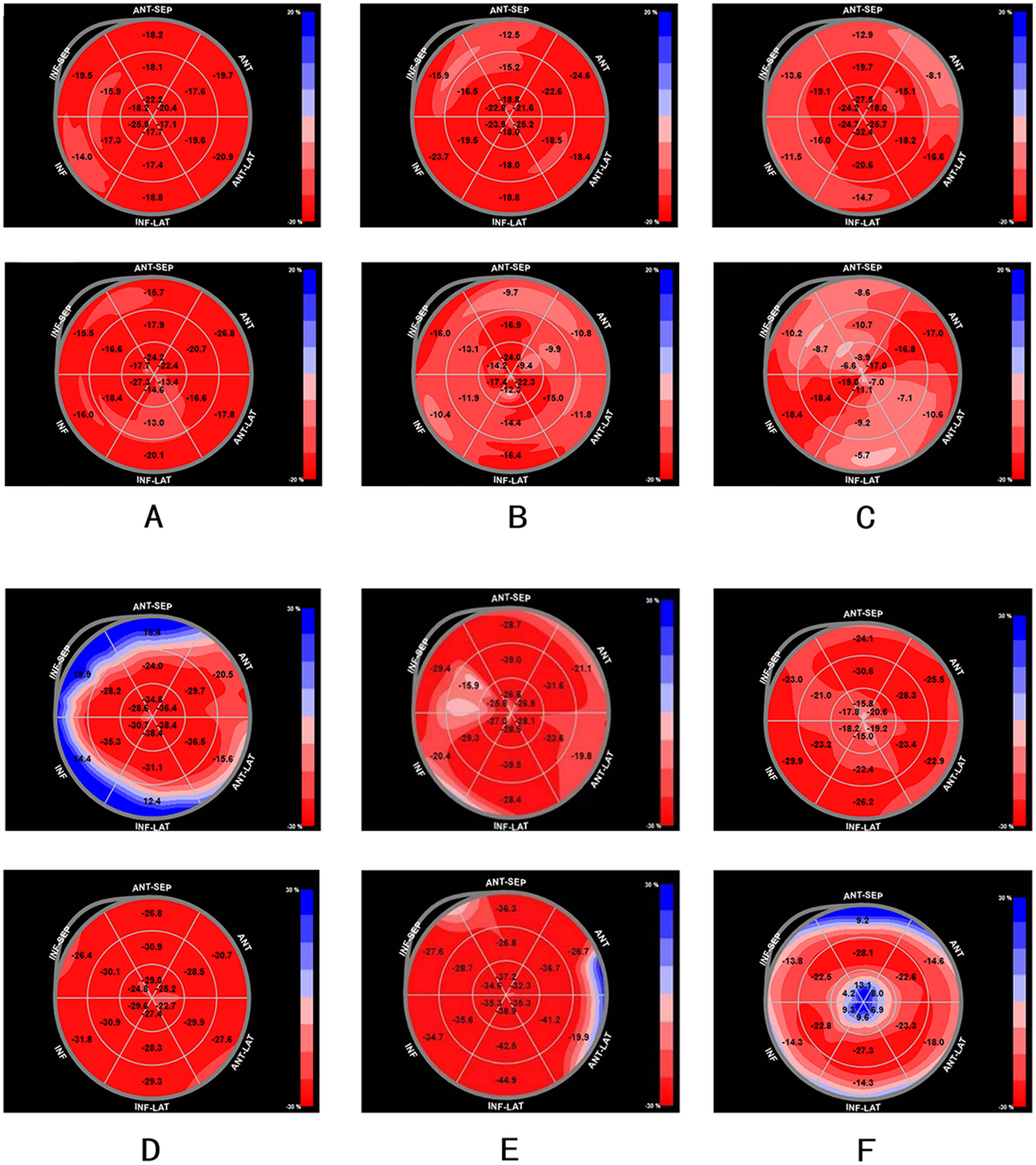

Figure 2 GLS in patients that received LBBAP (**A**) RVSP (**B**) or RVAP (**C**) at baseline (upper panels) and 6-months of follow-up (lower panels); GCS in patients that received LBBAP (**D**) RVSP (**E**) or RVAP (**F**) at baseline (upper panels) and 6-months of follow-up (lower panels).

LV Function

At 6-months of follow-up, there were no significant differences in LVEF, SV, CI, in patients that received LBBAP, RVSP, or RVAP (Table 3).

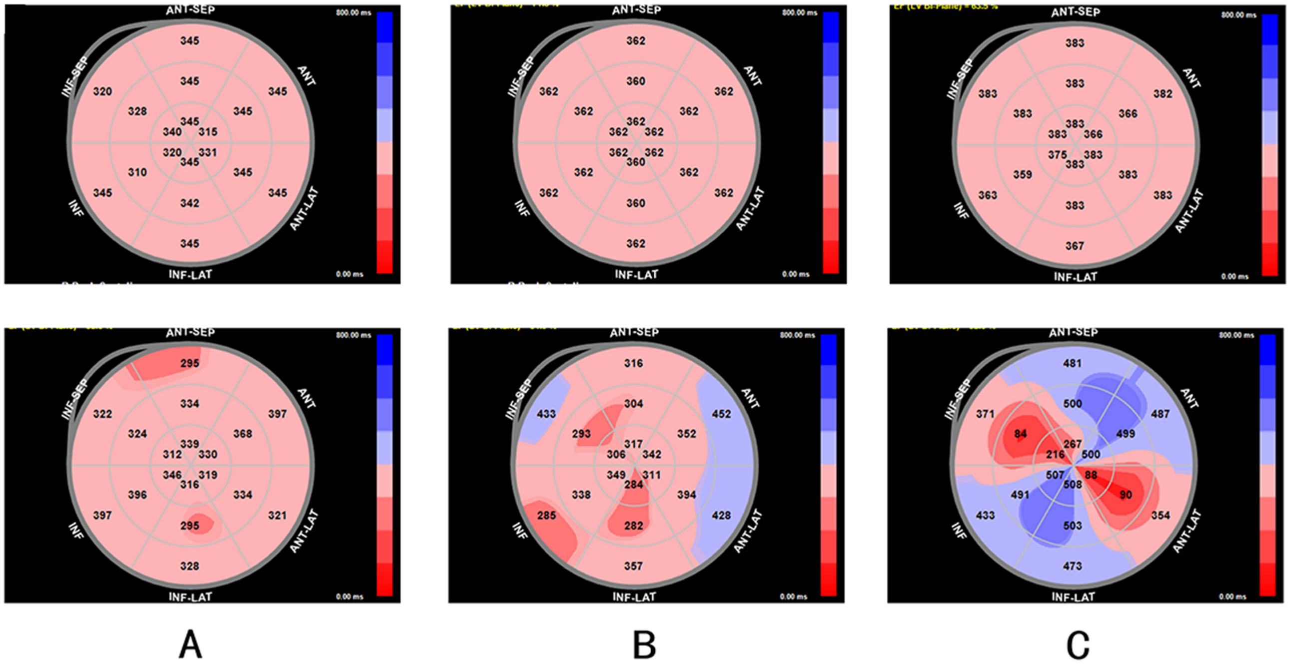

Figure 3 Longitudinal Tε-dif in patients that received LBBAP (**A**) RVSP (**B**) or RVAP (**C**) at baseline (upper panels) and 6-months of follow-up (lower panels). Bull's eye plots demonstrated that the time to peak systolic strain in the 18 segments varied between 295 and 397 ms in patients that received LBBP, 282–452 ms in patients that received RVSP, and 84–508 ms in patients that received RVAP.

New Onset AF

LBBAP (3/30) was associated with a reduced risk of AF compared to RVSP (5/30) or RVAP (7/30).

Discussion

This study evaluated the efficacy of LBBAP, RVSP, and RVAP in pacemaker-dependent patients, focusing mainly on the structure and function of the LA by echocardiography 6-months after pacemaker implantation. Major findings were: 1) LBBAP, as compared to RVSP and RVAP, effectively enhanced systolic and diastolic cardiac function, and improved BNP levels and the 6MWD. 2) LBBAP preserved LA function, as assessed by LA reservoir strain, LA contractile strain, and LAVI. In contrast, RVAP and RVSP were associated with a deterioration in these functional measures. 3) LBBAP enhanced mechanical synchrony, evidenced by reductions in both longitudinal and circumferential strain differences (Tε-dif) assessed by 2D-STE and TMSV-standard deviations of 16, 12, and 6 LV segments measured by RT-3DE; however, RVAP and RVSP resulted in mechanical desynchronization.

BNP is a quantitative biomarker for heart failure, reflecting systolic and diastolic functions of the LV.[14] The 6MWD is utilized in clinical practice for assessing the endurance of patients with cardiac conditions, and constitutes a significant prognostic indicator for evaluating the efficacy of therapeutic interventions in individuals with chronic heart failure. A previous investigation demonstrated improved NYHA functional classification and cardiac parameters in patients with heart failure that received LBBAP.[15] In the current study, LBBAP was practical and safe in our patient population. At 6-months of follow-up, patients that received LBBAP had considerably lower levels of BNP and better 6MWD compared to patients that received RVSP or RVAP, indicating that LBBAP can effectively enhance both systolic and diastolic performance and increase quality of life and exercise tolerance in pacemaker-dependent patients.

Although the precise etiology of AF induced by ventricular pacing remains elusive, the prevailing consensus supports the hypothesis that LA dysfunction, a consequence of LV dyssynchrony precipitated by ventricular pacing, may underlie this phenomenon. In the context of heart failure with preserved ejection fraction (HFpEF), elevated LA pressure pulsatility may signify a pronounced variation in myocardial wall stress, potentially contributing to the increased prevalence of AF.[16] The LA functions as a reservoir, a conduit, and a contractile chamber during the cardiac cycle, playing a critical role in controlling LV filling and optimizing overall cardiac function. Prior studies have found that the

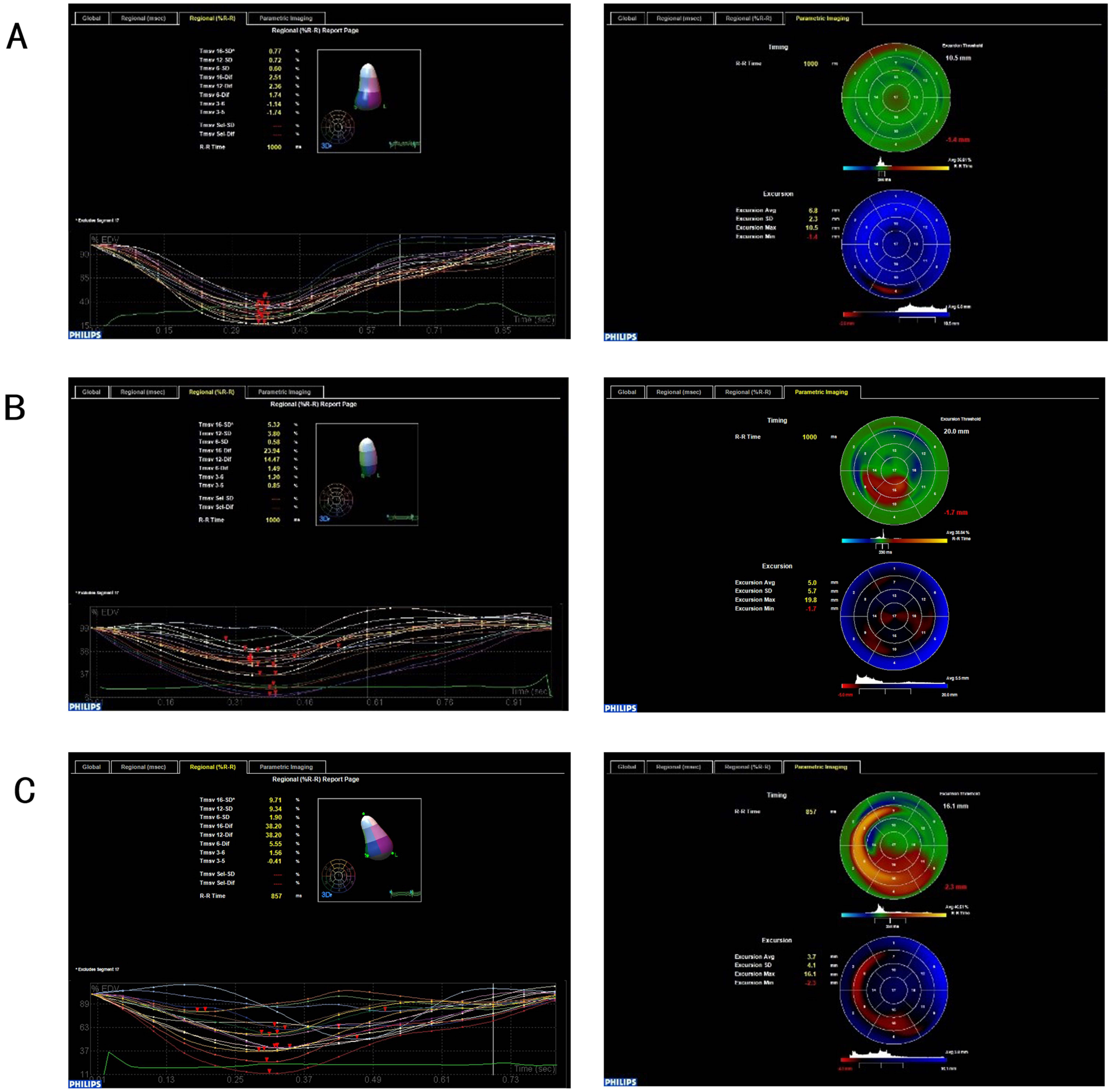

Figure 4 At 6-months of follow-up, the systolic dyssynchrony index (SDI) was significantly lower in patients that received LBBAP (**A**) compared to RVSP (**B**) or RVAP (**C**).

initial signs of diastolic dysfunction, which appear before structural alterations to the LA, are a decrease in LA reservoir function and LA pump function, as evaluated by STE.[17,18] A previous study with a 6-month follow-up revealed that LA strain was a significant predictor of AF after restoring sinus rhythm by electrical cardioversion. Patients who maintained sinus rhythm showed a greater improvement in peak atrial longitudinal strain compared to those who experienced relapse.[19] In the present study, at 6-months of follow-up, the E/A and E/e′ ratio in patients that received LBBAP were significantly better than RVSP and RVAP. Strain measurements during the reservoir phase and contractile phase of the LA cycle were significantly better in patients that received LBBAP compared to RVSP or RVAP, and the LAVI was significantly reduced in patients that received LBBAP compared to RVSP or RVAP. The implications of these functional improvements for the development and management of AF are significant, as they may provide insights into the mechanisms underlying the condition and potential therapeutic targets. Atrial fibrosis interferes with local electrical activity, facilitates loop reentry, and induces regional conduction disturbances, thereby creating an environment conducive to the onset of AF. Our research suggests that LBBAP improves left-heart synchronization, reduces LV filling pressure, and consequently mitigates the risk of atrial fibrosis. As a result, LBBAP is associated with a lower incidence of AF following pacemaker implantation.

Cardiac synchrony is crucial for preserving cardiac structure and function, and cardiac resynchronization reduces the risk of heart failure and can reverse LV remodeling. LV mechanical synchrony can be evaluated using 2D-STE and RT-3DE. Further to our prior study with a 4-week follow-up,[6] LBBAP continues to maintain favorable LV synchrony, as well as GLS and GCS at 6-months of follow-up. Numerous studies have found that LBBAP can serve as an effective alternative to cardiac resynchronization therapy (CRT), enhancing cardiac function and ameliorating cardiac electromechanical dyssynchronization.[20–22] Our research has demonstrated that LBBAP, as a more physiologically aligned pacing modality, effectively attains ventricular synchrony and concurrently maintains LA function.

Our study suggests that LBBAP, an emerging pacing strategy, decreases the risk of atrial fibrosis and significantly enhances cardiac synchronization, indicating its potential as a future pacing therapy. We posit that LBBAP pacing may lower the incidence of post-implant cardiomyopathy, heart failure, and new-onset AF, particularly as the follow-up period extends. Notably, we have observed that LBBAP demands a more significant learning curve than the alternative pacing techniques, is associated with increased radiation exposure and procedural duration, and results in elevated healthcare expenses.

Limitations

Data on LA and LV function and LV mechanical synchrony from this prospective trial imply that LBBAP may have a protective effect and achieve a more physiological cardiac activation than RVSP and RVAP in pacemaker-dependent individuals. However, this study was limited as it was conducted at a single institution, with a small sample size, and a short follow-up period. Randomized controlled trials with larger pacemaker-dependent populations with normal ejection fraction and long-term follow-up are warranted to confirm the safety and therapeutic advantages of LBBAP compared to RVSP or RVAP.

Conclusion

In pacemaker-dependent patients, LBBAP stands out for its physiological benefits, including better LA elasticity, strain, and ventricular activation over RVSP or RVAP. LBBAP improves LA and LV function and synchrony, potentially reducing the risk of new-onset AF. Over a 6-month follow-up, LBBAP shows promise as a leading pacing strategy for cardiac synchronization and prevention of atrial fibrosis.

Abbreviations

CI, cardiac index; 3DEF, three-dimensional echocardiographic ejection fraction; GCS, global circumferential strain; GLS, global Longitudinal strain; LAA, left atrium area; LAD, left atrial diameter; LAEF, left atrial ejection fraction; LAFI, left atrial functional index; LAVi, left atrial volume indexed to body surface area; LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; LS, longitudinal strain; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVED Mass, left ventricular end-diastolic mass; LVEDV, LV end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, LV end-systolic volume; MR, mitral regurgitation; NT-pro BNP, N-terminal pro-brain natriuretic peptides; RBBB, right bundle branch block; RV, right ventricle; RVSP, right ventricular septal pacing; RVAP, right ventricular apical pacing; SD, standard deviation; SV, stroke volume; Tε-dif, absolute max difference of time to peak strain; TMSV 16-SD (R-R%), standard deviation of time from the QRS starting point to the minimum systolic volume of 16 LV segments; TMSV 12-SD (R-R%), standard deviation of time from the QRS starting point to the minimum systolic volume of 12 LV segments; TMSV 6-SD (R-R%), standard deviation of time from the QRS starting point to the minimum systolic volume of 6 LV segments; TR, tricuspid regurgitation; 6MWD, Six-Minute Walk Distance.

Funding

This research was funded by Capital Medical University Major Science and Technology Innovation Research and Development Special Fund (code: KCZD202201); Capital's Funds for Health Improvement and Research (CRF 2024-2-2073); Capital's Funds for Health Improvement and Research (CRF 2020-2-2062); Beijing Jishuitan Research Funding (code: ZR-202415); and Beijing Hospital Authority Clinical Medicine Development of Special Funding Support (XMLX202112).

Disclosure

All authors declare no conflicts of interest in this work.

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